AMINATION OF 5-AZACINNOLINE. INSTANCES OF FACILE NUCLEOPHILIC SUBSTITUTION OF THE HYDROGEN ATOM BY AN AMINO GROUP

M. F. Budyka, P. B. Terent'ev, and A. N. Kost

UDC 547.852.9'717'821:542.958.3

Direct nucleophilic substitution of the hydrogen atom by an amino group was observed in the case of 5-azacinnoline. The reaction with amines in the presence of an oxidizing agent under mild conditions leads to 4-amino-5-azacinnoline derivatives. Both electronic and steric factors affect the trend of the reaction. In the case of reactive amines the yields of the final products are close to quantitative. The formation of 4,4'-bis-5-azacinnolyl was observed in the absence of oxidizing agents. A probable scheme for the process that takes into account both possible reaction pathways is proposed. The structures of the products were proved by a combination of physicochemical methods and the results of elementary analysis.

It is known that the amination of nitrogen heterocycles usually takes place either in the presence of alkali metals or their amides [1, 2].

In a study to develop methods for the synthesis of azacinnolines it was shown that 5-azacinnoline (I) is capable of reacting with hydrazine hydrate in the absence of any alkaline catalysts to give 4-hydrazino-5-azacinnoline [3, 4].

In order to ascertain the limits of applicability of this direct noncatalytic amination we studied the reaction of I with various amines. Thus 4-(1-piperidyl)-5-azacinnoline (II*l*) was isolated in 75% yield by refluxing a solution of azacinnoline I in piperidine. Signals of a piperidine residue and a singlet of a 3-H proton (instead of the doublet in the spectrum of the starting compound) are observed in the PMR spectrum of II*l*. The 4-H signal vanishes, but the peaks of protons of the pyridine ring are retained (Table 2); this provides evidence for substitution in the 4 position. A bathochromic shift of the long-wave maximum and a sharp increase in the extinction as compared with the spectrum of starting I are observed in the UV spectrum of III. A molecular ion peak of maximum intensity [214 (100)],* peaks corresponding to initial fragmentation of the piperidine residue, and peaks [131 (24) and 103 (97)] of the characteristic fragment ions for the fragmentation of the 5-azacinnoline ring [3] are observed in the mass spectrum of II*l* (Table 2). The amination of azacinnoline I also takes place, although more slowly, at room temperature; this made it possible to compare the reactivities of various amines by determining the yield of reaction product from the relative integral intensity of the signals of the 3-H and 4-H protons in the PMR spectrum of the reaction mixture (Fig. 1).

It follows from the data obtained (Table 1) that aromatic amines, the nucleophilicity of the amino group of which is low, do not react with azacinnoline I under the conditions selected. In addition, no reaction with ammonia is observed. Aliphatic amines with relative low basicities ($pK_a < 10.0$) react slowly; we were able to isolate the substitution products only by heating and by the addition of a sufficiently strong oxidizing agent. Primary amines undergo the reaction somewhat more readily than secondary amines. The effect of steric factors is pronounced, and we were consequently unable to effect reaction with tert-butylamine.

During the reaction oxygen is absorbed from the air in an amount equivalent to the amount of amine formed. Water was detected in the reaction mixture by gas–liquid chromatography (GLC).

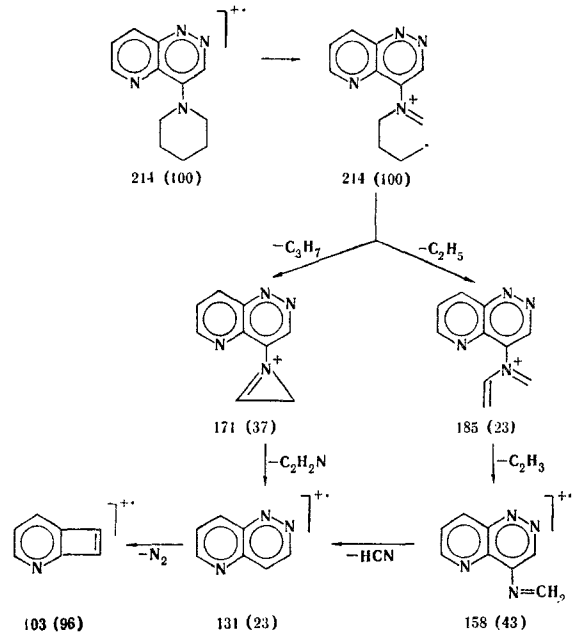
*Here and subsequently, the m/e values (intensities in percent relative to the maximum ion) are presented.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1554-1560, November, 1977. Original article submitted October 14, 1976.

 0009-3122/77/1311-1244 $07.50

TABLE 1. Reaction of 5-Azacinnoline with Amines at 20 deg C

Expt. No.	Reagent	pK_a (25°)	Reaction time, h	Yield of amine II, %
1	Ammonia (25% aqueous)	9,23	50	0
2	Methylamine (25% aqueous)	10,62	50	70
3	n-Butylamine	10,61	45	95
4	Benzylamine	9,37	50	0
5	Isopropyl amine	10,72	50	30
6	sec-Butylamine	10,56	50	20
7	Cyclohexylamine	10,64	50	50
8	Dimethylamine (33% aqueous)	10,77	50	20
9	Diethylamine	10,98	50	<5
10	Pyrrolidine	11,11	40	95
11	Piperidine	11,12	50	30
12	Morpholine	8,70	50	0
13	Aniline	4,58	50	0
14	p-Anisidine (in alcohol)	5,29	50	0
15	Ethylaniline	5,11	50	0
16	tert-Butylamine	10,53	50	0



Substitution of hydrogen in hetaryls usually proceeds particularly readily under the influence of hydroxyamine [2], since aromatization of the intermediate is facilitated by splitting out of the elements of water. It has been reported that 3-nitrocinnoline reacts with hydroxylamine at 27-30 deg C to give 4-amino-3-nitrocinnoline in 50-62% yield [5]. Azacinnoline I reacts with hydroxylamine in 15 min at room temperature to give 4-amino-5-azacinnoline (IIa) in quantitative yield.

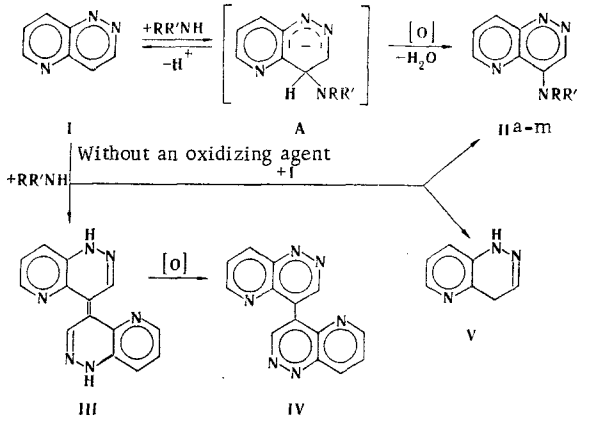


TABLE 2. Properties of 4-Amino-5-azacinnoline Derivatives

Compound	R	R'	R_f[a]	mp, °C	UV spectra, λ_{max}, nm (log ε)	PMR spectra, ppm[b]				Mass spectra, m/e (%)[c]
						3-H	6-H	7-H	8-H	
IIa	H	H	0,17 (0,14—0,19)	225[d]	250 (4,22) 347 (3,85)	8,6	8,7	7,6	8,2	147 (12), 146 (100), 118 (8), 91 (47), 78 (15), 65 (13), 64 (34), 63 (11)
IIb	H	CH_3	0,40 (0,35—0,43)	205[d]	255 (4,15) 361 (3,97)	8,3	8,6	7,5	8,1	161 (5), 160 (100), 159 (6), 132 (6), 131 (6), 104 (15), 103 (15), 97 (9)
IIc	H	C_2H_4OH	0,18 (0,13—0,21)	144	253 (4,20) 359 (4,03)	8,7	8,8	7,7	8,3	190 (24), 173 (11), 172 (17), 160 (10), 159 (100), 104 (17), 103 (10), 102 (14)
IId	H	C_4H_9	0,43 (0,31—0,48)	53	255 (4,17) 364 (4,05)	8,6	8,7	7,6	8,3	202 (23), 173 (14), 159 (100), 146 (14), 104 (20), 103 (19), 102 (17), 77 (17)
IIe	H	$CH_2C_6H_5$	0,43 (0,38—0,48)	115	251 (4,19) 357 (4,00)	8,6	8,8	7,7	8,4	237 (7), 236 (76); 131 (6), 106 (55), 105 (13), 104 (11), 103 (14), 91 (100)
IIf	H	$CH(CH_3)_2$	0,43 (0,35—0,50)	63	255 (4,11) 367 (4,00)	8,7	8,8	7,7	8,3	188 (46), 173 (100), 159 (19), 146 (10), 131 (10), 118 (21), 117 (17), 103 (17)
IIg	H	$CH(CH_3)C_2H_5$	0,40 (0,33—0,47)	156[e]	253 (4,21) 364 (4,07)	8,7	8,7	7,7	8,4	202 (20), 187 (4), 174 (7), 173 (100), 146 (2), 118 (2), 102 (3), 91 (4)
IIh	H	C_6H_{11}	0,39 (0,31—0,45)	123	255 (4,10) 365 (4,01)	8,8	8,9	7,8	8,4	228 (45), 185 (43), 171 (66), 157 (45), 147 (31), 146 (100), 130 (21), 103 (47)
IIi	CH_3	CH_3	0,48 (0,42—0,52)	104	256 (4,27) 371 (4,09)	8,6	8,8	7,6	8,2	175 (13), 174 (81), 159 (68), 146 (12), 145 (100), 121 (29), 104 (27), 103 (20)
IIj	C_2H_5	C_2H_5	0,43 (0,39—0,45)	85	257 (4,29) 368 (4,18)	8,6	8,8	7,6	8,2	202 (3), 174 (100), 173 (27), 159 (86), 146 (32), 104 (13), 103 (22), 91 (19)
IIk	$(CH_2)_4$		0,45 (0,30—0,51)	154	256 (4,26) 373 (4,19)	8,0	8,4	7,3	7,9	200 (100), 172 (33), 158 (50), 144 (26), 117 (19), 103 (96), 76 (33), 70 (92)
IIl	$(CH_2)_5$		0,47 (0,40—0,52)	128	257 (4,12) 382 (4,02)	8,7	8,8	7,6	8,3	214 (100), 171 (37), 159 (37), 158 (43), 157 (36), 146 (32), 131 (24), 103 (97)
IIm	$(CH_2)_2O(CH_2)_2$		0,44 (0,38—0,48)	193	255 (4,18) 373 (4,03)	8,5	8,7	7,7	8,1	216 (89), 198 (78), 185 (46), 173 (35), 171 (38), 159 (53), 104 (37), 103 (100)

[a]The bands of preparative isolation are given in parentheses. [b]In methanol; in trifluoroacetic acid in the case of IIm. Only the signals of the protons of the 5-azacinnoline ring are presented: 3-H, s; 6-H, 7-H, and 8-H, q; J_{67} = 4 Hz, J_{78} = 9 Hz, and J_{68} = 2 Hz. [c]The molecular peak and the seven most intense ion peaks are presented. [d]Sublimes. [e]This is the melting point of the picrate.

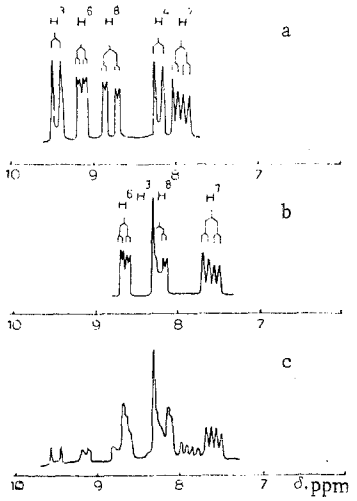


Fig. 1. PMR spectra: a) 5-azacinnoline (I); b) 4-methylamino-5-azacinnoline (IIb); c) reaction mixture 2 (Table 1, aromatic portion).

The reaction with ethanolamine proceeds in a more complex manner. At room temperature the reaction mixture takes on a lilac-crimson coloration, after which a dark precipitate of the dihydro dimer, to which we assigned structure III, begins to form gradually. In view of its easy oxidizability, III was recorded only by mass spectrometry; solutions of III in alcohol have a bright-crimson color that vanishes rapidly in air, during which 4,4'-bis-5-azacinnolyl (IV) precipitates. We assumed that ethanolamine, because of its high viscosity, is saturated with oxygen slowly, as a result of which amination, for which an oxidizing agent is necessary, is hindered and dimerization takes place. In fact, the reaction of I with butylamine in glycerol, the viscosity of which is close, leads to the slow formation of dimer IV rather than to amine IId. In addition, nucleophilic substitution product IIc was isolated when air was bubbled through a solution of azacinnoline I in ethanolamine.

When the reaction was carried out in an oxygen-free medium, the formation of dimer IV was observed in the case of all of the reactive amines but was not observed for the nonreactive amines (see Table 1). Dihydro-5-azacinnoline V and nucleophilic substitution product IIh were detected in a chromatographic mass-spectral investigation of the reaction mixture in an experiment with cyclohexylamine (in argon). If an oxidizing agent (for example, potassium ferricyanide salt) is added to the reaction medium, the corresponding amine II is formed even in an argon atmosphere, although the reaction is complicated, particularly when the mixture is heated, because of the oxidation of the amine and other side processes (the products of which we did not identify).

The first step in the reaction is evidently the formation of σ complex A [6], which is subsequently oxidized to nucleophilic substitution product II. The detection in the reaction medium of dihydro-5-azacinnoline V and amine IIh in the case of reaction in argon provides evidence that 5-azacinnoline I itself is capable of dehydrogenating the intermediate σ complex, probably by acceptance of a hydride ion. Of course, the extent of this process is only slight (< 1%), and the principal reaction pathway in the absence of an oxidizing agent is the formation of dimer IV. It is difficult to say whether the latter is formed through σ complex A or through one-electron transfer with subsequent dimerization of the ion radicals; however, dimerization also does not occur with amines that, because of insufficient nucleophilicity or steric hindrance, do not form nucleophilic substitution products of the II type with I. Dimerization processes of this type have also been described as side reactions in Chichibabin amination and in a number of other reactions involving nucleophilic substitution of a hydrogen atom [6]. The impossibility of the formation of dimer IV from amine II under the reaction conditions was proved by special experiments.

Unfortunately, we were unable to identify the σ complex in the reaction mixture by means of the UV spectra because of the presence in it of colored dimeric reaction products. However, the use of the PMR spectra for this purpose requires the presence of this complex in the reaction mixture in sufficient concentrations.

The assumption of the alternative occurrence of the reaction through covalent hydration with subsequent replacement of the hydroxyl group by an amino group is not confirmed, since none of the products possible in this case was detected (by TLC) in the reaction of I with aqueous trimethylamine.

The reactions of 5-azacinnoline with ethanolamine (pK_a 9.44) and particularly with hydroxylamine (pK_a 5.80), which despite their lower (and extremely low in the case of hydroxylamine) basicities as compared with other amines, quite readily form substitution products. The increased reactivities of the two reagents can probably be explained by the formation in the initial instant of the reaction of a hydrogen bond through the hydroxyl group and the p orbital pair of electrons of the nitrogen atom in the 5 position. This sort of approach of the reagents should considerably facilitate the subsequent nucleophilic attack; the increased reactivity of ethanolamine in other aromatic nucleophilic substitution reactions has been explained in a similar manner [7]. Another argument in favor of this explanation is provided by the fact that when O-methylhydroxylamine was subjected to the reaction, TLC analysis after 15 min showed the absence of any other compounds but starting I in the reaction mixture. Hydroxylamine hydrochloride is usually employed in the reaction with the subsequent addition of excess alkali [5]. We varied the ratio of these reagents and found that an alkaline medium is necessary for efficient amination, This may be associated with ionization of the N–H bond, which leads to the formation of a more nucleophilic anion.

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 external standard. The IR spectra were recorded with an IKS-22 spectrometer. The chromatographic mass-spectral studies were made with a Varian MAT-111 apparatus with a 2-m long column filled with SE-30 on Chromosorb. The mass spectra were obtained with the same apparatus with introduction of the substances into the ion source at an electron ionizing energy of 80 eV and also with an MKh-1303 spectrometer at 50 eV. Gas–liquid chromatography was carried out with an LKhM-8MD chromatograph with a 2-m long column filled with 5% Carbowax on Cellite. Thin-layer chromatography was accomplished on activity II aluminum oxide with a layer thickness of 0.7 mm (1.5 mm in the case of preparative separation) in a benzene–methanol–chloroform system (9 : 1 : 1). The chromatograms were developed with iodine vapors and in UV light.

Reaction of 5-Azacinnoline with Amines. A 2-ml sample of a 0.85 M solution of the azacinnoline I in the amine was allowed to stand at room temperature (18-20 deg C) for 50 days, after which the excess amine was removed by vacuum distillation, and the residue was dissolved in methanol. The PMR spectrum of this solution was recorded. Unchanged I was separated chromatographically from the yellow (dark in UV light) band with R_f 0.55-0.75, after which the corresponding amino derivative II was separated. The reaction times and the yields of the amines are presented in Table 1, and the properties of the compounds obtained are presented in Table 2.

The gas–liquid chromatogram was recorded in the case of the reaction with n-butylamine. The column temperature was 120 deg C, the vaporizer temperature was 200 deg C, and the retention time of the water peak was 1 min and 20 sec. The separation of the reaction mixtures and the isolation of the unchanged azacinnoline I (when it was present) and the reaction products in all of the examples presented below (except for the dimer) were also accomplished by preparative TLC.

4-Amino-5-azacinnoline (IIa). A solution of 230 mg (4 mmole) of potassium hydroxide in 1 ml of methanol was added dropwise to a solution of 40 mg (0.3 mmole) of I and 140 mg (2 mmole) of hydroxylamine hydrochloride in 3 ml of methanol. The mixture was worked up after 15-20 min to give 42 mg (95%) of IIa. IR spectrum: ν_{NH} 3320 (mineral oil); 3410 and 3525 cm^{-1} (chloroform).

4-(2-Hydroxyethylamino)-5-azacinnoline (IIc). Air was bubbled rapidly through a solution of 52 mg (0.4 mmole) of I in 1 ml of ethanolamine for 20 days, after which the excess ethanolamine was removed by vacuum distillation, and 45 mg (60%) of IIc was isolated.

4-Benzylamino-5-azacinnoline (IIe). A 1-ml sample of a solution containing potassium hydroxide and potassium ferrocyanide (1 M in each component) was added at 50 deg C to a solution of 52 mg (0.4 mmole) of I in 1 ml of benzylamine. After 5 days, the precipitate was removed by filtration, the solvent was removed from the filtrate by distillation, and the residue was extracted with alcohol. Workup of the extract gave 29 mg (31%) of IIe.

4-Dimethylamino-5-azacinnoline (IIi). A 1-ml sample of a solution containing potassium hydroxide and potassium ferrocyanide (0.8 M in each component) was added to a solution of 40 mg (0.3 mmole) of I in 1.5 ml of 33% aqueous dimethylamine. After 24 h, the mixture was extracted with benzene, and the extract was worked up to give 12 mg of unchanged azacinnoline I and 24 mg of amino derivative IIi (65% based on the converted 5-azacinnoline). The reaction proceeded similarly in argon.

4-Diethylamino-5-azacinnoline (IIj). A 1-ml sample of a solution containing potassium hydroxide and potassium ferrocyanide (1 M in each component) was added to a solution of 52 mg (0.4 mmole) of I in 1 ml of diethylamine. After 2 days, the mixture was extracted with benzene, and the extract was worked up to give 25 mg of unchanged azacinnoline I and 12 mg of amino derivative IIj (30% based on the converted 5-azacinnoline).

4-(1-Piperidyl)-5-azacinnoline (IIl). A solution of 100 mg (0.76 mmole) of I in 10 ml of piperidine was refluxed for 25 h, after which the excess piperidine was removed by distillation to give 50 mg of unchanged azacinnoline I and 60 mg of amino derivative IIl (75% based on the converted 5-azacinnoline). Found: N 25.6%. $C_{12}H_{14}N_4$. Calculated: N 26.2%.

4-(1-Morpholyl)-5-azacinnoline (IIm). A solution of 52 mg (0.4 mmole) of I in 2 ml of morpholine was heated at 90 deg C for 80 h, after which the excess morpholine was removed by vacuum distillation to give 20 mg of unchanged azacinnoline I and 35 mg of amino derivative IIm (65% based on the converted 5-azacinnoline).

4,4'-Bis(5-azacinnolyl) (IV). A) A solution of 52 mg (0.4 mmole) of I in 0.5 ml of amine was heated in an ampul with argon at 80 deg for 10 h, after which the precipitate was removed by filtration and washed with alcohol to give 51 mg (99%) of a product with mp > 350 deg C. PMR spectrum (CF_3COOH): 8.1 (q, J_{76} = 4 Hz, J_{78} = 9 Hz, 7-H), 8.9 (q, J_{86} = 2 Hz, J_{87} = 9 Hz, 8-H), 9.1 (q, J_{67} = 4 Hz, J_{68} = 2 Hz, 6-H), and 10.2 ppm (s, 3-H). Mass spectrum: 260 (25), 233 (17), 232 (100), 231 (18), 205 (18), 204 (81), 203 (22), 181 (17), 178 (13), 177 (16), 153 (12), 150 (9), 103 (17), 102 (20), 100 (13). Found: N 32.3%. $C_{14}H_8N_6$. Calculated: N 32.3%.

Dihydro dimer III was detected when the mass spectrum of the precipitate was recorded immediately after isolation without washing with alcohol: 262 (8), 261 (8), 260 (32), 233 (23), 232 (100), 231 (21), 205 (22), 204 (66), 203 (18), 181 (17), 178 (15), 177 (17), 153 (15), 151 (10), 150 (10), 131 (12), 103 (20), 102 (17).

In the reaction with cyclohexylamine the combined filtrates after washing the precipitated dimer IV were concentrated, and the chromatographic mass spectrogram was recorded. The column temperature was raised from 100 to 220 deg C at a rate of 10 deg/min; the injector temperature was 240 deg C, and the separator temperature was 220 deg C. The retention time of the dihydro-5-azacinnoline (V) peak was 13 min and 20 sec. Mass spectrum of V: 133 (15), 105 (30), 104 (67), 79 (100). Amino derivative IIh emerged from the column 60 min after injection; its mass spectrum was similar to the spectrum previously obtained.

B) A solution of 10 mg (0.05 mmole) of 4-(1-piperidyl)-5-azacinnoline (IIl) in 0.3 ml of piperidine was heated in an ampul under a nitrogen atmosphere at 80 deg C for 10 h. At the end of the heating period, TLC analysis showed the presence of only the starting compound in the reaction mixture.

LITERATURE CITED

1. T. Kauffmann and W. Schoeneck, Angew. Chem., 71, 285 (1959).
2. A. F. Pozharskii and A. M. Simonov, Chichibabin Amination of Heterocycles [in Russian], Izd. Rostovsk. Univ., Rostov-on-Don (1971).
3. V. G. Kartsev, Master's Dissertation, Moscow State University (1975).
4. A. N. Kost, P. B. Terent'ev, V. G. Kartsev, and M. F. Budyka, USSR Inventor's Certificate No. 533594 (1975); Byul. Izobr., No. 40, 63 (1976).
5. H. E. Baumgarten, J. Am. Chem. Soc., 77, 5109 (1955).
6. I. Ya. Postovskii and O. N. Chupakhin, Usp. Khim., 45, 909 (1976).
7. R. G. Shepherd and I. L. Fedrick, Adv. Heterocycl. Chem., 4, 145 (1965).
8. Landolt-Bornstein, Zahlenwerte und Funktionen, 6 Aufl., Bd. 2, Teil 7, Tab. 2781.