REACTIONS OF 6-METHYL- AND 4,6-DIMETHYL-2-ARYLAMINONICOTINONITRILES WITH ACIDS

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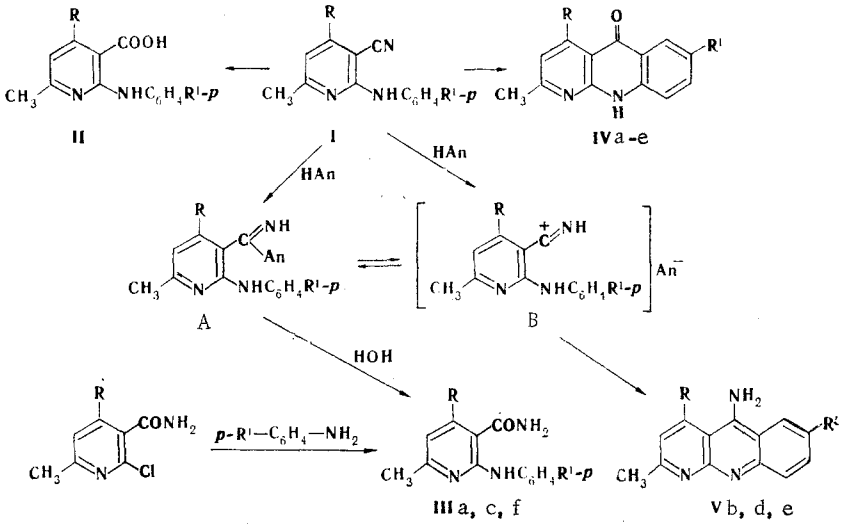
UDC 547.826.836.3

A substituted nicotininc acid is formed when 6-methyl-2-anilinonicotinonitrile is refluxed with concentrated hydrochloric acid, whereas 4,6-dimethyl-2-anilinonicotinonitrile is not hydrolyzed under these and more severe conditions because of steric hindrance. Both of these nitriles undergo cyclization to 10-aminobenzo[b]-1,8-naphthyridine derivatives under the influence of concentrated sulfuric acid. When 6-methyl-2-arylaminonicotinonitriles are heated in polyphosphoric acid (PPA), they are converted to 2-arylaminonicotinic acid amides and, in part, to benzo[b]-1,8-naphthyrid-10-one derivatives, while 4,6-dimethyl-2-arylaminonicotinonitriles are converted primarily to 10-aminobenzo[b]-1,8-naphthyridines.

It is known that 2-arylaminonicotinonitriles undergo cyclization to 10-aminobenzo[b]-1,8-naphthyridines under the influence of aluminum chloride [1]. The reactions of these compounds with protic acids have not been studied. At the same time, one might have expected that, under certain conditions under the influence of mineral acids, they would be converted to the corresponding acids and their amides or would undergo cyclization to benzo[b]-1,8-naphthyridine derivatives. All of these compounds are of interest as biologically active substances [2, 3].

To ascertain the possibilities of the synthesis of 2-arylaminonicotinic acids and their amides or naphthyridine derivatives on the basis of 6-methyl- and 4,6-dimethyl-2-arylaminonicotinonitriles and to compare the reactivities of these compounds we studied their reactions with concentrated hydrochloric, sulfuric, and polyphosphoric (PPA) acids.



Ia—Va R=R¹=H; Ib, IVb, Vb R=H, R¹=CH₃; Ic, IIIc, IVc R=H, R¹=CH₃O; Id, IVd, Vd R=CH₃, R¹=H; Ie, IVe, Ve R=R¹=CH₃; If, IIIf R=CH₃, R¹=Br

Acid IIa is formed in 65% yield when 6-methyl-2-anilinonicotinonitrile (Ia) is refluxed with concentrated HCl for 12 h. At the same time, nitrile Id is not hydrolyzed under the same conditions after refluxing for 12 and 24 h and is isolated unchanged. The inertness of nitrile Id as compared with Ia is evidently associated with steric hindrance on the part of the second ortho substituent. A similar phenomenon was previously noted [4] in the benzo-

Perm Pharmaceutical Institute, Perm 614600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 674-678, May, 1982. Original article submitted June 26, 1981.

0009-3122/82/1805-0511$07.50

nitrile series. 4,6-Dimethyl-2-anilinonicotinamide also does not undergo hydrolysis when it is refluxed in concentrated HCl for 12-24 h, probably also because of steric factors.

When nitriles Ia, d are heated in concentrated H_2SO_4 at 50°C for 15-16 h, they undergo cyclization to give 10-aminobenzo[b]-1,8-naphthyridine derivatives (Va, d). In this case the reaction in a highly acidic medium probably proceeds through a step involving protonation of the nitrile group and the formation of an iminocarbenium ion of the B type [5] and is ensured by both the significant reactivity of this ion and the closeness of the nucleophilic reaction center. Sulfonation is observed in addition to cyclization in the reaction of nitriles Ib, c with concentrated H_2SO_4, and a product cannot be isolated.

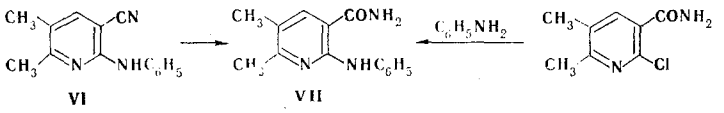
It is known that the reaction of nitriles with PPA gives imidoyl derivatives of this acid [6]; these derivatives undergo hydrolysis to amides upon dilution with water. It might have been assumed that nicotinonitriles Ia-f would also react with PPA and undergo conversion to imidoyl derivative A or iminocarbenium ion B, between which an equilibrium is possible. The direction of this equilibrium should be determined by the electronic and steric effects of the substituents in the pyridine ring.

The formation of a covalent bond between the carbon atom of the protonated nitrile group and the bulky anion will be hindered in the case of Id-f, which contain a methyl group adjacent to the reaction center, as a consequence of steric hindrance, and this should promote a shift of the equilibrium to favor the formation of ion B. A second ortho substituent is absent in nitriles Ia-c, the nitrile group is sterically more accessible, and the formation of intermediate A is more likely. Two variants of the transformations of intermediates A and B are possible. In the case of ion B, when the aryl group attached to the amino group is sufficiently nucleophilic, the reactive carbenium ion will attack the ortho position of the aryl group, which leads to cyclization. The imidoyl derivative is less reactive and, of course, will undergo cyclization with less ease or will not undergo cyclization at all.

In fact, experiments showed that heating nitriles Ia, c, which are inclined to undergo conversion to intermediates A, in PPA at 150°C for 5 h is accompanied by the production of primarily amides IIIa, c (40-43%) along with naphthyridones IVa, c (23-29%). Under the same conditions Ib undergoes cyclization to naphthyridine Va in connection with the sufficient nucleophilicity of the reaction center due to the electron-donor effect of the methyl group (compare the Hammett σ_m constants for the CH_3 and CH_3O groups). Nitrile If, in which the nucleophilicity of the aryl group is low, gives only amide IIIf, despite the formation of an intermediate ion of the B type from it, and cyclization does not occur. The structure of amides IIIa, c, f was proved by alternative synthesis by the reaction of 2-chloro-6-methyl- and 2-chloro-4,6-dimethylnicotinamides with arylamines, as well as by comparison with samples of some of them previously obtained in [3].

When 4,6-dimethyl-2-arylaminonicotinonitriles Id, e are heated in PPA (at 150°C for 5 h), they undergo cyclization chiefly to 10-aminobenzo[b]-1,8-naphthyridines (Vd, e) and partially to benzo[b]-1,8-naphthyrid-10-ones (IVd, e).

In order to confirm the idea that the determining factors in the formation of B ions by the action of PPA on nitriles Id, e are steric factors rather than the inductive effect of the methyl group attached to the C_4 atoms we synthesized 5,6-dimethyl-2-anilinonicotinonitrile (VI).



The experiments showed that in PPA (150°C, 5 h) nitrile VI undergoes hydration to amide VII, the structure of which was proved by alternative synthesis on the basis of 5,6-dimethyl-2-chloronicotinamide and aniline. In other words, nitrile VI behaves like Ia, c but not like Id, e. It should be noted that nitrile VI, like Ia, is hydrolyzed by hydrochloric acid to 2-anilino-5,6-dimethylnicotinic acid (VIII).

Whereas the yield of benzonaphthyridone IVd reaches 90% when 4,6-dimethyl-2-anilinonicotinonitrile Id is heated in PPA at 150°C for 10 h, the yield of naphthyridine Vd is less than 10%. This indicates that the formation of naphthyridones from nitriles I is a secondary process. To confirm this conclusion and to prove the structure of the compounds

TABLE 1. Characteristics of the Synthesized Compounds

Compound	R	R¹	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %[a]
				C	H	N		C	H	N	
Ib	H	CH_3	102—103	75,5	5,5	18,5	$C_{14}H_{13}N_3$	75,3	5,9	18,8	86
Ic	H	CH_3O	105—106	70,5	5,5	18,0	$C_{14}H_{13}N_3O$	70,3	5,5	17,6	65
IIa	H	H	156—158	68,8	5,5	12,8	$C_{13}H_{12}N_2O_2$	68,4	5,5	12,3	65
IIIa	H	H	178—179	68,8	5,5	18,8	$C_{13}H_{13}N_3O$	68,8	5,8	18,5	43
IIIc	H	CH_3O	132—133 [3]								40
IIIf	CH_3	Br	237—239			13,2	$C_{14}H_{14}BrN_3O$[b]			13,1	57
IVa	H	H	278—279	73,8	4,9	13,9	$C_{13}H_{10}N_2O$	74,3	4,8	13,3	23
IVb	H	CH_3	316—318	75,1	5,3	12,3	$C_{14}H_{12}N_2O$	75,0	5,3	12,5	22
IVc	H	CH_3O	316—319	70,3	5,0	11,3	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,6	29
IVd	CH_3	H	297—298	75,0	5,3	12,9	$C_{14}H_{12}N_2O$	75,0	5,4	12,5	4
IVe	CH_3	CH_3	319—320	75,9	5,5	11,8	$C_{15}H_{14}N_2O$	75,6	5,9	11,7	5
Va	H	H	266—268	74,5	5,5	19,4	$C_{13}H_{11}N_3$	74,6	5,3	20,0	48
Vb	H	CH_3	278—280	75,8	6,1	—	$C_{14}H_{13}N_3$	75,3	5,9	—	35
Vd	CH_3	H	225—227	75,9	5,7	19,3	$C_{14}H_{13}N_3$	75,3	5,9	18,8	47
Ve	CH_3	CH_3	250—253	—	—	17,7	$C_{15}H_{15}N_3$	—	—	17,7	42

[a]The yields of the compounds are indicated: IIa was obtained in experiments with concentrated HCl; IIIa, c, f, IVa-e, and Vb, d, e were obtained in experiments with PPA; and Va was obtained in experiments with concentrated H_2SO_4.
Found: Br 24.7%. Calculated: Br 25.0%.

we realized the hydrolysis of naphthyridines Vd, e to naphthyridones IVd, e, by refluxing in dilute hydrochloric acid.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer.

6-Methyl-2-(p-toluidino)nicotinonitrile (Ib). A mixture of 2.2 g (0.01 mole) of 6-methyl-2-chloronicotinonitrile [7] and 1.1 g (0.01 mole) of p-toluidine was heated at 150-180°C for 30 min, after which it was treated with hot water, and the residue was crystallized from ethanol.

6-Methyl-2-(p-anisidino)nicotinonitrile (Ic) was similarly obtained. The synthesis of 4,6-dimethyl-2-arylaminonicotinonitriles Id-e was described in [3].

Hydrolysis of 6-Methyl-2-anilinonicotinonitrile. A 2.1-g (0.01 mole) sample of 6-methyl-2-anilinonicotinonitrile (Ia) [8] was refluxed with 10 ml of concentrated HCl for 12 h, after which the mixture was cooled and treated with a solution of sodium carbonate to pH 5. The resulting precipitate was removed by filtration and crystallized from benzene to give acid IIa.

Transformation of 2-Arylaminonicotinonitriles under the Influence of PPA. A 0.01-mole sample of nitrile Ia-f was added to 10 g of PPA, and the mixture was heated at 150°C for 5 h. It was then cooled, diluted with water, and made alkaline with 10% ammonium hydroxide. The precipitate was removed by filtration and treated with dilute acetic acid. The resulting solution was separated from the insoluble residue and made alkaline with a 10% solution of sodium hydroxide. The precipitated amide IIIa, c, f or the corresponding 10-aminobenzo-[b]-1,8-naphthyridine Vb, d, e was removed by filtration and crystallized. The IR spectra (in chloroform) of Vb, d, e contain bands at 3540 and 3425 cm^{-1} (NH_2).

The acetic acid-insoluble residue was crystallized from butanol to give the benzo[b]-1,8-naphthyrid-10-one (IVa-e). The IR spectra (mineral oil suspension) of benzonaphthyridones IVa-e contain bands at 3220-3260 (N–H) and 1610 cm^{-1} (C=O).

Cyclization of 6-Methyl-2-anilinonicotinic Acid. A 2.3-g (0.01 mole) sample of 6-methyl-2-anilinonicotinic acid (IIa) was heated in 10 g of PPA at 160°C for 5 h, after which the mixture was cooled, diluted with water, and made alkaline with 10% sodium hydroxide solution. The precipitate was separated and crystallized to give 1.1 g (50%) of a product with mp 278-279°C (butanol). No melting-point depression was observed for a mixture of this product with IVa obtained in one of the preceding experiments.

Transformation of 2-Arylaminonicotinonitriles under the Influence of Concentrated H_2SO_4. A 2.2-g (0.01 mole) sample of 6-methyl-2-anilinonicotinonitrile was heated with 6 ml of concentrated H_2SO_4 at 50°C for 16 h, after which the mixture was cooled, diluted with water, and made alkaline to pH 10. The precipitate was removed by filtration and crystallized from butanol to give Va.

Compound Vd was obtained under similar conditions from nitrile Id. No melting-point depression was observed for a mixture of this product with Vd obtained by the reaction of nitrile Id with PPA.

6-Methyl-2-anilinonicotinamide (IIIa). A solution of 1.7 g (0.01 mole) of 6-methyl-2-chloronicotinamide [1] and 0.9 g (0.01 mole) of aniline in 15 ml of 50% acetic acid was refluxed for 6 h, after which it was cooled and neutralized with 10% sodium hydroxide solution. The precipitate was removed by filtration and crystallized from ethanol to give 1.3 g (58%) of a product with mp 178-179°C. No melting-point depression was observed for a mixture of this product with IIIa obtained by hydration of nitrile Ia in PPA.

Similar conditions were used to obtain 4,6-dimethyl-2-anilinonicotinamide [46%, mp 135-137°C (ethanol). Found: N 17.2%. $C_{14}H_{15}N_3O$. Calculated: N 17.4%] from 4,6-dimethyl-2-chloronicotinamide and aniline, as well as 4,6-dimethyl-2-(p-bromoanilino)nicotinamide (IIIf) [57%, mp 237-239°C (ethanol)]. No melting-point depression was observed for a mixture of a sample of the latter with IIIf obtained in the reaction of nitrile If with PPA.

5,6-Dimethyl-2-chloronicotinamide. A 1.7-g (0.01 mole) sample of 5,6-dimethyl-2-chloronicotinonitrile [9] was heated in 10 ml of concentrated H_2SO_4 at 100-110°C for 2 h, after which the mixture was diluted with water and neutralized with 10% ammonium hydroxide. The precipitate was crystallized from water to give 1.3 g (68%) of a substance with mp 190-192°C. Found: Cl 19.0; N 15.1%. $C_8H_9ClN_2O$. Calculated: Cl 19.2; N 15.1%.

5,6-Dimethyl-2-anilinonicotinonitrile (VI). A mixture of 1.7 g (0.01 mole) of 5,6-dimethyl-2-chloronicotinonitrile and 0.9 g (0.01 mole) of aniline was heated at 150-180°C for 2.5 h, after which it was treated with hot water, and the residue was crystallized to give 1.3 g (58%) of a product with mp 104-106°C (ethanol). Found: N 18.5%. $C_{14}H_{13}N_3$. Calculated: N 18.8%.

5,6-Dimethyl-2-anilinonicotinamide (VII). A) A 2.2-g (0.01 mole) sample of 5,6-dimethyl-2-anilinonicotinonitrile was heated with 10 g of PPA at 150°C for 5 h, after which the mixture was diluted with water and neutralized with 10% ammonium hydroxide. The precipitate was removed by filtration and crystallized to give 0.5 g (23%) of a product with mp 184-185°C (ethanol). Found: N 17.8%. $C_{14}H_{15}N_3O$. Calculated: N 17.4%.

B) The reaction of 1.9 g (0.01 mole) of 5,6-dimethyl-2-chloronicotinamide and 0.9 g (0.01 mole) of aniline under the conditions of the synthesis of amides IIIa, c, f gave 1.5 g (65%) of a substance with mp 184-186°C (ethanol), which was identical to amide VII obtained in the preceding experiment with respect to its melting point and the results of a mixed-melting-point determination.

5,6-Dimethyl-2-anilinonicotinic Acid (VIII). A 2.2-g (0.01 mole) sample of 5,6-dimethyl-2-anilinonicotinonitrile was refluxed in 20 ml of concentrated HCl for 20 h, after which the mixture was cooled and treated with a solution of sodium carbonate to pH 5. The precipitate was removed by filtration and crystallized to give 1.9 g (78%) of a product with mp 218-219°C (benzene). Found: N 12.0%. $C_{14}H_{14}N_2O_2$. Calculated: N 11.6%.

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1,3-DIPOLAR CYCLOADDITION OF DIAZOMETHANE TO β-ARYLACRYLYLOXIRANES

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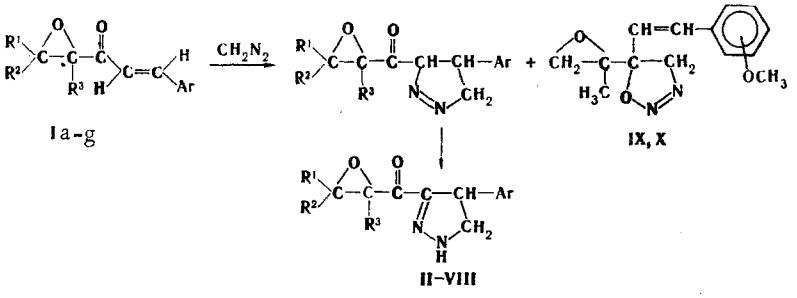
UDC 547.775'778.2

Diastereomeric 4-aryl-3-epoxypropionyl-2-pyrazolines were obtained by cycloaddition of diazomethane to β-arylacrylyloxiranes. It was established that, in addition to the formation of pyrazolines, competitive addition of diazomethane to the carbonyl group to give oxadiazolines occurs when electron-donor substituents are present in the aromatic ring in the 2 or 4 position. Some chemical properties of 4-aryl-3-epoxypropionyl-2-pyrazolines were studied.

In a continuation of our research on the reactivities of β-arylacrylyloxiranes in cycloaddition reactions [1] and in order to synthesize new α,β-epoxy ketones of the heterocyclic series, in the present research we studied the 1,3-dipolar cycloaddition of diazomethane to β-arylacrylyloxiranes.

We established that the reaction of β-arylacrylyloxiranes Ia-g with diazomethane leads to mixtures of two diastereomeric (A and B) 4-aryl-3-epoxypropionyl-2-pyrazolines II-VIII, which differ with respect to the configuration of the chiral center of the epoxy ring and are products of isomerization of the initially formed 1-pyrazolines. The indicated course of the reaction is confirmed by the isolation by chromatography on silica gel of the intermediate 4-phenyl-3-(2-methyl-2,3-epoxypropionyl)-1-pyrazoline when Ia is subjected to reaction with diazomethane at 0°C.



Ia-g IX, X II-VIII

Ia, II A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=Ph; Ib, III A, B $R^1=R^3=CH_3$, $R^2=H$, Ar=Ph; Ic, IV A, B $R^1=R^2=CH_3$, $R^3=H$, Ar=Ph; Id, V A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=4-BrC_6H_4; Ie, VII A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=4-FC_6H_4; If VII A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=4-$CH_3OC_6H_4$; Ig, VIII A, B $R^1=R^2=H$, $R^3=CH_3$, Ar=2-$CH_3OC_6H_4$

Bands of stretching vibrations of C=O and C=N bonds at 1660 and 1650 cm^{-1} and absorption of the NH group of a pyrazoline ring at 3420 cm^{-1}, which is characteristic for the investigated structures [2, 3], are present in the IR spectra of II-VIII. The IR spectrum of the intermediate 4-phenyl-3-(2-methyl-2,3-epoxypropionyl)-1-pyrazoline differs substantially from the IR spectrum of 2-pyrazoline II in that the characteristic absorption of the NH group of the pyrazoline ring is absent, while stretching vibrations of the C=O bond are ob-

Scientific-Research Institute of Physicochemical Problems, V. I. Lenin Belorussian State University, Minsk 220080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 679-683, May, 1982. Original article submitted July 28, 1981.

0009-3122/82/1805-0515$07.50