

REACTION OF 5-AZACINNOLINE WITH THIOLS

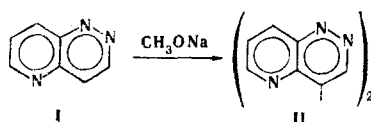
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UDC 547.852.9

Previous conclusions regarding the reactions of 5-azacinnoline with mild bases at the C(4) atom were confirmed: the corresponding 4-mercapto-5-azacinnoline derivatives are formed in the reaction of this compound with primary, secondary, and tertiary mercaptans and thiophenol under mild conditions. The effect of the temperature, basic catalysts, and oxidizing agents on the yields of the reaction products was studied. Assumptions regarding the mechanism of the process are expressed.

It has recently been shown [1] that 5-azacinnoline (I) reacts with aliphatic amines under mild conditions in the presence of oxidizing agents to give the corresponding 4-amino-5-azacinnolines. 4,4'-Bis(5-azacinnolyl) (II) is formed in the absence of an oxidizing agent.

We carried out a number of experiments with other nucleophiles and found that the reactions with various alkoxide anions at room temperature,  $-30^{\circ}\text{C}$ , and  $70-100^{\circ}\text{C}$  lead to the formation of only dimer II:



Alkanethiols react very slowly at room temperature with azacinnoline I (after 1 month, the yield of the reaction product is only 3-5%), and the reaction is complicated by oxidation of the thiol to the disulfide. However, the reaction mixture is resinified when it is heated. If the reaction is carried out in triethylamine, 4-alkylthio-5-azacinnolines IIIa-g are formed in up to 40% yields (Table 1). Replacement of triethylamine by an equivalent amount of a solution of sodium alkoxide in alcohol led only to resinification of the mixture; however, when catalytic amounts of the alkoxide are present, the reaction proceeds rapidly, and the product (IIIi) is obtained in almost quantitative yield. In the case of thiophenol we were able to show that arenethiols also react in this way.

It should be noted that thiols that have both an unbranched (IIIa,b,e) and a branched (IIIc,d,i) carbon skeleton readily undergo reaction with azacinnoline I. The yields in the n-butyl, isobutyl, and sec-butyl series change only slightly, whereas steric factors play a significant role in the reaction with amines [1]. Under alkaline catalysis conditions, tert-octyl mercaptan gives substitution product IIIi in high yield. This can probably be explained by the considerably greater size of the sulfur atom and the high nucleophilicity of the mercaptide ion, which equalizes the effect of the hydrocarbon chain.

The incorporation of an alkylthio group in the 4 position of the azacinnoline ring is manifested in the PMR spectra of 4-alkylthio-5-azacinnolines IIIa-i as disappearance of the signal of the 4-H proton and conversion of the 3-H doublet to a singlet, as in the case of amination [1]. This reaction pathway confirms the previous assumption that, according to the general valence molecular orbital (VMO) theory, the C(4) atom of the azacinnoline ring should be the most active atom in reactions with mild bases such as S-nucleophiles [2].

The UV spectra of IIIa-i (Table 2) are similar to one another and to the spectrum of unsubstituted 5-azacinnoline. The band at 360-400 nm ( $\log \epsilon \sim 2$ ) corresponds to an  $n-\pi^*$  transition and is often superimposed on the band of the  $\pi \rightarrow \pi^*$  transition, which is shifted bathochromically [330-350 nm ( $\log \epsilon \sim 4$ )] as compared with unsubstituted azacinnoline I and

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TABLE 1. Synthesis of 4-Mercapto-5-azacinnoline Derivatives (III)

Compound	R	Amount of I, mole · 10 <sup>-4</sup>	Reaction time, days	Yield, % <sup>a</sup>	R <sub>f</sub> <sup>b</sup>	mp, °C
IIIa	C <sub>2</sub> H <sub>5</sub>	3	55	60 (44)	0.51/0.63	153
IIIb	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	2	65	75 (41)	0.55/0.45	74
IIIc	<i>i</i> -C <sub>4</sub> H <sub>9</sub>	7	65	60 (29)	0.56/0.39	67
IIId	<i>s</i> -C <sub>4</sub> H <sub>9</sub>	5	55	65 (29)	0.61/0.43	85
IIIe	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	5	35	— (27)	0.56/0.58	71
IIIf	CH <sub>2</sub> CH=CH <sub>2</sub>	4	60	55 (24)	0.53/0.31	118
IIIg	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	4	30	— (41)	0.70/0.41	125
IIIh	C <sub>6</sub> H <sub>5</sub>	5	65	70 (34)	0.65/0.42	150
IIIh <sup>c</sup>	C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	2	10	95 (75)	0.64/0.46	105

<sup>a</sup>Based on the amount of converted azacinnoline, determined from the PMR spectra; the values in parentheses are the yields based on the amount of I subjected to reaction. <sup>b</sup>On Al<sub>2</sub>O<sub>3</sub>/Silufol; the R<sub>f</sub> values of 5-azacinnoline were 0.56/0.17. <sup>c</sup>A 1 ml sample of a 1 M solution of NaOCH<sub>3</sub> in CH<sub>3</sub>OH was used in place of triethylamine.

TABLE 2. UV Spectra and PMR Spectra of 4-Mercapto-5-azacinnoline Derivatives

Compound	λ <sub>max</sub> , nm (lg ε)	δ <sup>a</sup> , ppm			
		3-H	6-H	7-H	8-H
IIIa	235 (3.97), 349 (3.94)	9.1	8.8	7.7	8.4
IIIb	246 (4.17), 259 (4.23), 339 (4.13), 348 (4.13)	9.2	9.0	7.7	8.7
IIIc	235 (4.00), 255 (4.60), 339 (3.98), 348 (3.98)	9.1	9.0	7.7	8.6
IIId	235 (3.90), 255 (3.97), 340 (3.90), 350 (3.90)	9.2	9.0	7.7	8.6
IIIe	236 (3.52), 256 (3.60), 317 (3.28), 336 (3.48), 346 (3.47)	9.1	8.9	7.6	8.6
IIIf	235 (3.77), 332 (3.72), 344 (3.71)	8.7	8.4	7.2	8.0
IIIg	235 (4.10), 336 (4.10), 345 (4.10), 253 (4.10)	9.2	8.9	7.0 <sup>b</sup>	8.6
IIIh	225 (3.85), 340 (3.51)	8.1	8.8	7.6	8.3
IIIi	235 (4.87), 258 (4.94), 280 (4.52), 320 (4.61), 350 (4.81)	9.5	9.1	7.4	8.8

<sup>a</sup>Aromatic portion; solutions in CCl<sub>4</sub> (in deuteroacetone in the case of IIIf): 3-H, s; 6-H, 7-H, and 8-H, q; J<sub>6,7</sub> = 4 Hz, J<sub>7,8</sub> = 9 Hz, J<sub>6,8</sub> = 2 Hz. <sup>b</sup>Superimposed on the signal of the phenyl ring.

has a characteristic vibrational structure. The latter is absent in the case of 4-phenylthio-5-azacinnoline (IIIh).

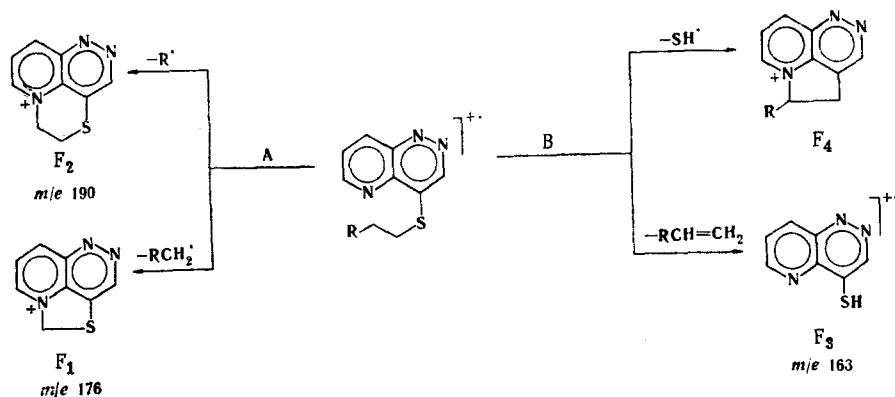
A rather appreciable molecular-ion peak, the intensity of which decreases as the aliphatic chain becomes longer or its degree of branching increases, is observed in the mass spectra of III (except for IIIb,e,i). The fragmentation of the molecular ions is similar in many respects to the dissociative ionization of 8-alkyl- or 8-alkoxyquinolines [3] and, in addition, is similar to the fragmentation of alkylthioarenes [4]. The first pathway leads to intense peaks of F<sub>1</sub> or F<sub>2</sub> ions, whereas the second leads to F<sub>3</sub> and F<sub>4</sub> ions. Fragmentation via pathway A is the predominant process in the case of unbranched alkyl groups, and fragmentation via pathway B predominates in the case of branched groups (Table 3).

Loss by the molecular ion of particles with 33 (SH) and 44 amu (CS) is observed in the spectra of IIIf-h; this is characteristic for aromatic sulfides. It should be noted that the

TABLE 3. Mass Spectra of 4-Mercapto-5-azacinnoline Derivatives

Compound	m/e (relative intensity, %)*
IIIa	191 (92), 190 (35), 176 (11), 163 (18), 162 (33), 158 (46), 148 (11), 107 (13), 106 (13), 105 (31), 104 (16), 103 (89), 91 (58), 85 (22), 83 (33), 57 (100), 56 (27), 55 (82)
IIIb	219 (4), 190 (74), 186 (36), 177 (18), 176 (58), 163 (41), 162 (15), 159 (16), 158 (70), 149 (61), 148 (35), 135 (26), 134 (19), 108 (18), 104 (28), 103 (100), 102 (30), 91 (48), 90 (15), 69 (19), 64 (34), 63 (52), 57 (26), 55 (34), 51 (37)
IIIc	219 (9), 204 (10), 186 (28), 177 (19), 176 (100), 163 (29), 135 (11), 104 (17), 103 (43), 102 (11), 91 (25), 76 (21), 75 (21), 64 (14), 63 (21), 57 (28), 55 (21), 51 (24)
IIId	219 (7), 204 (43), 190 (15), 186 (21), 176 (100), 163 (13), 97 (13), 85 (10), 83 (16), 81 (11), 71 (21), 69 (26), 57 (53), 56 (23), 55 (40)
IIIe	233 (5), 205 (12), 204 (28), 200 (33), 191 (18), 190 (83), 189 (14), 178 (16), 177 (53), 176 (83), 175 (17), 173 (25), 172 (100), 171 (20), 164 (17), 163 (83), 162 (57), 158 (30), 157 (19), 156 (18), 150 (13), 149 (46), 148 (43), 147 (12), 145 (12), 144 (33), 136 (14), 135 (40), 134 (22), 132 (14), 131 (12), 130 (22), 118 (11), 117 (23), 108 (21), 104 (28), 103 (56), 102 (22), 91 (33), 90 (17), 78 (18), 77 (13), 76 (21), 75 (16), 69 (16), 67 (14), 64 (16), 63 (19), 57 (13), 55 (17)
IIIf	203 (10), 175 (23), 174 (48), 170 (100), 142 (10), 130 (15), 103 (73), 91 (11), 90 (11), 76 (31), 75 (20), 64 (24), 63 (41), 57 (14), 51 (20), 50 (14)
IIIg	253 (21), 224 (27), 103 (12), 92 (13), 91 (100), 69 (10), 65 (39), 63 (13), 57 (10), 52 (12)
IIIh	239 (100), 238 (27), 211 (45), 210 (67), 167 (12), 166 (16), 139 (11), 110 (15), 109 (20), 102 (25), 83 (14), 81 (11), 77 (12), 71 (21), 69 (25), 67 (12), 57 (45), 55 (43)
IIIi	275 (0.02), 163 (42), 57 (100), 55 (15)

\*The molecular ions and ions with m/e > 50 and J > 10% are presented.



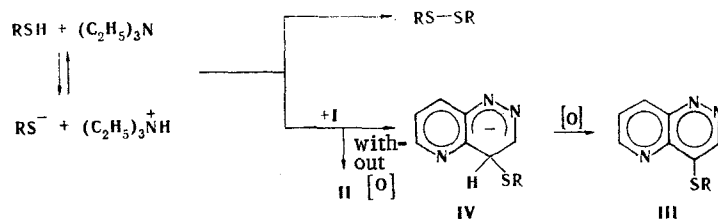
ease of formation of F<sub>1</sub> and F<sub>2</sub> ions once again emphasize the presence of an alkylthio group in the 4 position, since the intensities of the peaks of the F<sub>1</sub>-F<sub>4</sub> ions should have been insignificant in the case of the 3 or 6 isomers.

It may be assumed that the reaction of azacinnoline I with mercaptides proceeds through the formation of  $\sigma$  complex IV, since long-wave absorption maxima at 550-850 nm ( $\log \epsilon \sim 2$ ), which are characteristic for complexes of this type [5], appear in the UV spectrum of a mixture of thiophenol and I in alcohol. Unfortunately, because of its low concentration, we were unable to confirm the formation of a  $\sigma$  complex by means of PMR spectroscopy.

When the reaction was carried out under mild conditions, in addition to substituted 5-azacinnoline III, unchanged azacinnoline I and the disulfide were detected in the reaction mixture at the end of the process in most cases, and the starting thiol was not detected (the ratio of I and III was determined from the intensities of the signals of the 3-H protons in the PMR spectra of the reaction mixtures [1]). The presence of unchanged azacinnoline I in the mixture is evidently explained by the higher rate of oxidation of the thiol to the disulfide as compared with the rate of substitution.

A necessary condition for the occurrence of the substitution reaction is oxidation by oxygen. The disulfide apparently does not participate in the reaction, since in the case of

reaction of azacinnoline I with dibutyl disulfide in an argon atmosphere at 200°C a study of the reaction mixture by chromatographic mass spectrometry showed that substitution product III was absent in it. Thus the role of oxygen probably reduces to oxidation of the intermediately formed  $\sigma$  complex IV.



The attempted thiylation of azacinnoline I in the absence of an oxidizing agent led to the formation of dimer II, evidently via a scheme similar to the scheme in [1].

#### EXPERIMENTAL

The UV spectra of solutions of the compounds in heptane were recorded with a Cary-15 spectrophotometer. The PMR spectra were recorded on a T-60 or XL-100 instrument with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with a modified system for introduction of the substance into the ion source at an ionizing energy of 50 eV. The chromatographic mass-spectral study was made with a Varian MAT-111 spectrometer at an ionizing-electron energy of 80 eV.

The degree of purity of the compounds obtained was monitored by means of chromatography in a loose layer of aluminum oxide [neutral activity II (Brockmann classification)] on 12 × 18 cm plates with a layer thickness of 0.3 mm or on Silufol UV-254. A benzene-methanol-chloroform system (9:1:1) was used in all cases. The chromatograms were developed with UV light or iodine vapors. Preparative separation of the substances was carried out on 18 × 24 cm plates with a 1.5-3 mm thick layer of aluminum oxide or on 15 × 15 cm Silufol plates.

General Method for the Synthesis of Substituted 4-Mercapto-5-azacinnolines (III). A mixture of azacinnoline I, 5 ml of dry triethylamine, and 0.1 ml of the corresponding thiol (commercial preparations were used) was allowed to stand at room temperature with access to the air, after which the solvent was removed by vacuum distillation, and the residue was separated preparatively in a thick layer of aluminum oxide. After the solvent front reached the upper edge of the plate, the chamber was opened a third, and the plate was allowed to stand in it until the R<sub>f</sub> value of the upper yellow band reached 0.75. A mixture of I and III, which was separated on Silufol plates by the method described above, was isolated from the resulting bright-yellow (dark in UV light) band. The corresponding substituted 4-mercapto-5-azacinnoline III (Tables 1-3) was isolated from the upper yellow (dark in UV light) band. Elementary analysis was performed in the case of IIIe. Found: C 61.6; H 6.5; N 17.7%. C<sub>12</sub>H<sub>8</sub>N<sub>3</sub>S. Calculated: C 61.7; H 6.7; N 18.0%. The good agreement in the results shows that chromatographic monitoring of the purity of the compounds obtained is sufficient.

#### LITERATURE CITED

1. M. F. Budyka, P. B. Terent'ev, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, No. 11, 1554 (1977).
2. M. F. Budyka, P. B. Terent'ev, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, No. 6, 809 (1978).
3. S. D. Samble, D. A. Lighthner, O. Bunchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 97 (1967).
4. Y. K. MacLeod and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 1840 (1966).
5. *Sigma Complexes in Synthesis and Analysis* [in Russian], NIITEKhIM, Moscow (1976).