# SOME NUCLEOPHILIC SUBSTITUTION REACTIONS OF 2-CHLORO-3-CYANOPYRIDINES

Z. A. Bomika, M. B. Andaburskaya, Yu. É. Pelcher, and G. Ya. Dubur

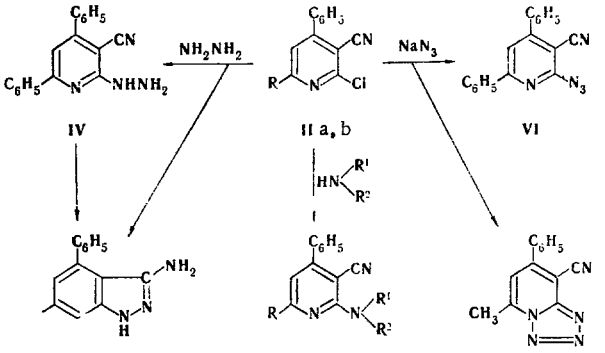
UDC 547.822.5.7'828'796.1

The chlorine atom in 2-chloro-3-cyanopyridines is readily replaced by primary and secondary aliphatic amines and heterocyclic amines to give 2-aminopyridines. 2-Chloro-3-cyanopyridines react with hydrazine hydrate and sodium azide to give hydrazinopyridines, pyridopyrazoles, azidopyridines, and pyridotetrazoles.

This paper is devoted to the synthesis of pyridopyrazoles and pyridotetrazoles from 3-cyano-4-phenyl-6-methyl-2-oxo-1,2-dihydropyridine (Ia) and 3-cyano-4,6-diphenyl-2-oxo-1,2-dihydropyridine (Ib) [1].

By modifying known methods [2, 3] we obtained 2-chloro-3-cyano-4-phenyl-6-methylpyridine (IIa) and 2-chloro-3-cyano-4,6-diphenylpyridine (IIb) by fusing 2-oxopyridines I with phosphorus pentachloride.

The chlorine atom in 2-chloro-3-cyanopyridines IIa, b becomes labile under the influence of the CN group and is readily substituted by nitrogen-containing nucleophilic agents – primary and secondary amines, hydrazine hydrate, and sodium azide. In contrast to 2-chloropyridines that are unsubstituted or substituted by electron-donor groups in the 3 position [4, 5], IIa, b react with primary and secondary amines in the absence of a catalyst. An exchange reaction does not occur in the case of ammonia, possibly because of its lower nucleophilicity as compared with aliphatic amines.



II, V a R=$CH_3$; b R=$C_6H_5$; III a R=$CH_3$, $R^1R^2=(-CH_2-)_5$; b R=$C_6H_5$, $R^1R^2=(-CH_2-)_5$; c R=$CH_3$, $R^1R^2=(-CH_2-)_4$; d R=$C_6H_5$, $R^1R^2=(-CH_2-)_4$; e R=$C_6H_5$, $R^1R^2=(-CH_2CH_2-)_2O$; f R=$CH_3$, $R^1=H$, $R^2=CH_2C_6H_5$; g R=$C_6H_5$, $R^1=H$, $R^2=CH_2C_6H_5$; h R=$C_6H_5$, $R^1=H$, $R^2=C_4H_9$; i R=$R^1=R^2=CH_3$; k R=$C_6H_5$, $R^1=CH_3$, $R^2=C_6H_{10}$; e R=$C_6H_5$, $R^1=R^2=H$

The IR spectra of amines IIIa-j contain bands of vibrations of the cyano group at 2202-2220 $cm^{-1}$; frequencies of the stretching vibrations of the amino group of secondary amines IIIf-h are observed at 3360-3390 $cm^{-1}$.

The PMR spectra of 2-aminopyridines III (Table 2) contain signals of all of the fragments of the molecule in the appropriate region, but the signals of the proton of the NH group for the secondary amines shows up as a multiplet at δ 5.13-5.66 ppm. It is interesting to note the large effect of the phenyl group in the 6 position on the signal of the proton attached to $C_5$, which is observed at δ 7.93-8.12 ppm, whereas the analogous signal for compounds that have a methyl group in the 6 position shows up at δ 6.47-6.98 ppm.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1085-1088, August, 1976. Original article submitted August 21, 1975.

TABLE 1. Characteristics of the Synthesized 2-Aminopyridines (III)

| Compound | mp, °C | Crystallization solvent | Empirical formula | Found, % | | | Calculated, % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | C | H | N | |
| IIIa | 145—146 | Ether | $C_{18}H_{19}N_3$ | 77,5 | 7,0 | 15,0 | 78,0 | 6,9 | 15,2 | 62 |
| IIIb | 123—123,5 | Petroleum ether | $C_{23}H_{21}N_3$ | 80,9 | 6,3 | 12,3 | 81,4 | 6,2 | 12,4 | 85 |
| IIIc | 135—137 | " | $C_{17}H_{17}N_3$ | 77,7 | 6,0 | 16,0 | 77.5 | 6,5 | 16,0 | 80 |
| IIId | 119,5—120,5 | Ether | $C_{22}H_{19}N_3$ | 81,3 | 6,2 | 12,9 | 81,2 | 5,9 | 12,9 | 80 |
| IIIe | 123,5—124,5 | " | $C_{22}H_{19}N_3O$ | 76,9 | 5,7 | 12,5 | 77,4 | 5,6 | 12,3 | 84 |
| IIIf | 109,5—110,5 | Petroleum ether | $C_{20}H_{17}N_3$ | 79,9 | 5,8 | 13,8 | 80.2 | 5,7 | 14,0 | 68 |
| IIIg | 170—171 | Ether | $C_{25}H_{19}N_3$ | 83,0 | 5,5 | 11,2 | 83,1 | 5,3 | 11,6 | 80 |
| IIIh | 123,5—124,5 | Petroleum ether | $C_{22}H_{21}N_3$ | 80,4 | 6,5 | 12,6 | 80,7 | 6,5 | 12,8 | 89 |
| IIIi | 98,5—100 | " | $C_{15}H_{15}N_3$ | 75,9 | 6,3 | 17,4 | 75,9 | 6,4 | 17,7 | 38 |
| IIIj | 142—143 | Ether | $C_{25}H_{25}N_3$ | 82,1 | 7,0 | 11,8 | 81,7 | 6,9 | 11,4 | 79 |
| IIIk | 188—189 | " | $C_{18}H_{13}N_3$ | 79,3 | 5,1 | 15,5 | 79,7 | 4,8 | 15,5 | 69 |

TABLE 2. IR and PMR Spectra of 2-Aminopyridines III

| Compound | IR spectra, $cm^{-1}$ | PMR spectra | |
|---|---|---|---|
| | | solvent | δ, ppm |
| IIIa | 1560, 1570, 2209 | $CCl_4$ | 1,71 ($3CH_2$); 2,41($CH_3$); 3,63 (N<$CH_2$ $CH_2$>); 6,55 (CH); 7,42 ($C_6H_5$) |
| IIIb | 1540, 1580, 2215 | $CCl_4$ | 1,81 ($3CH_2$); 3,82 (N<$CH_2$ $CH_2$>); 7,55 ($2C_6H_5$); 8,12 (CH) |
| IIIc | 1558, 2212 | $CCl_4$ | 2,00 ($2CH_2$); 2,46 ($CH_3$); 3,72 (N<$CH_2$ $CH_2$>); 6.40 (CH); 7,35 ($C_6H_5$) |
| IIId | 1545, 1570, 2210 | $CCl_4$ | 2,04 ($2CH_2$); 3,92 (N<$CH_2$ $CH_2$>); 7,45 ($2C_6H_5$); 8,00 (CH) |
| IIIe | 1545, 1580, 2220 | $CDCl_3$ | 3,84 ($4CH_2$); 7,54 ($2C_6H_5$); 8,06 (CH) |
| IIIf | 1560, 1590, 2210. 3390 | $CCl_4$ | 2,41 ($CH_3$); 4,72 ($CH_2$); 5,66 (NH); 6,47 (CH); 7,24 ($C_6H_5$); 7,43 ($C_6H_5$) |
| IIIg | 1568, 1585, 2210, 3360 | $CCl_4+CDCl_3$ | 3,41 ($CH_2$); 5,13 (NH); 7,52 ($2C_6H_5$); 8,12 (CH) |
| IIIh | 1560, 1580, 2220, 3370 | $CCl_4$ | 1,04 ($CH_3$); 1,58 ($2CH_2$); 3.58 ($CH_2$); 5,43 (NH); 7,42 ($2C_6H_5$); 8,00 (CH) |
| IIIi | 1560, 2202 | $CCl_4$ | 2,40 (C—$CH_3$); 3,25 (N<$CH_3$ $CH_3$>); 6,50 (CH); 7,42 ($C_6H_5$) |
| IIIj | 1550, 1570, 2210 | $CCl_4$ | 1,30—2,20 ($5CH_2$); 3,15 ($CH_3$); 7,46 ($2C_6H_5$); 7,39 (CH) |
| IIIk | 1578. 1642, 2207, 3199, 3320, 3478 | $CDCl_3+CCl_4$ | 5,45 ($NH_2$); 7,55 ($2C_6H_5$); 8,05 (CH) |

Pyridopyrazole Va is formed in the reaction of 2-chloropyridine IIa with hydrazine hydrate. After nucleophilic attack by hydrazine on the $C_2$ atom it evidently undergoes subsequent addition to the cyano group of pyridine with ring closing. In the case of 6-phenyl-2-chloropyridine IIb the intermediate 2-hydrazino-3-cyano-4,6-diphenylpyridine (XV) can be isolated. The IR spectrum of pyridine IV contains absorption bands of a nitrile group at 2210 $cm^{-1}$ and of $NH_2$ and NH groups at 3330 and 3230-3280 $cm^{-1}$. The IR spectra of pyridopyrazoles V do not contain the absorption band of a nitrile group, and the characteristic absorption of $NH_2$ and NH groups appears at 3200-3470 $cm^{-1}$.

Sodium azide reacts with 6-phenyl-2-chloropyridine (IIb) to give 2-azido-3-cyano-4,6-diphenylpyridine (VI) and with 6-methyl-2-chloropyridine (IIa) to give pyridotetrazole VII. The IR spectra of azide VI (both in the solid state and in carbon tetrachloride and acetone solutions) contain the absorption of a nitrile group at 2230 $cm^{-1}$ and of an azide group at 2160 and 2130 $cm^{-1}$. Only the absorption of a nitrile group at 2223 $cm^{-1}$ is observed in the spectrum of tetrazole VII.

2-Aminopyridine IIIk, which we could not obtain by the direct action of ammonia on 2-chloropyridine II, was synthesized by reduction of azide VI with stannic chloride.

## EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Perkin–Elmer R-12 spectrometer (60 MHz) with tetramethylsilane as the internal standard. Monitoring of the reactions and the individuality of all of the synthesized compounds was accomplished by means of thin-layer chromatography (TLC) on Silufol in an acetone–hexane system (1 : 1).

2-Chloro-3-cyano-4-phenyl-6-methylpyridine (IIa). A mixture of 1.5 g (7.1 mmole) of 2-oxopyridine Ia and 3.2 g (15.5 mmole) of $PCl_5$ was heated at 150° for 1.5 h, after which it was poured with stirring into ice water. The resulting precipitate was removed by filtration and crystallized from ethanol to give 0.9 g (55%) of a product with mp 154-156°. Found: C 68.1; H 3.9; Cl 15.6; N 12.4%. $C_{13}H_9ClN_2$. Calculated: C 68.4; H 4.0; Cl 15.5; N 12.3%. IR spectrum: 1530, 1592, 2228 $cm^{-1}$.

2-Chloro-3-cyano-4,6-diphenylpyridine (IIb). This compound, with mp 154-155°, was obtained in 76% yield from 2-hydroxypyridine Ib by the method used to prepare IIa. Found: C 74.4; H 3.7; Cl 12.6; N 9.6%. $C_{18}H_{11}ClN_2$. Calculated: C 74.4; H 3.8; Cl 12.2; N 9.7%. IR spectrum: 1528, 1585, 2225 $cm^{-1}$.

2-Piperidino-3-cyano-4-phenyl-6-methylpyridine (IIIa). A solution of 0.2 g (0.88 mmole) of chloropyridine IIa and 2 ml (24.5 mmole) of piperidine in 5 ml of dimethylformamide (DMF) was refluxed for 2 h after which it was poured into 10 ml of water. The resulting precipitate was separated and crystallized from ether.

Pyridines IIIb-j were similarly obtained. The reactions with primary amines were carried out in toluene, and those with secondary amines were carried in DMF. The dimethylamino derivative was obtained by bubbling gaseous dimethylamine into a solution of the chloropyridine. The characteristics of pyridines III are presented in Table 1.

2-Hydrazino-3-cyano-4,6-diphenylpyridine (IV). A solution of 0.5 g (1.72 mmole) of chloropydirine IIb and 0.2 ml (4.1 mmole) of hydrazine hydrate in 20 ml of dioxane was refluxed for 5 h, after which it was cooled, and the resulting precipitate was separated to give 0.3 g (50%) of a product with mp 196-197° (from ethanol). Found: C 75.0; H 4.9; N 19.3%. $C_{18}H_{14}N_4$. Calculated: C 75.5; H 4.9; N 19.6%. IR spectrum: 1585, 1625, 2210, 3220-3270, 3330 $cm^{-1}$.

3-Amino-4-phenyl-6-methyl-1H-pyrazolo[4,5-b]pyridine (Va). A mixture of 0.5 g (2.2 mmole) of chloropyridine IIa in 5 ml of ethanol and 0.2 ml of hydrazine hydrate was refluxed for 8 h, after which it was worked up to give 0.45 g (92%) of Va with mp 233-240° (sublimation). Found: C 69.6; H 5.4; N 25.0%. $C_{13}H_{12}N_4$. Calculated: C 69.6; H 5.4; N 25.0%. IR spectrum: 1580, 1590, 1630, 3200, 3290-3305, 3470 $cm^{-1}$.

3-Amino-4,6-diphenyl-1H-pyrazolo[4,5-b]pyridine (Vb). A solution of 0.2 g (0.7 mmole) of hydrazinopyridine IV and a catalytic amount of p-toluenesulfonic acid in 15 ml of toluene was refluxed for 1 h, after which the solvent was vacuum evaporated, and the residue was washed with water and crystallized from ethanol to give 0.18 g (90%) of a product with mp 220-221°. Found: C 75.8; H 4.9; N 19.4%. $C_{18}H_{14}N_4$. Calculated: C 75.5; H 4.9; N 19.6%. IR spectrum: 1595, 1630, 3195-3210, 3440-3450 $cm^{-1}$.

2-Azido-3-cyano-4,6-diphenylpyridine (VI). A mixture of 0.5 g (1.72 mmole) of chloropyridine IIb in 20 ml of DMF and 0.3 g (4.62 mmole) of sodium azide in 5 ml of water was refluxed for 3 h, after which the precipitate was removed by filtration and crystallized from ethanol to give 0.27 g (58%) of a product with mp 173-174°. Found: C 72.4; H 3.7; N 23.6%. $C_{18}H_{11}N_5$. Calculated: C 72.7; H 3.7; N 23.5%. IR spectrum: 1535, 1595, 1622, 2130, 2160, 2230 $cm^{-1}$.

4-Cyano-5-phenyl-7-methyltetrazolo[5,1-a]pyridine (VII). This compound, with mp 227-228°, was obtained in 77% yield by the method used to prepare VI. Found: C 66.0; H 3.9; N 29.6%. $C_{13}H_9N_5$. Calculated: C 66.4; H 3.9; N 29.8%. IR spectrum: 1570, 1635, 2232 $cm^{-1}$.

2-Amino-3-cyano-4,6-diphenylpyridine (IIIk). A mixture of 0.4 g (1.32 mmole) of azide VI in 10 ml of ethanol, 10 ml of hydrochloric acid and 0.5 g (2.64 mmole) of $SnCl_2$ in 5 ml of water was refluxed for 3 h, after which it was made alkaline to pH ~ 9 with 50% potassium hydroxide solution and extracted with chloroform. The extract was washed with water, dried with sodium sulfate, and vacuum evaporated. The residue was crystallized from ether.

## LITERATURE CITED

1. Z. A. Bomika, M. B. Andaburskaya, Yu. É. Pelcher, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 8, 1108 (1975).

2. J. F. M. Wajon and J. F. Arens, Rec. Trav. Chim., 76, 65 (1957).
3. R. Fuks, Tetrahedron, 26, 2161 (1970).
4. H. Hertog and J. Wibaut, Rec. Trav. Chim., 51, 381 (1932).
5. V. Rudy and F. Majer, Ber., 71, 1243 (1938).

# ALKYLATION OF 3-CYANO-2-OXOPYRIDINE DERIVATIVES

Z. A. Bomika, M. B. Andaburskaya, Yu. É. Pelcher, and G. Ya. Dubur

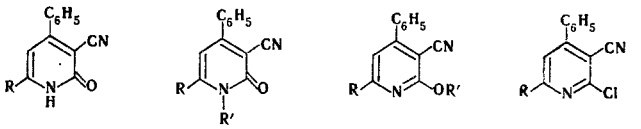
UDC 547.822.7'824'828:542.953

A number of N- and O-alkylpyridines were obtained by alkylation of 3-cyano-2-oxopyridines with alkyl halides and diazomethane.

This paper is devoted to the study of the alkylation of 3-cyano-2-oxopyridines I with alkyl or phenyl substituents in the 6 position [1]. Since 2-oxopyridines in alkaline media are capable of giving ambident anions [2], alkylation may occur both at the nitrogen atom and at the oxygen atom. It is known that the alkylation of 2-oxopyridines in the presence of alkali metal hydroxides proceeds primarily via an $S_N2$ mechanism at the nitrogen atom, whereas in the presence of silver salts alkylation takes place at the oxygen atom via an $S_N1$ mechanism [3].

In the present research we accomplished the alkylation of 2-oxopyridine salts with alkyl halides in the presence of potassium hydroxide. It was found that the structure of the final product is determined by the structure of the starting 2-oxopyridine (I) and the stability of the cation of the alkyl halide.

Thus oxopyridine Ia, with an electron-donor methyl group in the 6 position that increases the nucleophilicity of the nitrogen atom, is alkylated by methyl and ethyl iodides exclusively at nitrogen to give 1-alkyl-2-oxopyridines IIa, b (Table 1). As the length of the alkyl chain increases, the stability of the cation of the alkyl halide increases. and competitive reaction via an $S_N1$ mechanism becomes possible; this explains the formation of a mixture of N- and O-alkylpyridines (IIc, d and IIIc, d) in the butylation and benzylation of 2-oxopyridines Ia. Only N-hexyl product IIe was isolated in 43% yield in the case of hexylation.



I a, b  II a-f  III a-h  IV a, b

I a R=$CH_3$; b R=$C_6H_5$; II a R=$CH_3$, R′=$CH_3$; b R=$CH_3$, R′=$C_2H_5$; c R=$CH_3$, R′=$C_4H_9$; d R=$CH_3$, R′=$CH_2C_6H_5$; d R=$CH_3$, R′=$C_6H_{13}$; f R=$C_6H_5$, R′=$C_6H_{13}$; III a R=$CH_3$, R′=$CH_3$; b R=$CH_3$, R′=$C_2H_5$; c R=$CH_3$, R′=$C_4H_9$; d R=$CH_3$, R′=$CH_2C_6H_5$; e R=$C_6H_5$, R′=$C_2H_5$; e R=$C_6H_5$, R′=$C_4H_9$; g R=$C_6H_5$, R′=$C_6H_{13}$; f R=$C_6H_5$, R′=$CH_3$

In contrast to the methyl group, the phenyl group in the 6 position of oxopyridine Ib decreases the nucleophilicity at the adjacent nitrogen atom and sterically hinders the approach of the reagent to it. The methylation and butylation of Ib therefore give O-alkyl derivatives IIIf, h. Hexyaltion proceeds even less selectively, and the N-hexyl product can therefore be isolated in ~30% yield along with the O-hexyl product.

The solvent has a great effect on the alkylation of 2-oxopyridines I. Thus 2-oxopyridine Ia undergoes methylation, ethylation, butylation, and benzylation in ethanol, but hexylation occurs only in dimethyl sulfoxide (DMSO) or acetonitrile. 2-Oxopyridine Ib undergoes only methylation in ethanol. The remaining alkyl halides react with 2-oxopyridine Ib only in DMSO or acetonitrile.

In addition to the alkyl halides, diazomethane was also used as an alkylating agent. In this case, according to [4], the rather acidic hydrogen of 2-oxopyridine adds to the diazoalkane to give the methyldiazonium salt

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1089-1092, August, 1976. Original article submitted September 30, 1975.