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ACETALS OF LACTAMS AND AMIDES OF ACIDS. COMMUNICATION 80.[1] INVESTIGATION OF ALKYLATION OF 2,4-DIAMINOPYRIDINE DERIVATIVES. UNCONVENTIONAL SYNTHESIS OF SUBSTITUTED IMIDAZO[1,2-a]PYRIDINE

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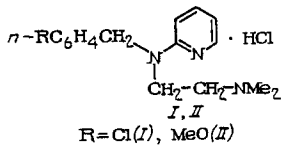
We know that among the pharmaceuticals used prophylactically and for the treatment of allergies, a significan role is played by antihistamines, whose structures typically include a diarylmethane moiety which contains a dialkylaminoalkoxy chain as a substituent at the central carbon atom or an aralkylhetarylamine moiety with an alkylaminoalkyl group at the exocyclic nitrogen atom [2]. Specifically, the highly efficacious suprastin (I) [2] and mepyramine (II) [3] aredrugs of this type whose synthesis is based on alkylation of 2-aminopyridine derivatives.



I, II

R=Cl(*I*), MeO(*II*)

Previously, we developed general methods for the synthesis of 2,4-aminopyridine derivatives containing a cyano group in the 3-position, based on using diethylacetals of dimethylformamide and dimethylacetamide, and primary and secondary enamino amides [4 – 6].

It is clear that the presence of additional functional substituents on the pyridine ring, especially one more electron-donor substituted amino group, can cause significant complications in the reaction of alkylation. Therefore, a special investigation of the alkylation of the compounds of this type was required to make it possible to synthesize systems similar to I and II, in order to study their biological activity. This paper is devoted to the alkylation of 2,4-aminopyridine derivatives, using the example of a number of substituted 2- and 4-dimethylamino-3-cyanopyridines with an additional secondary amino group in the 2- and 4-positions of the pyridine ring, respectively.

In the first step of the study, we showed that he chlorine atom in 2-chloro-3-cyano-4-anilinopyridine (IIIa) and 4-dimethylaminopyridine (IIIb) was rather mobile and can be substituted by a secondary amine, although under rather vigorous conditions (autoclave, 180°C). By reaction of IIIa, b with dimethylamine we obtained 2-dimethylamino-3-cyano-4-anilinopyridine (IVa) and 2,4-*bis*(dimethylamino)-3-cyanopyridine (IVb) in 90% and 80% yields, respectively. Therefore, we believed that it was possible to synthesize the desired systems without using an alkylation reaction, via the reaction of chloro derivatives IIIa, b with N-benzyl-N′,N′-dimethylethylenediamines (V) instead. However, it turned out that this reaction led to unexpected results. Thus, from the reaction mixture obtained by heating compounds IIIa and V, we isolated the diamino derivative IVa mentioned above [PMR for IVa ($CDCl_3$), δ, ppm: 3.25 (s, Me_2N), 6.26 (d, 5H, J_{5-6} = 6.0 Hz), 7.87 (d, 6-H), 6.70 (br. s, NH), 7.2 – 7.4 (Ph)] and a compound to which we assigned the structure of 1-benzyl-8-cyano-2,3,4,7-tetrahydroimidazo[1,2-a]pyridone-7 (VI) from the elemental analysis and spectral data. The mass-spectral data for thhe bicycle VI are given in Table 1. The IR spectrum of VI contains absorption bands at 1640 (CO) and 2200 (CN) cm^{-1}. There are signals from the following protons [(δ, ppm): 3.69 (m, 2-CH_2), 4.0 (m, 3-CH_2), 4.94 (s, CH_2Ph), 5.97 (d, 6-H, J_{5-6} = 7.7 Hz), 7.04 (d, 6-H), 7.30 – 7.40 (m, Ph)] in the PMR spectrum. After separation of the listed products, the mother liquor contained compounds IVa, VI, and a small amount of the desired product VIIa, judging from the spectral data. Compounds IIIb and V react similarly and result in the

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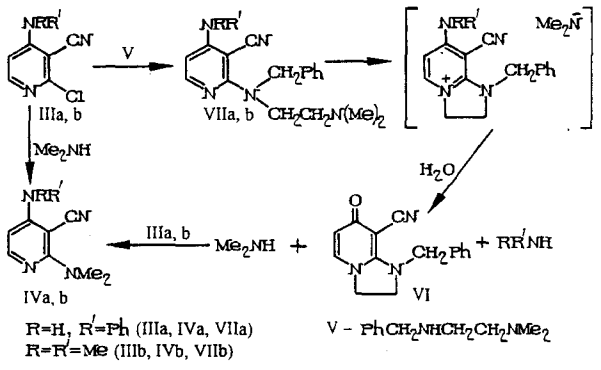
TABLE 1. Mass-spectra of the Compounds Synthesized

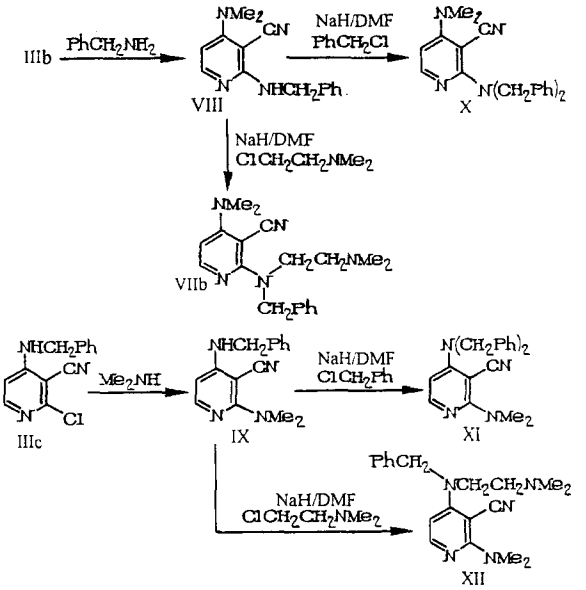
Compound	*m/z* Peak intensity (% of the maximum peak in the spectrum)
VI	252(12), 251(53) [M],$^+$ 250(2), 132(3), 105(3), 92(32), 91(100), 89(2), 82(2), 65(27), 62(3), 50(3)
IX	252(100)[M],$^+$ 237(50), 222(16), 208(20), 175(23), 148(65), 91(100), 77(14)
XIII	338(100)[M],$^+$ 323(7), 309(7), 291(8), 247(60), 218(20), 201(75), 158(48), 132(42), 105(41), 91(100), 65(80)
XIV	338(68)[M],$^+$ 265(70), 251(100), 247(23), 243(20), 173(24), 148(24), 105(19)
XVI	180(3)[M],$^+$ (1Cl)*, 153(7)*, 135(35)*, 108(77)*, 107(40)*, 77(100)*
XVII	189(61)[M],$^+$ 162(19), 144(40), 133(18), 117(31), 105(20), 87(100)

*The values of *m/z* for chlorine-containing ions are given with respect to the ^{35}Cl isotope.

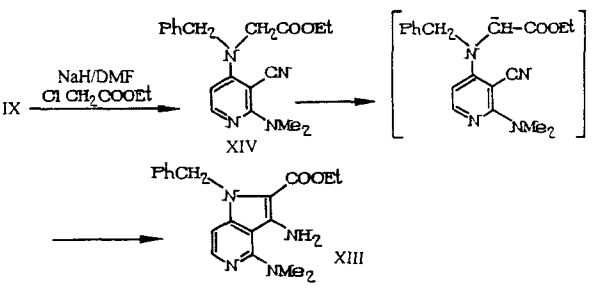
isolation of compound VI, the diamino derivative IVb, and 2-(N-benzyl-N-β-dimethylaminoethyl)amino-3-cyano-4-di methylaminopyridine (VIIb) (in low yield). When we studied this unusual cyclization in more detail, we ascertained that the ratio of the reaction products did not depend on temperature. Thus, when the reaction of IIIb with V was conducted at 190°C, we managed to isolate VI in about a 14% yield and to show the presence of compounds IVb and VIIb in the mother liquor by spectroscopic and chromatographic methods. If the temperature of the process decreases to 175°C, the yield of bicycle VI drops to 3%. According to the ^{1}H NMR spectrum, the mother liquor contains V, IVb, VIIb, and VI in ~ 35.5 : 7.5 : 6.5 : 0.1 ratio. From this mixture, we managed to isolate IVb and VIIb in 7 and 10% yields, respectively, using column chromatography. Therefore, the scheme for the formation of imidazopyridine VI can be presented as follows:



Since the reaction of the chloro derivatives IIIa, b with secondary amine V proceeds ambiguously, we next studied the alkylation of 2,4-diaminopyridine derivatives by various alkylating agents. For this purpose, we synthesized 2-benzylamino-3-cyano-4-dimethylaminopyridine (VIII) and 2-dimethylamino-3-cyano-4-dimethylaminopyridine (IX) [from IIIb and 2-chloro-3-cyano-4-benzylaminopyridine (IIIc, R = H, R′ = $PhCH_2$)] and subjected them to alkylation in DMF in the presence of sodium hydride. The reaction of benzylation was chosen as the model, which resulted in 2-N,N-dibenzylamino-3-cyano-4-dimethylaminopyridine (X) and 2-dimethylamino-3-cyano-4-N,N-dibenzylaminopyridine (XI) in 76 and 59% yields from VIII and IX, respectively. Under the same conditions, compounds VIIb and 2-dimethylamino-3-cyano-4-[N-benzyl-N-(β-dimethylaminoethyl)]aminopyridine (XII) were obtained in satisfactory yields.

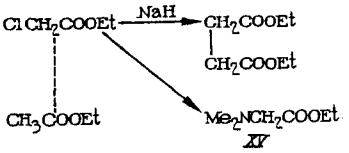


The synthesis of compounds which have additional functional substituents at the exocyclic nitrogen atom that can be transformed into various aminoalkyl chains was the subject of special interest. We considered these possibilitites for the example of derivative IX. We found that chloroacetonitrile cannot be used as an alkylating agent under these conditions, because of the considerable tarformation in the reaction mixture, from which only the starting IX could be isolated in 50% yield. Alkylation with β-chloropropionitrile also does not occur: the starting IX was isolated almost quantitatively, and GLC showed that dehydrochlorination of $ClCH_2CH_2CN$ occurerd quickly to form acrylonitrile. The reaction of IX with ethyl chloroacetate (in DMF in the presence of NaH) proceeds ambiguously in a complicated manner. In this case, we observed partial alkylation (45% of the starting IX was isolated from the reaction mixture) accompanied by Thorpe – Ziegler cyclization, forming 1-benzyl-2-ethoxycarbonyl-3-aminodimethylaminopyrrolo[3,2-c]pyridine (XIII), isolated as the hydrochloride in 20% yield.



The mass-spectrum of XIII contains the molecular ion peak M^+ 338; the type of fragmentation under electron impact is consistent with structure XIII (see Table 1). There are absorption bands at 3320 – 3280, 3400 (NH_2), 1670 (COOEt) cm^{-1} in the IR spectrum of XIII, and there is no absorption band for the CN group. In PMR we can observe the following signals from protons (δ), ppm: 1.25 (t, CH_3CH_2), 4.31 (q, CH_3CH_2), 3.42 (s, NMe_2), 5.59 (br. s, NH_2), 5.65 (s, CH_2Ph), 6.85 (d, 7H, J_{6-7} = 6.0 Hz), 7.91 (d, 6-CH), 6.98 (m), and 7.26 (m, Ph).

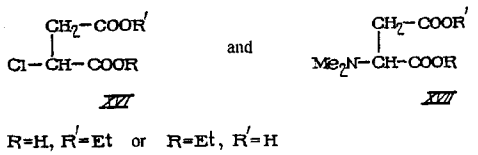
Closer examination of the reaction mixture by GLC and chromatographic/mass-spectrometric methods showed that the chloroacetate underwent a number of conversions under these conditions, which could be summarized as follows:



The comparison was conducted with already known samples, some of them were specially synthesized, e.g., the ethyl ester of N,N-dimethylglycine (XV).

Notice that when heating ethyl chloroacetate in DMF in the presence of sodium hydride (control experiment), we observed only its conversion to ethylacetate.

Additionally, dimer products (XVI and XVII) were found in the boiled down reaction mixture by chromatography/mass-spectrometry, to which the following structures can be assigned:



It should be noted that the processes considered above proceeded only if the interaction of IX and $ClCH_2COOEt$ occurs in a polar medium. Thus, in toluene, the starting IX (100%) was isolated, and traces of the mentioned products of alkylation (XVI) and cyclization (XVII) were found by chromatography/mass-spectrometry.

Study of the antihistaminic activity of the synthesized compounds (performed by Professor Kaminka and co-workers) showed that they exhibited no biological activity.

EXPERIMENTAL PART

The purity of the synthesized compounds was monitored by TLC on glass plates with an adherent silica gel layer (Merck Kieselgel $60F_{250}$). The elemental analysis data were consistent with the calculated values. Melting points for the compounds obtained are given in Table 2. The PMR spectra are recorded on a Varian (200 MHz) spectrometer (USA); solvent – $CDCl_3$; standard – HMDS (δ = 0.05) (see Table 2). Mass spectra were obtained on a Finnigan SSQ-770 chromatograph/mass-spectrometer with ionizing electrons energy 70 eV and direct injection of samples. The temperature of the ion source was 150°C. The reaction mixtures were introduced through the chromatograph: capillary column DV-5; T_{inj} = 250°C; T_{det} = 240°C; T_{col} = 80 – 250°C (10 deg/min); l_{col} = 30 m; d = 0.25 m; pressure of carrier gas (helium) was 0.07 atm (see Table 1). The GLC analysis was conducted on a Carlo Erba GC 6000 Vega series 2 with a flame ionization detector on a glass column (100 × 0.3 cm) packed with 5% Tridox on Chrom T. The temperature of the column was programmed from 100°C (5 min) to 200°C with a rate of 20°C per min. The temperature of the evaporator was 250°C; carrier gas flow rate (nitrogen) 30 cm^3/ml.

2-Dimethylamino-3-cyano-4-anilinopyridine (IVa). A mixture of IIIa (2.3 g, 0.01 mole) [4] and 23 ml of 20% dimethylamine solution in methanol was kept in an autoclave at 180°C for 18 h. The reaction mixture was evaporated *in vacuo*, the residue was crystallized from heptane to yield 2.1 g (90%) of IVa. Hydrochloride of IVa: to a solution of IVa (2.0 g) in 200 ml of ether, a methanol solution of HCl was added dropwise, the precipitate of hydrochloride IVa formed [2.0 g (87%)] was filtered off.

2,4-*Bis*(dimethylamino)-3-cyanopyridine (IVb). Compound IVb was obtained in a similar manner, by reaction of chloropyridine IIIb [4] with benzylamine; yield was 80%.

Reaction of 2-chloro-3-cyano-4-anilinopyridine (IIIa) with N-benzyl-N',N'-dimethylethylenediamine (V). A solution of IIIa (2.3 g, 0.01 mole) and N-benzyl-N,N'-dimethylethylenediamine (5.34 g, 0.03 mole) [7] in 2-propanol (30 ml) was kept in an autoclave at 190°C for 18 h. The reaction mixture was cooled, and 1-benzyl-8-cyano-2,3,4,7-tetrahydroimidazo[1,2-a]-7-pyridone (VI) (0.4 g) was filtered off. The mother liquor was evaporated under vacuum, the residue was dissolved in benzene (15 ml), 30 ml of 5% NaOH was added, and an additional 0.3 g portion of VI was filtered off. The total yield of VI was 27.7%. IR spectrum (ν_{max}, cm^{-1}): 1640 (CO), 2200 (CN). The benzene layer was evaporated until dry, the residue was extracted with boiling heptane; after cooling, IVa (0.3 g, 8%) was filtered off.

Reaction of 2-chloro-3-cyano-4-dimethylaminopyridine (IIIb) with N-benzyl-N',N'-dimethylethylenediamine (V). (a) A solution of IIIb (1.8 g, 0.01 mole) and V (5.34 g, 0.03 mole) in isopropanol (25 ml) was kept in an autoclave at 190°C for 18 h. The reaction mixture was evaporated *in vacuo*, the residue was dissolved in benzene (15 ml), 30 ml of 5% NaOH was added, and VI (0.34 g, 13.5%) was filtered off. (b) A similar reaction was carried out at 175°C for 18 h; from 2.73 g of IIIb, a mixture was obtained consisting of amine V (71%), IVb (15%), VIIb (13%), and VI (~ 0.2%) (in mole %), these data correspond with the following yields: IVb – 17%, VIIb – 16%, and VI about 2.5%. The mixture obtained was dissolved in isopropanol, water was added, and the precipitate

TABLE 2. Characteristics of the Compounds Synthesized

Compound	M. p., °C (solvent for crystallization)	Empirical formula	PMR spectrum
IVa	108 – a10 (heptane)	$C_{14}H_{14}N_4$	3.25 (s, NMe_2), 6.26 (d, 5-CH), 7.87 (6-CH, $J_{5,6}$ = 6.0 Hz), 6.70 (br. s, NH), 7.2 – 7.4 (m, Ph)
IVa · HCl	224 – 226 (95 % ethanol)	$C_{14}H_{15}N_4Cl$	
IVb	56 – 57 (50 % ethanol)	$C_{10}H_{14}N_4$	3.14, 3.16 (s, 2-NMe_2, 4-NMe_2), 6.03 (d, 5-CH), 7.87 (d, 6H, $J_{5,6}$ = 6.1 Hz)
VI	198 – 200 (2-propanol)	$C_{15}H_{13}N_3O$	3.69 (m, 2-CH_2), 4.10 (m, 3-CH_2), 4.94 (s, CH_2Ph), 5.97 (d, 6-CH), 7.04 (d, 5-CH, $J_{5,6}$ = 7.7 Hz), 7.30 – 7.40 (m, Ph)
VIIb	86 – 87 (CH_3CN)	$C_{19}H_{25}N_5$	2.20 (s, CH_2NMe_2), 2.57 (m, CH_2NMe_2), 3.09 (s, 4-NMe_2), 3.66 (m, 2-N-CH_2CH_2), 4.86 (s, 2-N-CH_2Ph), 7.25 – 7.30 (m, Ph), 6.07 (d, 5-CH), 7.89 (d, 6-CH, $J_{5,6}$ = 7.7 Hz)
VIIb · HCl	208 – 210 (2-propanol)	$C_{19}H_{26}ClN_5$	–
VIII	120 – 123 (CH_3CN)	$C_{15}H_{16}N_4$	–
IX	90 – 91 (aqueous CH_3CN)	$C_{15}H_{16}N_4$	–
X	68 – 70 (2-propanol)	$C_{22}H_{22}N_4$	–
X · HCl	221 – 223 (ethanol)	$C_{22}H_{23}ClN_4$	–
XI	122 – 124 (CH_3CN0)	$C_{22}H_{22}N_4$	3.13 (s, NMe_2), 4.63 [s, $(CH_2Ph_2]$], 7.15 – 7.30 [m, $(CH_2Ph)_2$], 6.14 (d, 5-CH), 7.87 (d, 6-CH, $J_{5,6}$ = 6.0 Hz)
XI · HCl	221 – 223 (2-propanol)	$C_{22}H_{23}ClN_4$	–
XII*	158 – 160 (aqueous 2-propanol)	$C_{21}H_{27}N_5O_4$	2.21 (s, CH_2NMe_2), 2.61 (m, 4-NCH_2CH_3), 3.13 (s, 2-NMe_2), 3.61 (m, 4-NCH_2-CH_3), 4.74 (s, CH_2Ph), 6.10 (d, 5-CH), 7.15 – 7.35 (m, Ph), 7.84 (d, 6-CH, $J_{5,6}$ = 6.0 Hz)
XIII · HCl	206 – 208 (ethanol)	$C_{19}H_{23}ClN_4O_2$	1.25 (t, CH_3CH_2), 4.31 (q, CH_3CH_2), 3.42 (s, NMe_2), 5.59 (br. s, NH_2), 5.65 (s, CH_2Ph), 6.98 (m, Ph) and 7.26 (m, Ph), 6.85 (d, 7-CH), 7.91 (d, 6-CH, $J_{5,6}$ = 6.0 Hz)

* PMR data are given for the base.

formed was separated and dissolved in ethylacetate, the solution was introduced into a column (18 × 450 mm) packed with silica gel suspension 40 – 100 μm (LASMA, Belgorod) in ethylacetate and eluted with ethylacetate. A fraction with R_f = 0.3 containing 0.2 g (7%) of IVb and a fraction with R_f = 0.1 containing 0.5 g (10%) of VIIb were separated.

2-Benzylamino-3-cyano-4-dimethylaminopyridine (VIII). A mixture of IIIb (5.0 g, 0.027 mole) and 15 ml of benzylamine was heated at 160°C for 2 h. The reaction mixture was poured into 200 ml of water. The precipitate formed was filtered off, washed with methanol, and crystallized from acetonitrile to yield 5.11 g (75%) of VIII.

2-Dimethylamino-3-cyano-4-benzylaminopyridine (IX). A mixture of IIIc (5.0 g, 0.2 mole) and 50 ml of 22% dimethylamine solution in methanol was kept in an autoclave at 170 – 180°C for 6 h. The reaction mass was evaporated *in vacuo*, the residue was ground with 50 ml of water. The precipitate was filtered off and recrystallized from 50% aqueous acetonitrile to yield 4.2 g (83%) of IX.

2-Dibenzylamino-3-cyano-4-dimethylaminopyridine (X). To a solution of VIII (4.36 g, 0.017 mole) in 40 ml of DMF, sodium hydride (0.61 g, 0.025 mole) was added and held at 75 – 80°C for 30 min. The reaction mixture was stirred without heating for 1 h, then benzyl chloride (3.44 g, 0.027 mole) was added dropwise and stirred for 3 h at 40°C. The precipitate was filtered off, the mother liquor was evaporated *in vacuo* and the residue was ground with water. The residue was filtered off, dried, and crystallized from petroleum ether to yield 4.51 g (71%) of X. Hydrochloride of X: to a solution of X (3.1 g) in ether (70 ml) a methanol solution of HCl was added. The precipitate was filtered to yield 3.42 g (99%) of the hydrochloride of X.

2-Dimethylamino-3-cyano-4-dibenzylaminopyridine (XI). Compound XI and its hydrochloride were obtained in a manner similar to that used for the X and IX preparation; yield 58%.

2-[N-benzyl-N-(b-dimethylaminoethyl)amino]-3-cyano-4-dimethylaminopyridine (VIIb). Compound VIIb and its hydrochloride were obtained from IX and β-chloroethyldimethylamine similarly to the method used for X; yield 69%.

2-Dimethylamino-3-cyano-4-[N-benzyl-N(b-dimethylaminoethyl)amino]pyridine oxalate (XII). Compound XII was obtained from IX in a manner analogous to that for VIIb as an oil, which was dissolved in 50 ml of acetone and a solution of oxalic acid was added to pH 6. The precipitate was filtered off, washed with acetone, and recrystallized from 95% methanol; the yield of oxalate XII was 50%.

1-Benzyl-2-ethoxycarbonyl-3-amino-4-dimethylamino-1H-pyrrolo[3.2-c]pyridine (XIII). Sodium hydride (0.61 g, 0.025 mole) was added to a solution of 4.35 g (0.017 mole) IX in DMF (40 ml) and held at 75 – 80°C for 30 min. The reaction mixture was stirred without heating for 1 h, then ethyl chloroacetate (3.31 g, 0.027 mole) was added and stirred for 3 h at 40°C. The reaction mixture was filtered and boiled down *in vacuo*. The residue was dissolved in chloroform, introduced into a column (20 × 500 mm) packed with silica gel (40 – 100 μm, LASMA, Belgorod), and eluted with ethylacetate. Fractions with R_f = 0.8 containing 0.56 g of the starting IX and R_f = 0.5 containing 3.24 g of the base of bicycle XIII were separated; the latter was ground with 10% HCl; the precipitate formed was washed with water, and dried to yield

hydrochloride XIII (1.2 g, 19%). IR spectrum (ν_{max}, cm^{-1}): 3410, 3320 – 3280 (NH_2), 1670 (CO) [there is no band at 2000 (CN)]. The mother HCl solution was made alkaline and an additional portion of the starting IX (1.42 g) was isolated, the total yield of IX was 45%.

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