REACTION OF 5-AZACINNOLINE WITH INDOLES

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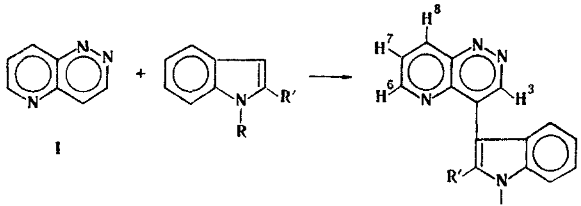
On the basis of the application of general valence molecular orbital (VMO) theory it is proposed that nucleophilic substitution of the hydrogen atom in the 5-azacinnoline molecule by indoles should proceed with the participation of the 4-C atom of azacinnoline and the 3-C atom of the indole and that the reaction of the reagents should be intensified in alkaline media in view of an increase in the level of the upper occupied molecular orbital (UOMO) of indole. All of the theoretical assumptions have been confirmed in practice. The corresponding indolylazacinnolines were isolated in the reaction of azacinnoline with indole and 2-methyl- and 1,2-dimethylindoles and were characterized by means of their PMR, UV, and mass spectra. 2,3-Dimethylindole does not undergo reaction.

General valence molecular orbital (VMO) theory makes it possible to successfully predict the reactivity of 5-azacinnoline (I) in its reaction with aromatic amines [1]. We have used a similar approach to estimate the possibility of nucleophilic substitution of the hydrogen atom in azacinnoline I on reaction with indoles. The energy diagram for this reaction (see Fig. 1) is similar to the diagram for arylamination. The reaction of the reagents in the presence of alkali should proceed more rapidly than the thermal reaction in the absence of bases, since when alkali is present, the level of the upper occupied molecular orbital (UOMO) of indole increases during the formation of the indolyl anion in view of the decrease in $h_{\ddot{N}}$. At the same time, it follows from the data in Table 1 that the 3-C atom of indole, for which the $c_{m,j}$ coefficient has its maximum value, should undergo reaction. As pointed out in [1], the 4-C atom, for which the $c_{n+1,i}$ coefficient has its maximum value, is the reaction center in azacinnoline molecule I.

We investigated the reaction of azacinnoline I with indole and 2-methyl-, and 1,2- and 2,3-dimethylindoles in isobutyl alcohol at 100°C and in the presence of alkali at 18-20°C; in both cases the reaction was stopped after 30 h, and the product (II) of substitution of a hydrogen atom was isolated.



I

IIa-c

II a $R=R'=H$; b $R=H$, $R'=CH_3$;
c $R=R'=CH_3$

In conformity with the conclusions of general VMO theory and the general specificity of electrophilic substitution reactions in indole, the 3-C atom of indole underwent reaction. Evidence for this was obtained from the results of the reaction of azacinnoline I with methylindoles (Table 2) — 2,3-dimethylindole did not undergo reaction — and from a study of the PMR spectra of the resulting indolylazacinnolines (Table 3). Thus, whereas a broad signal of an N–H proton at weak field and a signal from the α proton of the indole ring, which is superimposed on the quartet of the 8-H proton, are observed in the PMR spectrum of IIa, the signal of an α proton is, of course, absent in the PMR spectrum of IIb, and the signal of the N–H proton also vanishes in the spectrum of IIc. The disappearance of the signal of the 4-H proton and the conversion of the doublet of the 3-H proton to a singlet constitute evidence for substitution in the 4 position of the azacinnoline ring. Signals of all the re-

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TABLE 1. Coefficients of the AO for the UOMO of Indole [2]

Atom j	1 (N)	2	3	4	5	6	7
$[c_{m,j}]$	0,37	0,33	0,55	0,42	0,17	0,33	0,34

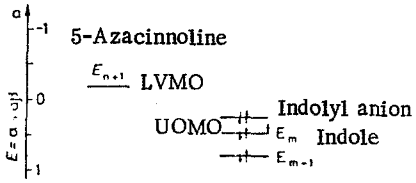

Fig. 1. Energy diagram for the reaction of 5-azacinnoline with indole.

TABLE 2. Reaction of 5-Azacinnoline with Indoles

Reagent	Yield, %		No.
	thermal	cat.	
Indole	28	21	IIa
2-Methylindole	46	39	IIb
1,2-Dimethylindole	65	0	IIc
2,3-Dimethylindole	0	0	—

maining protons — 6-H, 7-H, and 8-H — of the azacinnoline ring at 7.9-9.2 ppm and of the protons of the benzene ring at 7.0-7.5 ppm are observed in the PMR spectra of all three compounds (IIa-c). The absorption bands of the azacinnoline and indole rings are superimposed in the UV spectra of the indolylazacinnolines (Table 3) at 250-300 nm; in addition, a bathochromic shift and a sharp increase in the extinction of the long-wave absorption maximum of the azacinnoline ring are observed.

A study of the mass spectra of the compounds obtained (Table 3) confirms the structures proposed for them; the fragmentation of these substances under the influence of electron impact is the sum of the fragmentations of the 5-azacinnoline ring and the corresponding indole ring. Thus in the dissociative ionization of IIa processes that characterize the fragmentation of the indole ring [4] — loss of a hydrogen atom and hydrogen cyanide and acetylene molecules — are observed in addition to processes that characterize fragmentation of the 5-azacinnoline ring [3] — successive loss of nitrogen and hydrogen cyanide molecules.

It is apparent from the data in Table 2 that the yield of the thermal reaction product increases significantly as the number of methyl groups in the indole molecule increases. Within the framework of general VMO theory this increase in the reactivity is explained by an increase in the level of the UOMO under the influence of donor substituents, which intensifies the reaction between the reagents. In addition to this acceleration of the reaction, in the case of a number of substituted indoles one observes an overall acceleration of the reaction under the influence of alkali: the yields of reaction products in the presence of alkali at 20°C are almost equal to the yields of the thermal reaction products at 100°C. In the case of 1,2-dimethylindole the formation of a substitution product was observed only in the thermal reaction, probably in view of the impossibility of the formation of an anion under the influence of alkali under the selected conditions; as we have already mentioned, 2,3-dimethylindole did not give a final product, since the active 3 position is blocked by a methyl group.

Thus on the basis of the application of general VMO theory we have predicted and realized in practice direct nucleophilic substitution of a hydrogen atom in 5-azacinnoline by indoles; the theoretically most reactive atoms in the molecules of both reagents undergo reaction.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with a Cary-15 spectrophotometer. The PMR spectra of solutions of the compounds in DMSO were recorded

TABLE 3. Properties of Indolylazacinnolines IIa-c

Compound	R	R′	R_f*	mp., °C	UV spectrum, λ_{max}, nm (log ε)	PMR spectra (arom. region)						Mass spectra, m/e (intensity in percent on the maximum peak)
						N—H	α-H	3-H	6-H	7-H	8-H	
IIa	H	H	0,22—0,30 0,27	245—246	214 (4,84) 268 (4,21) 283 (4,15)	12,0	8,65	9,9	9,2	7,95	8,7	247 (7), 246 (42), 245 (16), 219 (2), 218 (5), 217 (5), 216 (3), 191 (4), 190 (4), 165 (4), 164 (3), 163 (4), 123 (13), 122 (27), 105 (42), 69 (100)
IIb	H	CH_3	0,30—0,37 0,34	232—233	214 (4,79) 275 (4,17) 286 (4,10)	11,6	—	9,7	9,2	7,95	8,9	261 (3), 260 (14), 259 (4), 232 (3), 231 (4), 230 (3), 205 (2), 204 (2), 125 (7), 123 (10), 122 (10), 112 (13), 111 (18), 109 (13), 105 (10), 69 (100)
IIc	CH_3	CH_3	0,46—0,55 0,51	186—187	214 (4,76) 283 (4,13) 292 (4,10)	—	—	9,5	9,1	7,9	8,8	275 (10), 274 (62), 273 (10), 259 (4), 246 (4), 245 (13), 244 (4), 231 (11), 230 (4), 229 (4), 218 (3), 217 (3), 205 (3), 204 (3), 203 (3), 145 (4), 144 (10), 143 (3), 125 (10), 123 (10), 122 (10), 112 (16), 111 (23), 109 (16), 69 (100)

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*The R_f values of the preparative isolation band and of the spot are presented.

with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were recorded with an MKh-1303 mass spectrometer with a modified system for introduction of the substances into the ion source at an ionizing-electron energy of 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 with iodine vapors and in UV light.

Reaction of 5-Azacinnoline with Indoles. Method A. A solution of 33 mg (0.25 mmole) of azacinnoline I and 0.3 mmole of the corresponding indole in 2 ml of isobutyl alcohol was heated at 100°C for 30 h, and the resulting mixture was separated by preparative TLC with isolation of the unchanged I and the corresponding indolylazacinnoline (Table 3).

Method B. A 33-mg (0.25 mmole) sample of azacinnoline I and 0.3 mmole of the corresponding indole were dissolved in 1 ml of methanol, 0.2 ml of a 4 M solution of KOH in methanol was added, and the mixture was maintained at 20°C for 30 h. The reaction mixtures were separated as in the preceding method.

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