tions of the compounds in ethanol were recorded with a Specord spectrophotometer. The course of the reaction was monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 in benzene. The molecular weight was determined by mass spectrometry with an MKh-1303 mass spectrometer.

Reaction of 1,2,4,6-Tetramethyl-3-nitropyridinium Iodide with Amines (General Method). A solution of 0.1 mole of the amine in 4 ml of water was added with stirring to 1.5 mmole of the pyridinium salt dissolved in the minimum amount of water, after which the mixture was allowed to stand at 20°C for 2-3 days. It was then extracted with benzene, and the extract was dried with $MgSO_4$ and evaporated. The residue was separated with a column filled with L-40/100 silica gel (elution with benzene). The amount of N-methyl-3,5-dimethyl-2-nitroaniline (IIa) in the reaction with n-butyl-, isobutyl-, and sec-butylamines was determined by comparison with the intensities of the signals of the protons of the 3- and 5-CH_3 groups in the PMR spectrum of a mixture of IIa with para isomers IIIc, IIIe, and IIIg. The constants of N-methyl-3,5-dimethyl-2-nitroaniline (IIa) and N-methyl-3,5-dimethyl-4-nitroaniline (IIIa) were in agreement with the literature values [2]. The properties of the nitroanilines obtained are presented in Table 2.

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RECYCLIZATION OF 3-ALKYL- AND 1,3-DIALKYLISOQUINOLINIUM SALTS TO NAPHTHYLAMINES

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3-Methyl- and 3-benzylisoquinolinium salts undergo rearrangement to 2-alkylaminonaphthalenes under the influence of alcohol solutions of alkylamines. The rearrangement of 1,3-dimethyl- and 1-methyl-3-benzylisoquinolinium salts leads to both 1- and 2-alkylaminonaphthalenes with predominance of the former.

We have previously shown [1] that isoquinolinium salts that contain an alkyl or arylalkyl substituent in the 1 position undergo rearrangement to give substituted α-naphthylamines under the influence of alkylamines. The reaction evidently proceeds via nucleophilic addition of the OH^- ion in the 3 position with subsequent cleavage of the $N-C_3$ bond and the formation of a new ring with the establishment of a $C-C_3$ bond. Since it is known that nucleophilic attack on the isoquinoline ring takes place primarily at the C_1 atom [2, 3], when an alkyl or arylalkyl substituent is present in the 3 position, one might expect a similar rearrangement with cleavage of the C_1-N bond, which would lead to the formation of β-naphthylamines.

In fact, when 2,3-dimethylisoquinolinium iodide (Ia) is heated with an alcohol solution of methylamine in a sealed ampul at 150°C for 30 h, the expected recyclization takes place,

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*Deceased.

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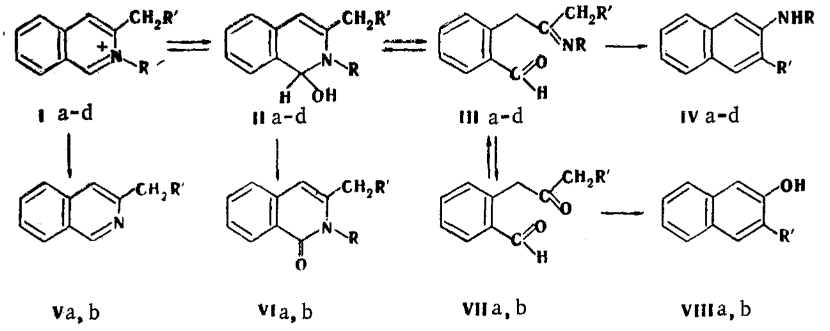
and 2-methylaminonaphthalene (IVa) is formed in 28% yield. Consequently, under the influence of a nucleophile the pyridine ring opens up at the C_1–N bond and then closes again at the 3-CH_3 group. In addition, as a result of the reaction the isoquinolinium salt is dealkylated [3-methylisoquinoline (Va) was isolated in 30% yield] due to attack by the nucleophile at the carbon atom of the methyl group bonded to the nitrogen atom of the isoquinoline ring. Lowering the temperature and reducing the reaction time lead to a decrease in the yield of the recyclization product.

The role of competitive reactions becomes more important when an aqueous solution of methylamine is used as the reagent, and the yield of 2-methylaminonaphthalene (IVa) is reduced to 15%. In this case, in addition to 2-methylaminonaphthalene and 3-methylisoquinoline, 2,3-dimethyl-1-isoquinolone (VIa), which is formed due to attack by the hydroxide ion in the 1 position of the isoquinoline ring and subsequent oxidation of the resulting pseudobase (IIa), was isolated in 30% yield.

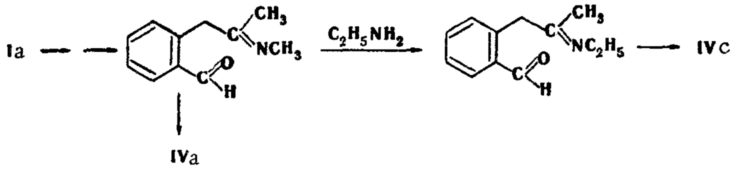


I–VIII a $R=CH_3$, $R'=H$; b $R=CH_3$, $R'=C_6H_5$; c $R=C_2H_5$, $R'=H$; d $R=C_2H_5$, $R'=C_6H_5$

Recyclization products were not detected when salt Ia was refluxed with aqueous alkali. Only 2,3-dimethyl-1-isoquinolone (VIa) was isolated in 46% yield. β-Naphthol was isolated in 2% yield in addition to VIa (36%) when the aqueous alkali solution was replaced by an alcohol solution of alkali. Consequently, under these conditions the rearrangement takes place to only a small extent and proceeds with hydrolysis of the open intermediate (IIIa), i.e., with replacement of the heteroatom.

It should be noted that the formation of open intermediate IIIa through pseudobase IIa is not the only possible pathway. It must be assumed that the process takes place through the anhydro base, which arises through splitting outof a proton from the methyl group of isoquinolinium cation Ia.

Two rearrangement products, viz., 2-methylaminonaphthalene (IVa) (2%), which is the product of direct recyclization, and 2-ethylaminonaphthalene (IVc) (48%), which is the product of recyclization with exchange of the methylamine fragment by an ethylamine fragment, were detected in the reaction of salt Ia with an alcohol solution of ethylamine by means of gas–liquid chromatography (GLC).



3-Methyl-2-ethylisoquinolinium iodide (Ic) reacts with an alcohol solution of ethylamine to give 2-ethylaminonaphthalene (IVc) in 54% yield, whereas a mixture of amines IVa and IVc (in 24 and 2% yields, respectively) is formed with an alcohol solution of methylamine, i.e., the rearrangement also takes place primarily with exchange of the alkylamino group. The yield of the dealkylation product in this reaction reaches 42%. It must be noted that the contribution of dealkylation is associated with the size of the alkylamine grouping. On passing from methylamine to ethylamine, the yield of the product of dealkylation of 2-methyl-3-ethylisoquinolinium iodide (Ic) decreases from 42% to 25%.

It is known that the CH acidity of the methylene group in the benzyl group is considerably higher than that of the methyl group. One therefore might have expected that replacement of the CH_3 group in the 3 position of the isoquinoline ring by a benzyl group

TABLE 1. Products of the Reactions of Isoquinolinium Salts with Basic Reagents

Expt. No.	Starting salt	Reagent	Reaction product	mp,[a] °C	Found, %		Empirical formula	Calc., %		Yield, %
					C	H		C	H	
1	Ia	CH_3NH_2	IVa	52[b,c]						28
2	Ic	$C_2H_5NH_2$	IVc	48—49[b,d]						54
3	Ib	CH_3NH_2	IVb	91—92	83,1	6,1	$C_{19}H_{17}NO$[e]	83,0	6,2	50
4	Id	$C_2H_5NH_2$	IVd	108—109[b]	83,2	7,0	$C_{20}H_{19}NO$[f]	83,1	6,6	60
5	IXa	CH_3NH_2	Xa	40—42	84,1	7,8	$C_{12}H_{13}N$	84,3	7,7	68
			XIa	104—105[b]	78,6	7,2	$C_{14}H_{15}NO$	78,9	7,1	7
6	IXb	CH_3NH_2	Xb	46—47			$C_{18}H_{17}N$[g]			66
			XIb	112—113			$C_{18}H_{17}N$[g]			22
7	IXc	$C_2H_5NH_2$	Xc	72—73			$C_{19}H_{19}N$[g]			67
			XIc	93—94			$C_{19}H_{19}N$[g]			23
8	Ia	KOH	VIa	101—102	76,6	6,7	$C_{11}H_{11}NO$	76,4	6,4	46
9	Ib	KOH	VIb	163—165	82,2	6,2	$C_{17}H_{15}NO$	82,0	6,1	22
			VIIIb	115—116	87,1	5,6	$C_{16}H_{12}O$	87,3	5,5	2

[a] The compounds were recrystallized: IVa, VIa, VIIIb, Xc, and XIa, b from hexane, IVb, c, Xa, b, and XIc from pentane, and IVd and VIb from heptane. [b] Acetyl derivative. [c] According to the data in [5], this compound has mp 50-51°C. [d] According to the data in [6], this compound has mp 49-50°C. [e] Found: N 5.3%. Calculated: N 5.1%. [f] Found: N 5.0%. Calculated: N 4.9%. [g] The molecular-ion peaks for Xb, c and XIb, c correspond to the calculated values.

would promote rearrangement with the formation of a β-naphthylamine. In fact, 2-methylamino-3-phenylnaphthalene (IVb) was obtained in 50% yield when 2-methyl-3-benzylisoquinolinium iodide (Ib) was heated with an alcohol solution of methylamine. Dealkylation with the formation of 3-benzylisoquinoline (Vb) in 30% yield also took place simultaneously.

A complex mixture, from which we were able to isolate four compounds, viz., naphthylamine IVb (15%), isoquinoline Vb (10%), 2-methyl-3-benzyl-1-isoquinolone (VIb) (30%), and 3-phenyl-2-naphthol (VIIIc) (6%) by means of column chromatography, is formed in aqueous methylamine. The structures of these compounds were proved by means of IR, UV, PMR, and mass spectroscopy and elementary analysis (Tables 1 and 2).

The rearrangement of salt Ib also takes place under the influence of an aqueous solution of alkali but to a very small extent and is accompanied by hydrolysis of the open intermediate (IIIb); this leads to 3-phenyl-2-naphthol (VIIIb). The latter is obtained in only 2% yield, while isoquinolone VIb was obtained in 22% yield.

2-Ethyl-3-benzylisoquinolinium iodide (Id) undergoes rearrangement under the influence of an alcohol solution of ethylamine to give 2-ethylaminonaphthalene (IVd) in 60% yield. One also observes 14% dealkylation in this case.

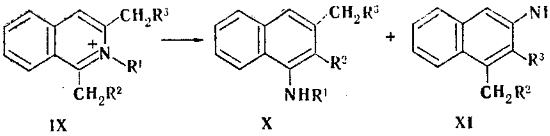
We also studied the reactions of 3-benzylisoquinolinium salts with alkylamines, the alkyl groups of which differ from the quaternizing groups. The reactions proceed with virtually complete exchange of the alkylamino group in the reaction of 2-methyl-3-benzylisoquinolinium iodide with ethylamine and of 2-ethyl-3-benzylisoquinolinium iodide with methylamine. According to the results of thin-layer chromatography (TLC), the products of rearrangement without exchange of the alkylamino group are found only in trace amounts.

If the isoquinoline molecule contains only one methyl group in the 1 or 3 position, recyclization can take place only with the participation of precisely this group. However, if the methyl groups are found simultaneously in positions 1 and 3, one may expect reactions via both pathways. In fact, a mixture of 1-methylamino-3-methylnaphthalene (Xa) (68%) and 2-methylamino-4-methylnaphthalene (XIa) (7%) is formed in the reaction of 1,2,3-trimethylisoquinolinium iodide (IXa) with an alcohol solution of methylamine (at 150°C). The yields of amine decrease at lower temperatures, but their ratio (according to GLC data) remains the

TABLE 2. Spectral Characteristics of the Compounds Obtained

Compound	PMR spectra, δ, ppm	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}
IVa	2,6 (3H, s, CH$_3$N), 3,4 (1H, s, NH), 6,3—6,5 (2H, m, 1-H, 3-H), 6,9—7,5 (5H, aromatic protons)	215 (4,60), 246 (4,82), 285 (4,00), 295 (3,97), 347 (3,50)	3435 (NH)
IVc	1,05 (3H, t, CH$_3$), 3,0 (2H, q, CH$_2$), 3,3 (1H, s, NH); 6,5—6,7 (2H, m, 1-H, 3-H), 7,0—7,6 (5H, m, aromatic protons)	213 (4,52), 246 (4,73), 284 (3,93), 290 sh (3,93), 3,50 (3,42)	3425 (NH)
IVb	2,7 (3H, s, CH$_3$N), 3,8 (1H, s, NH), 6,75 (1H, s, 1-H), 7,1—7,7 (10H, m, aromatic protons)	212 (4,58), 253 (4,72), 286 (3,71), 365 (3,28)	3440 (NH)
IVd	1,1 (3H, t, CH$_3$), 3,1 (2H, q, CH$_2$), 3,65 (1H, s, NH); 6,7 (1H, s, 1-H), 7,0—7,7 (10H, aromatic protons)	212 (4,62), 253 (4,77), 286 (3,92), 362 (3,46)	3440 (NH)
Xa	2,35 (3H, s, CH$_3$), 2,7 (3H, s, CH$_3$N), 3,95 (1H, s, NH), 6,25 (1H, s, 2-H), 6,85 (1H, s, 4-H), 7,1—7,65 (4H, m, aromatic protons)	216 (4,76), 253 (4,40), 338 (3,86)	3460 (NH)
XIa	2,5 (3H, s, CH$_3$), 2,75 (3H, s, CH$_3$N), 3,45 (1H, s, NH), 6,4 (2H, s, 1-H, 3-H), 7,0—7,7 (4H, m, aromatic protons)	215 (4,58), 246 (4,89), 288 (4,07), 297 (4,04), 350 (3,53)	3435 (NH)
Xb	2,8 (3H, s, CH$_3$N), 4,0 (1H, s, NH), 4,05 (2H, s, CH$_2$), 6,35 (1H, s, 2-H), 7,05—7,8 (10H, m, aromatic protons)	216 (4,76), 253 (4,47), 337 (3,83)	3450 (NH)
XIb	2,3 (3H, s, CH$_3$), 2,85 (3H, s, CH$_3$N), 3,35 (1H, s, NH), 6,8 (1H, s, 1-H), 7,3—8,1 (9H, m, aromatic protons)	213 (4,64), 251 (4,75), 276 sh (3,86), 289 (3,91), 300 (3,79), 355 (3,49)	3445 (NH)
Xc	1,3 (3H, t, CH$_3$), 3,15 (2H, q, CH$_2$), 3,9 (1H, s, NH), 4,05 (2H, s, CH$_2$), 6,4 (1H, s, 2-H), 7,0—7,8 (10H, m, aromatic protons)	216 (4,76), 253 (4,47), 337 (3,92)	3440 (NH)
XIc	1,15 (3H, t, CH$_3$), 2,3 (3H, s, CH$_3$), 3,15 (2H, q, CH$_2$), 3,25 (1H, s, NH), 6,75 (1H, s, 1-H), 7,2—8,0 (9H, m, aromatic protons)	213 (4,65), 251 (4,78), 276 sh (3,86), 289 (3,92), 300 (3,79), 355 (3,49)	3430 (NH)
VIa	2,25 (3H, s, CH$_3$), 3,45 (3H, s, CH$_3$N), 6,2 (1H, s, 4-H), 7,15—8,45 (4H, m, aromatic protons)	208 (4,56), 228 (4,30), 248 sh (3,90), 283 (4,04), 290 (4,03), 335 (3,70)	1660 (CO)
VIb	3,55 (3H, s, CH$_3$N), 4,15 (2H, s, CH$_2$), 6,5 (1H, s, 4-H), 7,0—8,7 (9H, m, aromatic protons)	208 (4,82), 227 sh (4,78), 250 (4,03), 285 (4,11), 290 (4,10), 333 (3,80)	1660 (CO)
VIIIb	4,9 (1H, s, OH), 7,1—7,6 (11H, m, aromatic protons)	214 (4,59), 248 (4,72), 268 (3,90), 339 (3,36)	3525 (OH)

same (9:1). This can be explained by the fact that the 1-CH$_3$ group has higher CH acidity than the 3-CH$_3$ group because of the greater electron deficit in the 1 position as compared with the position 3 of the isoquinoline ring [4].



IX–XI a, b $R^1 = CH_3$; a $R^2 = R^3 = H$; b, c $R^2 = H$, $R^3 = C_6H_5$; c $R^1 = C_2H_5$

Proceeding from the data on the recyclization of 3-methylisoquinoline (Ia, c) and 3-benzylisoquinoline (Ib, d) salts one must assume that when the methyl group is replaced by a benzyl group, the probability of recyclization via this group will increase. It was found that in the reaction of 1,2-dimethyl-3-benzylisoquinolinium (IXb) and 1-methyl-2-ethyl-3-benzylisoquinolinium (IXc) iodides, respectively, with methylamine and ethylamine the yield of α-naphthylamine Xb or Xc remains virtually the same as in the case of 1,2,3-trimethylisoquinolinium iodide (67%); however, the yields of β-naphthylamines XIb and XIc increase to 24%. In other words, in the case of 1-methyl-3-benzylisoquinolinium salts the rearrangement takes place primarily at the methyl group in position 1, despite the fact that a benzyl group is located in position 3. Dealkylation takes place to a very small extent in the reactions of 1,3-disubstituted isoquinolinium salts with alcohol solutions of alkylamines, whereas the degree of dealkylation does not exceed 1-2% in the reactions of salts IXb and IXc with ethylamine. When the alkyl group of the reagent differs from the quaternizing group of the isoquinolinium salt, the rearrangement (according to the results of TLC), as in the preceding cases, proceeds with virtually complete exchange of the alkylamino group. Thus the introduction of substituents in positions 1 and 3 of the isoquinoline ring creates steric limitations for the dealkylation of the isoquinolinium salt but does not hinder exchange of the alkylamino group, which takes place in the step involving the open intermediate. The use of aqueous solutions of bases promoted competitive processes associated with hydrolysis of the intermediate forms.

EXPERIMENTAL

The IR spectra of films of IVa, c, d, Xb, and XIa, b, mineral oil suspensions of IVb, VIa, b, VIIIb, and Xa, and solutions of Xc and XIc in CCl_4 were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in methanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in CCl_4 (in $CDCl_3$ in the case of VIa, b and VIIIb) were obtained with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The mixtures of compounds obtained were analyzed with an LKhM-8MD (model 111) gas—liquid chromatograph with a flame-ionization detector; the columns were filled with Chromaton N-AW (0.125-0.160 mm) moistened with 5% SE-30 silicone, the carrier gas was nitrogen, and the gas-flow rate was 30 ml/min. The course of the reactions was monitored by TLC on Silufol in benzene, benzene—hexane (1:1), and benzene—ethyl acetate—heptane (1:1:1) systems.

Reaction of Isoquinolinium Salts with an Alcohol Solution of the Alkylamine. A mixture of 1 mmole of the alkylisoquinolinium iodide and 10 ml of a 35% solution of the alkylamine in alcohol was heated in a sealed ampul at 150°C for 30 h, after which the ethanol was removed from the mixture by distillation, and the residue was separated with a column filled with silica gel (40/100 μ) by elution with benzene (experiments Nos. 1-4 in Table 1) or benzene—hexane (experiments Nos. 5-7 in Table 1). In a number of experiments the reaction products were isolated and analyzed in the form of the acetyl derivatives. For this, the substance obtained after separation with the column filled with silica gel was refluxed with 1 ml of acetic anhydride for 15 min, the excess anhydride was removed by distillation, and the residue was recrystallized.

Reaction of Isoquinolinium Salts with Aqueous Alkali Solution. A mixture of 1 mmole of alkylisoquinolinium iodide and 10 ml of 20% aqueous KOH solution was refluxed for 10 h, after which it was acidified with HCl and extracted with chloroform. The extract was dried with magnesium sulfate, the solvent was removed by distillation, and the residue was separated with a column filled with silica gel (40/100 μ) by elution with benzene (experiment No. 8, Table 1) or benzene—ethyl acetate—heptane (1:1:1) (experiment No. 9, Table 1). The solvent was removed by distillation, and the residue was recrystallized.

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PYRIMIDINES.

72.* SYNTHESIS AND SOME PROPERTIES OF 5-AMINO-2-R-4,6-DIPHENYLPYRIMIDINES AND THE PRODUCTS OF THEIR TRANSFORMATIONS

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UDC 547.853.7'854'855.3.07

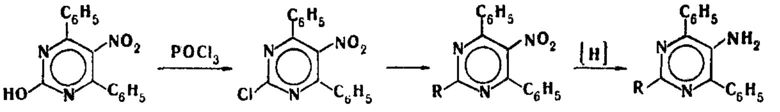
The corresponding 5-aminopyrimidines were obtained by reduction of 2-substituted 5-nitro-4,6-diphenylpyrimidines, and reactions involving the amino group were studied. A Schiff base was obtained, and acetylation and diazotization reactions were carried out. The corresponding diazonium salts were converted to 2-dimethylamino-5-hydroxy-4,6-diphenylpyrimidine and 5-azido-2-methoxy-4,6-diphenylpyrimidine. 2-Methoxy-4-phenyl-5H-pyrimido[5,4-b]indole was obtained by photocyclization of the latter.

Very little study has been devoted to the relatively difficult-to-obtain sterically hindered heterocyclic amines. In the pyrimidine series only 2-substituted 5-amino-4,6-dimethylpyrimidines and their derivatives involving the amino group are known [2, 3].

We have previously obtained 5-amino-2-hydroxy-4,6-diphenylpyrimidine [4]. We assumed that the latter could serve as the starting compound for the synthesis of 5-amino-2-R-4,6-diphenylpyrimidine. However, this method for the production of 5-aminopyrimidines proved to be unsuitable because of the difficulty encountered in converting the corresponding 2-hydroxypyrimidine to 2-chloro-5-amino-4,6-diphenylpyrimidine. It is known [4] that 5-nitro-2-hydroxy-4,6-diphenylpyrimidine reacts with phosphorus oxychloride to give 2-chloro-5-nitro-4,6-diphenylpyrimidine in good yield. We used the latter to obtain substituted 5-aminopyrimidines that are analogs of sterically hindered anilines.

Compounds IIa-d were obtained from 2-chloro-5-nitro-4,6-diphenylpyrimidine, in which the chlorine is readily replaced by a methoxy group or a substituted amino group by the action of sodium methoxide or an alcohol solution of the amine.

The corresponding 5-aminopyrimidines (IIIa, b, e) were obtained in good yields by reduction of I and IIa, b with stannous chloride in hydrochloric acid [5]. To avoid possible complications in the reduction of IId that are associated with hydrolysis of the methoxy group [6] we carried out the reduction of IId to IIId by the action of iron in acetic acid (with heating) [7]. Other 5-nitropyrimidines can also be reduced under these conditions; this was verified in the case of the reduction of I to IIIe.



I II a-d III a, b, d, e

II, III a $R=N(CH_3)_2$; b $R=N(C_2H_5)_2$; II c $R=NHCH_3$; II, III d $R=OCH_3$; III e $R=Cl$

The properties of the resulting 5-aminopyrimidines III, the amino group of which is shielded by two adjacent phenyl groups and the basicities of which are reduced because of the acceptor properties of the pyrimidine ring, were studied.

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*See [1] for Communication 71.

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