A STUDY OF NAPHTHYRIDINES

III.* SYNTHESIS OF 4,4-DIARYL-1,4-DIHYDRO-2,3-BENZO-1,8-NAPHTHYRIDINES

M. E. Konshin and V. P. Chesnokov

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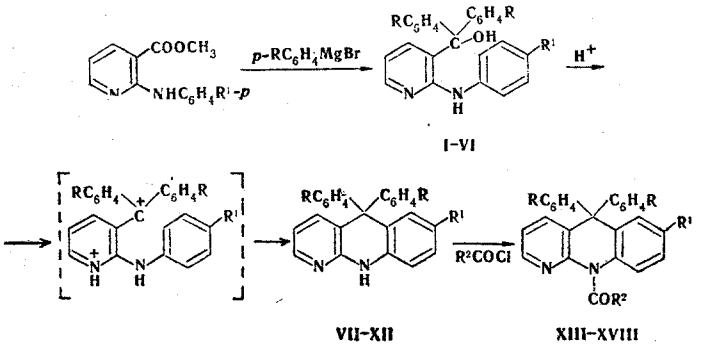
4,4-Diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines have been synthesized by the cyclization of diaryl 2-arylaminopyridin-3-yl carbinols. The latter were obtained by the reaction of methyl 2-arylaminonicotinates with arylmagnesium halides. With acid chlorides, the 4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines form 1-acyl derivatives. The pK_a values of the 4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines in nitrobenzene have been determined, and a correlation has been found of the pK_a values with the σ^* constants of the substituents ($r = 0.955$, $\rho^* = -1.53$, pK_a° calc $= 2.51$, $s = 0.01$).

4,4-Diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines have not been studied. The closest structural analogs of these compounds are the 9,9-diaryldihydroacridines, which are obtained by the intramolecular cyclization of diaryl 2-arylaminoamyl carbinols [2, 3]. It appeared of interest to perform the synthesis of diaryl 2-arylaminopyridin-3-yl carbinols and to study the possibility of converting them into 4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines, since the latter are promising for the synthesis of potentially physiologically active compounds.



The diaryl 2-arylaminopyridin-3-yl carbinols (I-VI, Table 1) were obtained with good yields by the reaction of arylmagnesium halides with methyl 2-arylaminonicotinates. They are colorless crystalline substances readily soluble in organic solvents. With concentrated sulfuric acid they give a rapidly disappearing coloration, the appearance of which is apparently due to the formation of a doubly-charged pyridium–carbonium ion. The IR spectra of compounds (I-VI), in which only the bands of free hydroxy and amino groups are observed, shows the absence of intramolecular hydrogen bonds in these compounds. The reason for this is the low basicity of the amino groups in the carbinols (I-VI).

When acetic acid solutions of the carbinols were heated with catalytic amounts of concentrated sulfuric acid, intramolecular cyclization took place with the formation of the 4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines (VII-XII, Table 2) with good yields. Since with concentrated sulfuric acid the carbinols

*For Communication II, see [1].

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TABLE 1. Diaryl-2-Arylaminopyridin-3-yl Carbinols (I-VI)

Compound	R	R′	Mp, °C	Empirical formula	N, % found	N, % calc.	IR spectrum, cm^{-1} ν_{OH}	IR spectrum, cm^{-1} ν_{NH}	Yield, %
I	H	H	168—170	$C_{24}H_{20}N_2O$	7,9	7,9	3600	3407	56
II	H	CH_3	170—172	$C_{25}H_{22}N_2O$	7,6	7,6	3600	3407	49
III	H	CH_3O	150—151	$C_{25}H_{22}N_2O_2$	7,3	7,3	3603	3411	40
IV	H	Cl	177—179	$C_{24}H_{19}ClN_2O$	7,2	7,2	3603	3400	31
V	H	Br	182—183	$C_{24}H_{19}BrN_2O$	6,5	6,5	3603	3396	32
VI	*p*-CH_3	CH_3O	180—182	$C_{27}H_{26}N_2O_2$	6,8	6,8	3603	3407	45

TABLE 2. 4,4-Diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines (VII-XII)

Compound	R	R′	Mp, °C	Empirical formula	N, % found	N, % calc.	IR spectrum, cm^{-1}	pK$_a$ in nitrobenzene	ΔpK_a*	Yield, %
VII	H	H	282—284	$C_{24}H_{18}N_2$	8,5	8,4	3424	2,52±0,04	5,98	80
VIII	H	CH_3	255—257	$C_{25}H_{20}N_2$	7,9	8,0	3426	2,76±0,06	5,74	84
IX	H	CH_3O	232—234	$C_{25}H_{20}N_2O$	7,7	7,7	3432	2,66±0,05	5,84	60
X	H	Cl	254—255	$C_{24}H_{17}ClN_2$	7,5	7,6	3428	2,10±0,05	6,40	74
XI	H	Br	270—272	$C_{24}H_{17}BrN_2$	6,8	6,8	3428	2,11±0,06	6,39	80
XII	*p*-CH_3	CH_3O	222—224	$C_{27}H_{24}N_2O$	7,1	7,2	3426	—	—	55

*pK_a for diphenylguanidine in nitrobenzene 8.5 ± 0.02.

TABLE 3. 1-Acyl-4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines (XIII-XVIII)

Compound	R	R^1	R^2	Mp, °C	Empirical formula	N, % found	N, % calc.	Yield, %
XIII	H	H	CH_3	241—243	$C_{26}H_{20}N_2O$	7,5	7,4	85
XIV	H	H	C_6H_5	271—273	$C_{31}H_{22}N_2O$	6,4	6,4	34
XV	H	CH_3C	CH_3	196—198	$C_{27}H_{22}N_2O_2$	6,8	6,9	37
XVI	H	Cl	C_6H_5	211—213	$C_{31}H_{21}ClN_2O$	6,0	5,9	72
XVII	H	Br	CH_3	240—242	$C_{26}H_{19}BrN_2O$	6,3	6,2	59
XVIII	*p*-CH_3	CH_3O	C_6H_5	200—202	$C_{34}H_{28}N_2O_2$	5,7	5,6	43

give halochromic salts, the hypothesis may be put forward that the mechanism of the cyclization of these compounds into the naphthyridines (VII-XII) in an acid medium consists in the formation of a carbonium ion which plays the role of an electrophilic agent, attacking the neighboring benzene ring. The high activity of the carbonium ion, and also the spatial propinquity of the phenyl radical, which is the nucleophilic reaction center, lead to a high rate of cyclization which it is impossible to control under the usual conditions. An attempt to study the UV spectra of the doubly-charged cation (I) or (III) was unsuccessful, since immediately after the preparation of solutions of (I) and of (III) in concentrated sulfuric acid they give the spectra of the cations (VII) and (IX), and not those of the halochromic cations. The naphthyridines (VII-XII) are colorless crystalline substances sparingly soluble in the usual organic solvents. The structures of these compounds were confirmed by their IR spectra, which contained a ν_{NH} band at 3424-3434 cm^{-1} and, unlike the spectra of (I-VI), lacked the band of a hydroxy group. Their ionization constants in nitrobenzene were studied, and the values of ΔpK_a relative to the pK_a value of diphenylguanidine in the same solvent were calculated (Table 2). The pK_a values of (VII-XI) depend on the substituents in the benzene ring of the heterocyclic system and fall in the sequence of compounds with the following substituents: $CH_3 > CH_3O > H > Br > Cl$. Since the substituents in (VII-XI) are separated from the pyridine ring by an o-phenylene group, and also several σ bonds, the hypothesis can be put forward that the pK_a values of these compounds will correlate with Taft's σ^* constants of the substituents [4]. An analysis of the pK_a–σ^* relationship showed that a good correlation is observed with the following correlation parameters: $r = 0.995$; $\rho^* = -1.53$; $pK^\circ_{a\,calc} = 2.51$; $s = 0.01$. Compounds (VII-XII) are acylated by acid chlorides in a benzene medium in the presence of triethylamine with the formation of 1-acyl-4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines (XIII-XVIII, Table 3) with yields of 34-85%.

EXPERIMENTAL

The IR spectra were taken on a IKS-14 instrument using 0.005 M solutions in carbon tetrachloride (LiF prism). The ionization constants of the 4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines were determined by the potentiometric titration with a 0.1 N dioxane solution of perchloric acid of 0.005 M solutions of (VII-XI) in nitrobenzene, using a LPM-60M potentiometer with glass and silver chloride electrodes. The calculation was performed by the usual method [5] from eight points corresponding to 10-90% neutralization.

Diaryl 2-Arylaminopyridin-3-yl Carbinols (I-VI). A solution of 0.1 mole of a methyl 2-arylaminonicotinate [6] in 50 ml of anhydrous ether was added to the Grignard reagent obtained in the usual way from 0.03 mole of an aryl bromide at 0.03 g-atom of magnesium. The mixture was heated for 1 h 30 min to 2 h and was then decomposed with a saturated solution of ammonium chloride. The ethereal solution was separated off and was treated with steam. The residue was crystallized from ethanol.

4,4-Diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines (VII-XII). A drop of concentrated sulfuric acid was added to a solution of 1 g of diaryl 2-arylaminopyridin-3-yl carbinol in 10 ml of glacial acetic acid, and the mixture was heated on the water bath for 30 min and was cooled and poured into 100 ml of water, and the precipitate that deposited was filtered off, treated with 10% sodium carbonate solution, washed with water, and crystallized from dioxane.

1-Acyl-4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridines (XIII-XVIII). A solution of 1 g of a 4,4-diaryl-1,4-dihydro-2,3-benzo-1,8-naphthyridine in 50 ml of anhydrous benzene was treated with 1 ml of triethylamine, and then 0.1 mole of an acyl chloride was added dropwise, after which the mixture was left at room temperature for 1 h and was poured into 10-16 ml of ice water and treated with steam. The residue was crystallized from acetone.

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