REACTION OF 3-[N-(2-NAPHTHYL)FORMIMIDOYL]PYRIDINE WITH SUBSTITUTED ACETOPHENONES

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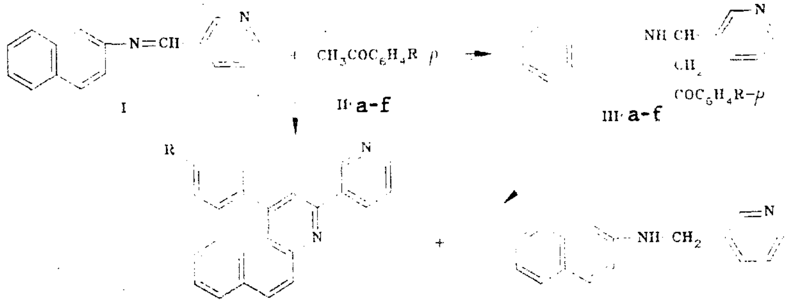
The reaction of 3-[N-(2-naphthyl)formimidoyl]pyridine with substituted acetophenones in the presence of a proton catalyst leads to 1-aryl-3-(3-pyridyl)benzo[f]quinolines. Noncyclic amino ketones – [1-aryl-3-(3-pyridyl)-3-(2-naphthylamino)]-1-propanones – precede the formation of the cyclic products. The IR, UV, PMR, and mass spectra of the synthesized compounds are discussed.

The introduction of a 3-pyridyl radical into the 1 position of the benzo[f]quinoline molecule made it possible to obtain substances that have anticholinesterase, antiviral, and hypotensive activity [1, 2]. In order to make a further search for new biologically active compounds in the benzo[f]quinoline series we studied the condensation of 3-[N-(2-naphthyl)formimidoyl]pyridine with acetophenone and its p-substituted derivatives in the presence of a proton catalyst; this made it possible to synthesize benzo[f]quinolines that contain a 3-pyridyl radical in the 3 position of the benzo[f]quinoline ring.



II—IV a R=H; b R=Br; c R=Cl; d R=CH$_3$; e R=OCH$_3$; f R=NO$_2$

The first step in the investigated reaction is nucleophilic addition at the azomethine bond of the enolized (under the influence of the catalyst) carbonyl compound with the formation of noncyclic β-arylamino ketones IIIa-f, which were isolated for all of the investigated CH acids when the reaction was carried out under mild conditions: heating the starting reagents at 50°C for 30-40 min. The β-arylamino ketones are capable of undergoing heterocyclization by refluxing alcohol solutions of them in the presence of a catalyst and an oxidizing agent; they are converted to 1-aryl-3-(3-pyridyl)benzo[f]quinolines IVa-f in this case. The latter can also be obtained by reaction of the starting azomethine and the corresponding CH acid in the presence of a catalyst. The hydrogen liberated during the heterocyclization reduces the starting azomethine to N-(3-pyridylmethyl)-2-naphthylamine V, which was isolated in a number of cases as an individual substance.

The structures of the synthesized compounds were confirmed by IR, UV, PMR, and mass spectral data (Tables 1 and 2).

The IR spectra of amino ketones III contain absorption bands of a conjugated carbonyl group (1675-1695 cm^{-1}) and an NH group (3250-3400 cm^{-1}). The shift of the band of the stretching vibrations of the amino group to the lower-frequency side is due to the

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TABLE 1. Physicochemical Characteristics of IIIa-f and IVa-f

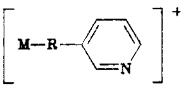
Compound	Empirical formula	mp, °C*	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	Yield, %
			C=O	NH		
IIIa	$C_{24}H_{20}N_2O$	173...174	1675	3400		71,0
IIIb	$C_{24}H_{19}BrN_2O$	164...165	1695	3260		83,0
IIIc	$C_{24}H_{19}ClN_2O$	165...166	1690	3260		78,0
IIId	$C_{25}H_{22}N_2O$	166...167	1690	3250		71,0
IIIe	$C_{25}H_{22}N_2O_2$	177...178	1675	3265		66,0
IIIf	$C_{24}H_{19}N_3O_3$	156...157	1695	3255		83,0
IVa	$C_{24}H_{16}N_2$	154...156			253 (4,50), 282 (4,64), 347 (3,74), 364 (3,74)	29
IVb	$C_{24}H_{15}BrN_2$	195...196			257 (4,57), 282 (4,71), 347 (3,77), 364 (3,87)	39
IVc	$C_{24}H_{15}ClN_2$	188...189			256 (4,56), 281 (4,70), 347 (3,76), 364 (3,76)	37
IVd	$C_{25}H_{18}N_2$	145...146			245 (4,37), 283 (4,59), 347 (3,61), 362 (3,61)	22
IVe	$C_{25}H_{18}N_2O$	145...146			243 (4,47), 281 (4,65), 346 (3,81), 362 (3,76)	25
IVf	$C_{24}H_{15}N_3O_2$	231...232			281 (4,79), 346 (3,91)	50

*The compounds were crystallized: IIIa-e from 2-propanol–benzene (3:1), IIIf and IVb-d, f from 2-propanol–toluene (4:1), and IVa, e from 2-propanol.

formation of an intermolecular hydrogen bond; in the spectra of 1 mmole/liter solutions of these compounds in CCl_4 the absorption bands of the NH group appear at 3425 cm^{-1}. The IR spectra of benzo[f]quinolines IV contain absorption bands of C–C and C–H bonds of aromatic rings at 1450-1600 and 3010-3060 cm^{-1}, respectively. The absorption bands at 750-760, 835, and 870 cm^{-1}, which are indifferent to the effects of substitution, can be assigned to the out-of-plane deformation vibrations of the C–H bonds of the benzo[f]quinoline ring [3]. 3-Substituted pyridine gives two absorption bands at 800-815 cm^{-1} and 710-712 cm^{-1} [4, p. 230].

The UV spectra of III are similar to the spectra of the amino ketones that we previously obtained in the reaction of 2(or 4)-[N-(2-naphthyl)formimidoylpyridines with p-substituted acetophenones [5, 6] and contain a system of absorption bands that are associated with local excitation of the phenyl chromophore [7, p. 32]. The UV spectra of IV, like the spectra of the benzo[f]quinolines that we studied [8], consist of a system of three bands: β (243-257 nm), p (281-283 nm), and α (346-364 nm), which have a vibrational structure. Electron-donor substituents (CH_3, OCH_3) do not affect the positions and intensities of the p and α bands but shift the β band hypsochromically with a simultaneous decrease in its intensity. The electron-acceptor NO_2 group increases the intensities of all of the absorption bands.

In the mass spectra of the β-arylamino ketones one observes a molecular-ion peak M^+ of medium intensity, rather intense peaks of $[M - RC_6H_4COCH_2]^+$ and $[M - C_{10}H_7NH]^+$ ions, which attest to the elimination of carbonyl and amino fragments, respectively, and a large number of peaks of fragment ions. In the mass spectra of the 1-aryl-3-(3-pyridyl)benzo[f]quinolines the most intense peaks are the molecular ion M^+ peaks, and peaks of $[M - H]^+$ and $[M - R]^+$ ions and the ion depicted below are also observed.



The ejection of neutral HCN molecules from the M^+ and $[M - R]^+$ ions with the formation of, respectively, $[M - HCN]^+$ and $[M - R - HCN]^+$ ions is characteristic. The presence of doubly charged M^{++} and $[M - R - HCN]^{++}$ ions in the spectra is typical for condensed aromatic systems.

The broad singlet at δ 4.91 ppm in the PMR spectrum of amino ketone IIIe is due to the resonance of the amino proton; the methylene protons give a multiplet at δ 3.52 ppm,

TABLE 2. PMR spectra of Benzo[f]quinolines IVa-e

Compound	Chemical shift, δ, ppm													SSCC, J, Hz							
	2-H, s	5-H, d	6-H, d	7-H, d	8-H, m	9-H, m	10-H, d	2'-H, 6'-H	3'-H, 5'-H	2''-H, br.d	4''-H, dd	5''-H, dd	6''-H, dt	$J_{5,6}$	$J_{7,8}$	$J_{9,10}$	$J_{2',3'}=J_{5',6'}$	$J_{2'',6''}$	$J_{4'',5''}$	$J_{4'',6''}$	$J_{5'',6''}$
IVa*	7,77	8,08	7,98	7,84	7,52	7,14	7,65			9,40	8,67	7,41	8,52	8,9	8,2	8,7		2,0	4,9	2,0	8,0
IVb	7,70	8,06	7,96	7,84	7,47	7,19	7,68	7,30 d	7,63 d	9,30	8,67	7,40	8,51	8,9	7,4	8,1	8,3	2,0	5,0	2,0	8,0
IVc	7,73	8,08	7,98	7,86	7,49	7,21	7,67	7,39 d	7,51 d	9,38	8,67	7,43	8,52	9,1	8,2	8,7	8,6	1,9	4,9	1,9	8,6
IVd**	7,77	8,09	7,99	7,85	7,48	7,19	7,75	7,34 s	7,34 s	9,39	8,68	7,43	8,54	9,0	8,1	7,2		2,0	4,9	2,0	8,3
IVe***	7,74	8,05	7,95	7,83	7,46	7,17	7,76	7,36 d	7,02 d	9,37	8,65	7,41	8,41	9,0	7,9	8,4	8,8	1,9	4,8	1,9	8,3

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*Signals of the protons of the benzene ring: 7.52 (2H, m, 2'-H and 6'-H), 7.46 ppm (3H, m, 3'-H, 4'-H, and 5'-H).

**The spectrum of IVd contains a singlet of protons of a methyl group at 2.50 ppm (3H, s, CH_3).

***The signal of the OCH_3 group of IVe is located at 3.89 ppm (3H, s, OCH_3).

while the methylidyne proton shows up as a broad triplet at δ 5.17 ppm (J = 5.7 Hz). Signals of aromatic protons are found at 6.64-8.78 ppm. The methoxy group gives a singlet at 3.87 ppm. In the PMR spectrum of cyclic product IVb one observes two doublets due to the resonance of the 5-H and 6-H protons at δ 8.06 and 7.96 ppm, respectively (J_{56} = 8.9 Hz), which are characteristic for the angular structure of the benzoquinoline ring. The presence of a one-proton singlet at δ 7.70 ppm indicates the presence of substituents in the 1 and 3 positions. The 4"-H and 5"-H protons of the 3-pyridyl ring form doublets of doublets at δ 8.67 and 7.40 ppm, respectively ($J_{4''5''}$ = 5.0, $J_{4''6''}$ = 2.0, $J_{5''6''}$ = 8.0 Hz), while the 2"-H proton gives a broad doublet at δ 9.36 ppm. The 6"-H proton shows up in the spectrum as a doublet of triplets at δ 8.51 ppm ($J_{6''5''}$ = 8.0, $J_{6''4''}$ = $J_{6''2''}$ = 2.0 Hz). The R substituent does affect the chemical shift of the protons of the substituted benzene ring but has virtually no effect on the chemical shifts of the protons of the benzo[f]quinoline ring. One should note the change in the position of the signal of the 10-H proton, which is close to the benzo[f]quinoline ring; this signal is shifted to weaker field when electron-donor CH_3 and OCH_3 groups are present. Other benzo[f]quinoline derivatives also have similar structures (see Table 2).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol (c = 10^{-4} mole/liter) were obtained with a Specord UV-vis spectrophotometer. The mass spectra were recorded with a Varian MAT-311A apparatus with direct introduction of the substances into the ion source at an ionizing-radiation energy of 70 eV and a vaporization temperature of 100-180°C. The PMR spectra of solutions in $CDCl_3$ were obtained with a Bruker WM-360 spectrometer (360 MHz) with tetramethylsilane (TMS) as the internal standard. The individuality of the compounds was determined by TLC on Silufol UV-254 plates in a CCl_4—ethanol—acetic acid system (10:1:1) with development in UV light. The results of analysis for C, H, and N were in agreement with the calculated values.

3-[N-(2-Naphthyl)formimidoylpyridine (I, $C_{16}H_{12}N_2$). A mixture of 1.43 g (10 mmole) of 2-naphthylamine, 1.07 g (10 mmole) of 3-formylpyridine, and 20 ml of ethanol was heated at 70-80°C for 5 min, after which it was cooled, and the resulting precipitated I was removed by filtration and crystallized from ethanol to give 2.21 g (95.3%) of I with mp 92-93°C and M^+ 232. IR spectrum 3080, 3060, 3030 (C—H); 1630 (C=N); 1616, 1585, 1510 (C=C); 1320 cm^{-1} (C—N).

[1-(4-Bromophenyl)-3-(3-pyridyl)-3-(2-naphthylamino)]-1-propanone (IIIb). A mixture of 2.32 g (10 mmole) of I, 2.19 g (11 mmole) of p-bromoacetophenone, 20 ml of 2-propanol, and four drops of concentrated HCl was heated at 50°C for 30-40 min. The residue obtained after evaporation of the solvent was treated three to four times with ether to remove the resinous impurities, neutralized with 25% ammonium hydroxide, washed with water until the wash water was neutral, and crystallized from 2-propanol—benzene to give 3.56 g of IIIb.

Amino Ketones IIIa, c-f. These compounds were similarly obtained.

1-(4-Bromophenyl)-3-(3-pyridyl)benzo[f]quinoline (IVb). A mixture of 2.32 g (10 mmole) of I, 2.19 g (11 mmole) of p-bromoacetophenone (IIb), 20 ml of 2-propanol, and 16-20 drops of concentrated HCl was heated for 1 h at 50°C and then for 2 h at 80-82°C. The precipitate that formed after cooling was removed by filtration, neutralized with 25% ammonium hydroxide, washed with water until the wash water was neutral, and crystallized from 2-propanol—toluene to give 1.6 g of IVb.

Benzo[f]quinolines IVa, c-f. These compounds were obtained similarly.

The mother liquor after the removal of product IVb was evaporated to give 0.24 g (10.4%) of N-(3-pyridylmethyl)-2-naphthylamine (V, $C_{16}H_{14}N_2$) with mp 123-125°C (two crystallizations from 2-propanol) and M^+ 234. IR spectrum: 3320 (N—H); 3060, 3030, 3020 (C—H); 1635 (N—H); 1605, 1580, 1550 (C=C); 1315, 1230 cm^{-1} (C—N).

Cyclization of [1-(4-Bromophenyl)-3-(3-pyridyl)-3-(2-naphthylamino)]-2-propanone. A mixture of 1.02 g (2.3 mmole) of IIIb, 20 ml of butanol, 10 drops of concentrated HCl, and 1 ml of nitrobenzene was heated for 4 h at 140-150°C. The precipitate that formed after cooling was removed by filtration, neutralized with 25% ammonium hydroxide, and washed with water until the wash water was neutral. This procedure gave 0.53 g (56%) of IVb.

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ADDITIVE CHARACTER OF THE RESONANCE CONSTANTS OF AZINYL GROUPS

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The increments for the endocyclic nitrogen atoms in various positions of the azine ring, which make it possible to calculate the resonance constants of azinyl groups via an additive scheme, were found. A correlation between the resonance constants and the π-electron charges in the corresponding ipso positions of the azine ring was noted. Correlated constants of the Hammett type, which quantitatively describe the CH acidities of methyl azines and the NH acidities of amino azines were derived.

The concept [1] of the dependence of the π-acceptor character of the azine ring on the number of endocyclic nitrogen atoms is generally accepted in the chemistry of heterocycles. A qualitative dependence was established on the basis of numerous data on the reactivities of functional derivatives of azines and their physical characteristics. However, a quantitative form of this dependence has not yet been found.

For a systematic study of the electronic effects of azinyl groups (Az) as substituents we compared the resonance constants of pyridyl (Py) [2], pyridazinyl (Pyd) [3], pyrimidyl (Pym) [4, 5], and triazinyl groups (s-Tr [6], as-Tr [7]) with the constants of the phenyl group (Ph); the phenyl group was regarded as the zero member of the series of azinyl substituents presented. The averaged values of the $\sigma_R{}^0$ and $\sigma_R{}^-$ resonance constants that were previously found by NMR spectroscopy for suitable model structures are presented in Table 1. The data pertaining to the phenyl group and regarded by us as reference points are discussed in greater detail below.

The $\sigma_R{}^0$ constants of the azinyl groups, which characterize only their mesomeric effect, were determined from the ^{13}C NMR spectra of phenylazines and the ^{19}F NMR spectra of fluorophenylazines in DMSO. A value of −0.11, which was derived as a result of statistical treatment of data for several correlation series [8], is usually adopted for the phenyl group. However, the sampling of the values of the constants that is used in this case primarily

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*Deceased.

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