LITERATURE CITED

1. É. I. Stankevich, A. Ya. Ozola, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., 231 (1975).
2. E. A. Silinsh and L. F. Taure, Phys. Stat. Sol., 2, 847 (1969).
3. Ya. F. Freimanis, E. A. Silin'sh, O. Ya. Neiland, and L. F. Taure, Izv. Akad. Nauk Latv. SSR, Ser. Fiz., 3, 28 (1967).
4. A. Ya. Ozola, É. I. Stankevich, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., 1147 (1973).
5. Ya. F. Freimanis and G. Ya. Vanag, Zh. Obshch. Khim., 31, 1945 (1961).
6. A. Ya. Ozola, É. I. Stankevich, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., 632 (1971).
7. L. É. Neiland, Author's Abstract of Candidate's Dissertation, Riga (1965).
8. L. E. Neiland and G. Vanag, Khim. Geterotsikl. Soedin., 93 (1965).
9. I. V. Turovskii, O. Ya. Neiland, L. É. Neiland, and Ya. P. Stradyn', Khim. Geterotsikl. Soedin., 1382 (1972).
10. O. Ya. Neiland, S. V. Kalnin', É. I. Stankevich, and A. Ya. Ozola, Khim. Geterotsikl. Soedin., 527 (1974).

INVESTIGATION OF NAPHTHYRIDINES.

VII.* SYNTHESIS OF 10-ALKYLAMINO-1,2,3,4-TETRAHYDROBENZO[b]-1,6-NAPHTHYRIDINES

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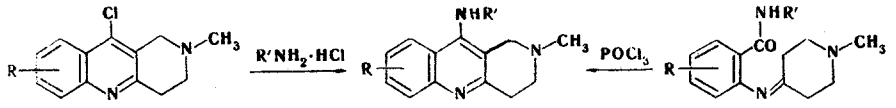
UDC 547.836.3

10-Alkylamino-2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines were obtained by cyclization of alkylamides of N-(1-methyl-4-piperidylidene)anthranilic acids and also by reaction of 10-chloro-2-methyl-1,2,3,4-tetrahydrobenzo-[b]-1,6-naphthyridines with amine hydrochlorides.

In the present research we attempted to synthesize 10-alkylamino-1,2,2,4-tetrahydrobenzo-[b]-1,6-naphthyridines by nucleophilic substitution of the halogen in 10-chloro-2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines (I-V) by an alkylamino group.



I-V VII-XX XXI-XXVIII

However, the chlorine in I-V, as in 2,3-polymethylenequinolines [2], proved to have low lability, probably because of the steric and nucleophilic effect of the piperidine ring fused to the quinoline ring. Thus, reaction between benzylamine and I does not occur when they are heated in excess amine at 140° for 7 h, nor when they are heated at 180° for 1 h in phenol. In the latter case we isolated only phenoxy derivative VI.

It is known [3] that the reaction of 4-chloroquinolines with amines is catalyzed by acids; we observed that the corresponding naphthyridines are formed in 16-32% yields in the reaction of amine hydrochlorides with I-V and the hydrochloride of IV with benzylamine (Table 2, method A).

*See [1] for communication VI.

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TABLE 1. 10-Chloro-2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines (I-V)

Compound	R	mp, °C	Empirical formula	N, % found	N, % calc.	Yield, %
I	H	96—98	$C_{13}H_{13}ClN_2$	12,1	12,0	43
II	7-NO_2	161—163	$C_{13}H_{12}ClN_3O_2$	15,1	15,1	25
III	8-Cl	81—83	$C_{13}H_{12}Cl_2N_2$	10,3	10,5	25
IV	8-Br	274—275*	$C_{13}H_{12}BrClN_2 \cdot 2HCl$	7,7	8,0	30
V	8-CH_3	90—91	$C_{14}H_{15}ClN_2$	11,1	11,3	30

*The data for the dihydrochloride are presented.

TABLE 2. 10-Alkyl(aralkyl)amino-2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines (VII-XX)

Compound	R	R′	mp, °C	Empirical formula	Yield, % N	Yield, % Hal	Found, % N	Found, % Hal	Calc., % method A	Calc., % method B
VII	H	H	166—167	$C_{13}H_{15}N_3$	19,4	—	19,7	—	20	—
VIII	H	CH_3	100—102	$C_{14}H_{17}N_3$	18,3	—	18,5	—	21	—
IX	H	C_2H_5	85—87	$C_{15}H_{19}N_3$	17,1	—	17,4	—	25	—
X	H	*n*-C_3H_7	66—67	$C_{16}H_{21}N_3$	16,2	—	16,5	—	—	55
XI	H	*n*-C_4H_9	82—84	$C_{17}H_{23}N_3$	14,2	—	14,5	—	29	53
XII	8-CH_3	*n*-C_3H_7	64—65	$C_{17}H_{23}N_3$	15,4	—	15,6	—	—	54
XIII	8-Cl	*n*-C_4H_9	89—90	$C_{17}H_{22}ClN_3$	13,9	11,8	13,8	11,7	—	64
XIV	8-Cl	*iso*-C_4H_9	92—94	$C_{17}H_{22}ClN_3$	13,7	11,4	13,8	11,7	—	60
XV	8-Br	*n*-C_4H_9	85—86	$C_{17}H_{22}BrN_3$	12,2	22,9	12,1	23,0	—	52
XVI	H	$C_6H_5CH_2$	110—111	$C_{20}H_{21}N_3$	13,5	—	13,8	—	30	43
XVII	8-Cl	$C_6H_5CH_2$	100—102	$C_{20}H_{20}ClN_3$	12,2	10,3	12,4	10,5	32	—
XVIII	8-Br	$C_6H_5CH_2$	149—150	$C_{20}H_{20}BrN_3$	10,7	21,1	11,0	21,0	31	52
XIX	8-CH_3	$C_6H_5CH_2$	101—103	$C_{21}H_{23}N_3$	12,5	—	12,8	—	25	—
XX	7-NO_2	$C_6H_5CH_2$	148—150	$C_{20}H_{20}N_4O_2$	15,8	—	16,1	—	16	—

TABLE 3. N-(1-Methyl-4-piperidylidene)anthranilic Acid Alkyl(aralkyl)amides (XXI-XXVIII)

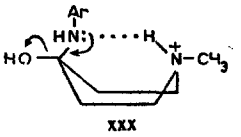
Compound	R	R′	mp, °C	Empirical formula	Found, % N	Found, % Hal	Calc., % N	Calc., % Hal	Yield, %
XXI	H	*n*-C_3H_7	173—174	$C_{16}H_{23}N_3O$	14,6	—	14,8	—	50
XXII	H	*n*-C_4H_9	159—160	$C_{17}H_{25}N_3O$	16,5	—	16,6	—	66
XXIII	5-Cl	*n*-C_4H_9	150—152	$C_{17}H_{24}ClN_3O$	12,9	11,2	13,1	11,1	50
XXIV	5-Cl	*iso*-C_4H_9	163—164	$C_{17}H_{24}ClN_3O$	13,0	11,0	13,1	11,1	71
XXV	5-Br	*n*-C_4H_9	154—155	$C_{17}H_{24}BrN_3O$	11,6	21,6	11,5	21,9	58
XXVI	5-CH_3	*n*-C_3H_7	144—145	$C_{17}H_{25}N_3O$	14,7	—	14,6	—	52
XXVII	H	$C_6H_5CH_2$	217—218	$C_{20}H_{23}N_3O$	13,2	—	13,1	—	50
XXVIII	5-Br	$C_6H_5CH_2$	210—211	$C_{20}H_{22}BrN_3O$	10,3	19,8	10,5	20,0	45

The catalytic action of hydrochloric acid is apparently associated with an increase in the electron-acceptor properties of the nitrogen atom of the pyridine ring in naphthyridines I-V when it is protonated and with an increase, as a consequence of this, of the fractional positive charge on the C_{10} atom, which facilitates its nucleophilic substitution.

Carrying out the reaction in fused phenol does not increase the yields of the desired products and does not make it possible to reduce the heating time, and this indicates the absence of a catalytic effect of phenol. However, less resinification is observed when the syntheses are accomplished in a phenol medium. An attempt to carry out the synthesis in dimethylformamide (DMF) was unsuccessful.

Inasmuch as naphthyridines are obtained in low yields by method A, we studied the possibility of their synthesis from N-(1-methyl-4-piperidylidene)anthranilic acid alkylamides (XXI-XXVIII, Table 3). The latter were obtained by condensation of anthranilic acid alkylamides (XXIX) with 1-methyl-4-piperidine in the presence of a catalytic amount of hydrochloric acid; the reaction in this case proceeds considerably more slowly than the reaction

of alkylamides XXIX with cyclohexanone [4]. This is probably associated with the fact that an intramolecular hydrogen bond that hinders splitting out of a hydroxide ion and slows down the formation of the imine is formed in intermediate hydroxy amine XXX.



XXX

Two absorption bands with maxima at 236 and 320 nm are observed in the UV spectra of alcohol solutions of VII-XX containing alkali. The spectra of hydrochloric acid solutions of these compounds are shifted to the red region, and this constitutes evidence for protonation, during salt formation, of the nitrogen atoms of the naphthyridine system rather than the amino group attached to C_{10}.

EXPERIMENTAL

The IR spectra of 0.01 M solutions of the compounds in CCl_4 were recorded with a UR-20 spectrometer. The UV spectra of ethanol solutions were recorded with an SF-4 spectrophotometer.

10-Chloro-2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines (I-V, Table 1). An 0.1-mole sample of 1-methyl-4-piperidone was added slowly dropwise to a solution of 0.1 mole of anthranilic acid in 100 ml of phosphorus oxychloride, after which the mixture was refluxed for 2 h. The phosphorus oxychloride was then removed by vacuum distillation, the residue was dissolved in chloroform, and the chloroform solution was poured into 1 liter of cooled (to 0°) concentrated ammonium hydroxide. The chloroform layer was washed with water until it was neutral, after which it was dried, and the solvent was removed by distillation. The product was extracted from the residue with five 100-ml portions of hexane and crystallized from hexane.

10-Phenoxy-2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridine (VI). A mixture of 1 g of naphthyridine I, 1.5 g of benzylamine, and 1 g of phenol was heated on a metal bath for 1 h at 180°, after which the melt was dissolved in chloroform, and the solution was treated with 10% KOH solution. The excess benzylamine was removed by steam distillation, and the residue was crystallized from petroleum ether to give 0.3 g (25%) of a product with mp 124-126°. Found, %: N 9.8. $C_{19}H_{18}N_2O$. Calculated, %: N 9.6.

10-Alkyl(aralkyl)amino-2-methyl-1,2,3,4-tetrahydrobenzo[b]-1,6-naphthyridines (VII-XX, Table 2). Method A. A mixture of 4 mmole of naphthyridine I-V, 8 mmole of alkyl(aralkyl)-amine hydrochloride, and 1 g of phenol was heated on a metal bath at 140-180° for 1 h, after which the melt was dissolved in chloroform. The chloroform solution was washed with 10% KOH solution, and the volatile impurities were removed by steam distillation. The residue was crystallized from hexane.

Method B. A 1-g sample of alkylamide XXI-XXVIII was dissolved in 10 ml of toluene, after which 4 ml of phosphorus oxychloride was added, and the mixture was refluxed for 2 h. It was then poured into water, the toluene was separated, and the aqueous layer was neutralized with dilute ammonium hydroxide. The reaction product was extracted with chloroform, the extract was dried with $MgSO_4$, and the solvent was removed by distillation. The residue was crystallized from hexane.

Naphthyridines VII-XX were yellowish crystalline substances that were quite soluble in organic solvents. The IR spectra of these compounds contain bands of stretching vibrations at 3428-3430 (NH), 3034 and 3070 (benzene ring CH), 2952-2955 and 2850 (CH_2), and 2790 (CH_3) cm^{-1}.

N-(1-Methyl-4-piperidylidene)anthranilic Acid Alkyl(aralkyl)amides (XXI-XXVIII, Table 3). A solution of 0.01 mole of anthranilic acid alkyl(aralkyl)amide and 0.013 mole of 1-methyl-4-piperidone in 20 ml of toluene was heated with a Dean–Stark trap in the presence of two to three drops of an alcohol solution of hydrogen chloride for 20-60 h, after which the mixture was cooled, and the resulting precipitate was removed by filtration, washed on the filter with dilute sodium bicarbonate solution and water, and crystallized from benzene.

LITERATURE CITED

1. A. I. Mikhalev and M. E. Konshin, Khim. Geterotsikl. Soedin., 968 (1974).
2. L. I. Sargent and L. Small, J. Org. Chem., 11, 359 (1946).
3. R. Elderfield (editor), Heterocyclic Compounds, Vol. 4, Wiley.
4. M. E. Konshin and P. A. Petyunin, Khim.-Farmats. Zh., No. 1, 10 (1971).

NUCLEOPHILIC SUBSTITUTION OF HYDROGEN (9-H) IN ACRIDINIUM SALTS BY PHENOLS

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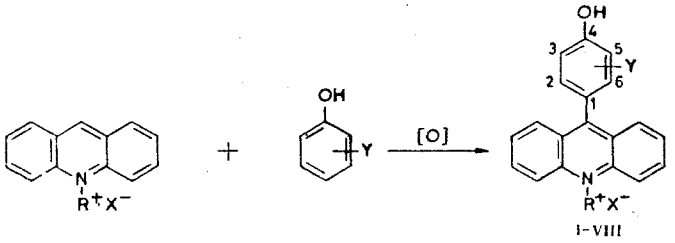
Under oxidative conditions, quaternary and protic acridinium salts undergo substitution of the hydrogen atom in the 9 position by a phenol residue to give 9-hydroxyarylacridines. The latter may be formed under the same conditions from complexes of acridine hydrochloride with phenols obtained by an independent method.

Nucleophilic substitution of hydrogen in charge-activated aza-aromatic compounds is presently realized with various nucleophilic agents [1-3]. The introduction of phenol residues into azinium cations has been described only in the case of quinoline in a little-known Japanese study [4] that has not been included in Chemical Abstracts. The structures of the reaction products were not studied, and the results of elementary analysis are presented for only one compound.

In the present paper we have investigated the reaction of phenols with acridinium salts. Experiments showed that quaternary and protic acridinium salts react with mono- and polyhydric phenols in an oxidative medium to give 9-(4-hydroxyaryl)acridines.



I-VIII

The oxidative dehydrocondensation with phenols was carried out under the conditions previously used* for the replacement of hydrogen in azines by residues of arylamines and their derivatives [3], CH-active compounds [5], and other nucleophiles. We were able to obtain condensation products I-VIII (Table 1) of acridine hydrochloride (AHC) with aminophenols, resorcinol monomethyl ether, 8-hydroxyquinoline, and polyphenols in good yields. The reaction of AHC with pyrogallol in dimethyl sulfoxide (DMSO) is realized at room temperature.

The reaction begins only at 160-170° in a melt with a threefold excess of sulfur. The yields of final products under these conditions are reduced to 20% because of a competitive reaction — thionation of acridine. The scope of this reaction can be expanded if the reagents are simply fused at a high temperature (200-210°) in air. This method was used to obtain condensation products with phenol, cresols, and naphthols that cannot be synthesized by the methods in [3, 5].

*By fusion with sulfur or by bubbling air through a solution in dimethylformamide.

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