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AMINATION OF 5-AZACINNOLINE WITH AROMATIC AMINES

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The 5-azacinnoline molecule was subjected to quantum-mechanical calculation by the Hückel method. The formation of 4-amino derivatives in the case of the reaction of 5-azacinnoline with aliphatic amines in the presence of an oxidizing agent and of 4,4'-bis(5-azacinnolinyl) in the case of dimerization in an oxygen-free medium was substantiated theoretically. The possibility of reactions with anions of aromatic amines was predicted by means of the Klopman method. It is shown that, in practice, the reaction is actually accelerated and that, in conformity with theory, the reaction center is the nitrogen atom of the aromatic amine. Possible products involving reaction with the participation of the p-carbon atom of the arylamine were not recorded. As in the case of aliphatic amines, the formation of a dimer was observed in an oxygen-free medium. The structures of the compounds obtained were proved by means of a combination of physicochemical methods.

We have recently shown [1] that 5-azacinnoline (I) reacts smoothly without catalysts with aliphatic amines (at 18-20°C for several days) to give the corresponding 4-amino-5-azacinnolines. However, aromatic amines did not undergo reaction under these conditions.

According to the concepts developed by Klopman [2], the reactivities of two compounds, one of which is a donor and the other an acceptor, are determined by the relative difference in the energies of the lower vacant molecular orbital (LVMO, E_{m+1}) of the acceptor and the upper occupied molecular orbital (UOMO, E_n) of the donor. If ($E_{m+1} - E_n$) is large and (E_n − E*$_{n-1}$) is small, the energy of the interaction between the boundary orbitals is insignificant, and the reaction is controlled by the distribution of charges in the molecules of the reagents. However, if ($E_{m+1} - E_n$) is small and ($E_n - E_{n-1}$) is large (degeneration of the boundary orbitals), the reaction is controlled by the distribution of the electron density on the boundary orbitals. The interaction (perturbation) energy can be estimated as $E = 2c_{i,m+1}c_{j,n}$, where $c_{i,m+1}$ and $c_{j,n}$ are the coefficients of the atomic orbitals (AO), respectively, for the LVMO of the acceptor and the UOMO of the donor. The strongest interaction will be observed between the atom (i) of the acceptor and that atom (j) of the donor for which these coefficients are maximal. If the molecule of one of the reagents (for example, the donor) contains only one reaction center (j is invariant), the reaction is controlled by the coefficients for the other reagent ($c_{i,m+1}$ of the acceptor).

Using the simple Hückel method [3] and the parameters in [3, 4] ($h_N = 0.5$, $h_{N'} = 0.55$, $h_{C'} = 0.1$, $K_{CN} = 0.8$, and $K_{NN} = 0.6$) we calculated the electron density distribution on the atoms in the 5-azacinnoline molecule and the $c_{i,m+1}$ coefficients for the LVMO (Table 1). The maximum positive π charge is observed for the carbon atom in the 6 position, and the maximum value of the $c_{i,m+1}$ coefficient from the carbon atoms is observed for the carbon atom in the 4 position. The coulombic interaction is small in the case of the reaction with aliphatic amines, the reaction is controlled by the boundary electron density, and the ring 4-C atom should be the most reactive atom. In fact, the formation of products of nucleophilic substitution of the 4-H atom by aliphatic amines has been observed [1].

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*The symbol E_{n-1} indicates the energy of the occupied orbital of the donor closest to E_n.

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TABLE 1. Charges and Coefficients of the AO for the LVMO of 5-Azacinnoline

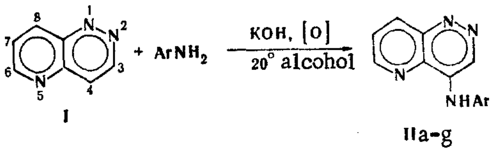
Atom i	1	2	3	4	5	6	7	8
Charge	−0,1874	−0,1210	0,0624	0,1008	−0,2212	0,1036	0,0344	0,0950
$c_{i,m+1}$	0,5375	−0,4718	0,0091	0,3752	−0,3042	0,3116	0,1658	−0,3363

The quantum-mechanical calculation also explains the formation of 4,4'-bis(5-azacinnolinyl) in the dimerization of I. In the radical of an aromatic compound the probability of finding the unpaired electron on any of the ring atoms is determined by the square of the coefficient of the corresponding AO for the LVMO [3]. Thus the electron is localized to a considerable degree in the 4 position of the 5-azacinnoline ring.

The application of the Klopman method for the reaction of azacinnoline with aromatic amines is particularly illustrative, since the calculated MO energies for the substrate and reagent are expressed in the same α and β units: $E_l = \alpha + q_l\beta$. One must compare the energies and coefficients of the AO for azacinnoline and the arylamine. The data for aniline [$c_{j,n}$ (Table 2) and E_n] taken from the tables in [5] ($h_N = 1$, and $K_{CN} = 1$) are presented below.

It is apparent from a graphical comparison that the ($E_{m+1} - E_n$) difference is comparable to ($E_n - E_{n-1}$) for neutral reagents. The boundary orbitals interact weakly, and in practice this is expressed in the fact that the reaction does not take place [1]. To intensity the activity one must lower E_{m+1}; this can be achieved by, for example, quaternization of azazinnoline. However, in this case another problem arises — which of the three nitrogen atoms will react? We therefore selected a second method — the effect on the nucelophile. During the formation of the anion from aniline the E_n value increases (h_n decreases) and approaches the value for the benzyl anion. Thus the $(E_n - E_{n-1}) > (E_{m+1} - E_n) \to 0$ criterion [2] is satisfied, and the relative reactivities of the various positions in the azacinnoline and arylamine molecules are determined by the product $c_{i,m+1} \cdot c_{j,n}$. It follows from a comparison of the coefficients of the LVMO for azacinnoline and the UOMO for aniline (we note that $c_{j,n}$ is also maximal for the benzyl anion) that the reaction of the nitrogen atom of aniline with the 4-C atom of azacinnoline is energetically most favorable. Similar relationships are observed during the theoretical examination of the reaction with α-naphthylamine.

In fact, it was found that the reaction of azacinnoline with aromatic amines is accelerated in the presence of alkali. 4-Arylamino-5-azacinnolines II (Table 3) are formed in an oxidative medium: In this case the signal of the 4-H proton vanished in the PMR spectrum, and the signal of the 3-H proton was converted from a doublet to a singlet; the UV spectra were similar to the spectra obtained in [1] for 4-alkylamino-5-azacinnolines. A bathochromic shift of the long-wave absorption band as compared with unsubstituted azacinnoline and a sharp increase in the extinction were observed; the IR spectrum (of IIa) contained a broad band of stretching vibrations of an associated amino group at 3410-3430 cm^{-1}. A dimerization product — 4,4'-bis(5-azacinnolinyl) — is formed without an oxidizing agent.



	a	b	c	d	e	f	g
Ar	C_6H_5	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3OC_6H_4$	$4\text{-}ClC_6H_4$	$\alpha\text{-}C_{10}H_7$	$\beta\text{-}C_5H_4N$	$4\text{-}NO_2C_6H_4$
$\bar{\sigma}$	0,00	−0,06	−0,08	0,25	0,05	0,5*	0,72
Yield of amine II, %	30	30	29	50	34	48	0

However, in contrast to aliphatic amines, the separation of the reaction mixtures was hindered: resinification was observed when the solutions were concentrated (probably because of the presence of alkali), and the bands of unchanged azacinnoline and arylamine, as well as the reaction product, were frequently overlapped during preparative separation on Al_2O_3.

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*Hypothetically.

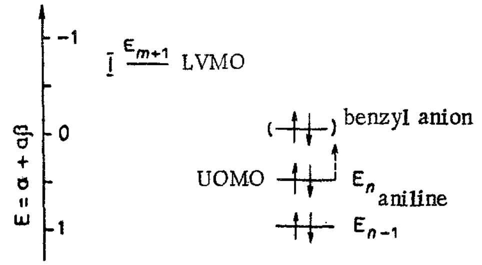

Fig. 1. Energy diagram for the reaction of 5-azacinnoline with aniline.

TABLE 2. Coefficients of the AO for the UOMO of Aniline

Atom j	1	2	3	4	7
$c_{j,x}$	0,3071	0,3872	−0,1119	0,4437	−0,6195

In the reaction under consideration the relative reactivities of aromatic amines should be determined by the ease of formation of the anion under the influence of alkali. Since direct data on the acidities of N–H protons are not available, one can estimate them by means of the σ constants (the average values from [6] are presented). A qualitative correlation is observed during the comparison: the yield of II increases as the acidity of the N–H bond increases. A more distinct correlation is impossible because of the difficulties involved in the complete isolation of amines II. It might have been expected that 4-nitroaniline would be the most reactive amine. However, the latter is inclined to undergo self-condensation in alkaline media: The reaction mixture resinified rapidly, and 80% of the starting azacinnoline was isolated during preparative separation.

Although the calculation predicts the highest reactivity for the nitrogen atom of the arylamine, one might also have expected participation of the carbon atom in the para position relative to the amino group in the reaction. This is known for the reaction of anilines with some nitrogen heterocycles under severe conditions (for example, see [7]); however, substances of this type cannot be detected in the reaction of azacinnoline with aniline. The reaction does not occur with diphenylamine and dimethylaniline.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with a Cary-15 spectrophotometer. The PMR spectra were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-20 spectrometer. The mass spectra were recorded with a Varian MAT-III with introduction of the substances into the ion source at an ionizing-electron energy of 80 eV and with an MKh-1303 spectrometer at 50 eV. Thin-layer chromatography (TLC) was carried out on activity II aluminum oxide at a layer thickness of 0.5 mm (1.5 mm in the case of preparative separation) in a benzene–methanol–chloroform system (9:1:1) with development by iodine vapors and in UV light.

Reaction of 5-Azacinnoline with Aromatic Amines. A 0.2-ml sample of a 4 M solution of KOH in methanol was added to a solution of 40 mg (0.3 mmole) of azacinnoline I and 1 mmole of arylamine in 1.5 ml of methanol, and the mixture was allowed to stand at room temperature (18-20°C) with access to the air for 20 days. It was then concentrated (but not to dryness), and the unchanged azacinnoline I (if present) was separated from the upper yellow (dark in UV) band with R_f 0.40-0.50, and the corresponding amino derivative II was separated from the yellow-brown (dark in UV) band. The yields and properties of the compounds obtained are presented in Table 3.

The reactions with diphenylamine and dimethylaniline were carried out similarly. At the end of the reactions, analysis by TLC showed the presence of only the starting reagents in the mixtures.

The reaction of azacinnoline I with aniline in an argon medium was carried out similarly. At the end of the reaction, the resulting precipitate was removed by filtration and

TABLE 3. Properties of 4-Amino-5-azacinnoline Derivatives IIa-f

Amine	R_f[a]	mp, °C	UV spectra, λ_{max}, nm (log ε)	PMR spectra,[c] ppm (aromatic portion)					M		Yield,[b] %
				3-H	6-H	7-H	8-H	arylamine residue	found[d]	calc.	
IIa	0,33—0,43 (0,40)	183	255 (4,15) 370 (3,96)	9,2	9,0	7,85	8,6	7,45s	212	212	33
IIb	0,32—0,43 (0,39)	129	256 (4,23) 373 (4,02)	8,6	8,65	7,5	8,1	7,0 s	236	236	30
IIc	0,37—0,37 (0,34)	153	256 (4,27) 369 (4,08)	8,9	8,7	7,6	8,4	7,25s	252	252	30
IId	0,30—0,38 (0,35)	169	254 (4,30) 372 (4,08)	8,9	8,9	7,75	8,5	7,35d 7,0 d	256	256	60
IIe	0,32—0,40 (0,36)	138	254 (4,17)[e] 370 (4,03)	8,5	8,6	7,6[f]	8,3	7,6m, 7,3 m	262	262	45
IIf	0,29—0,35 (0,32)	185	254 (4,22) 369 (4,08)	8,9	8,8	7,35	8,4	7,7m, 6,9 m	213	213	56

a) The R_f values of the preparative isolation band and the spot (in parentheses) are presented. b) Based on the converted azacinnoline. c) In dioxane—water (IIb in methanol, IIe in dioxane): 3-H, s; 6-H q, J_{67} = 4 Hz, J_{68} = 2 Hz; 7-H q, J_{76} = 4 Hz, J_{78} = 9 Hz; 8-H q, J_{86} = 2 Hz, and J_{87} = 9 Hz. d) By mass spectrometry; a detailed discussion of the mass spectra will be published separately. e) Shoulder. f) superimposed on the signal of the naphthylamine residue.

washed with alcohol. The yield of 4,4'-bis(5-azacinnolinyl), with mp >350°C, was quantitative, and its spectrum was identical to the spectrum obtained in [1].

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