5-AZACINNOLINES

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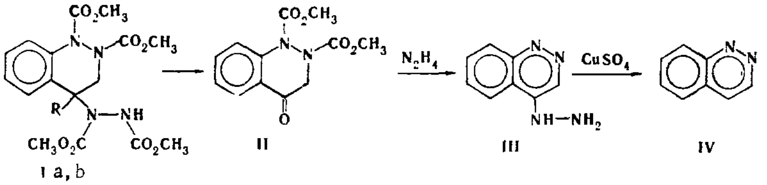
Adducts of 4-phenyl-1,2,4-triazoline-3.5-dione with 2-vinylpyridines were converted to 5-azacinnolines and 4-hydrazino-5-azacinnolines on reaction with hydrazine hydrate.

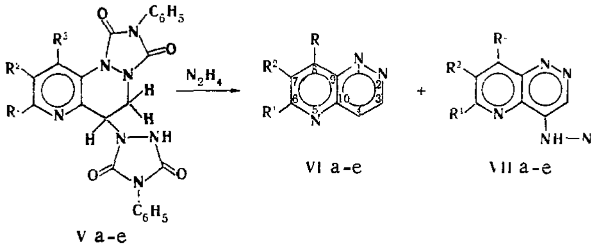
In a study of the structure of adducts of styrene derivatives with dimethyl azodicarboxylate Alder and Niclas [1] showed that the diadduct with structure Ia is hydrolyzed to ketone II, which can be converted to cinnoline IV via the scheme



I a R=OCH$_3$, b R=C$_6$H$_5$

The adduct (Ib) of α-phenylstyrene with dimethyl azodicarboxylate undergoes a different series of transformations under the influence of hydrazine hydrate. In this case, the final product is N-amino-3-phenylindole.

We have previously shown [2] that 2-vinylpyridine and its derivatives react with 4-phenyl-1,2,4-triazoline-3,5-dione to give adducts with structure V. We investigated the behavior of the latter in the reaction with hydrazine hydrate. It was found that the starting material had vanished after V had been refluxed for 7 h in excess hydrazine hydrate, and 5-azacinnolines VI and 4-hydrazino-5-azacinnolines VII – compounds that are the first representatives of the previously unknown 5-azacinnoline heterocyclic system – were obtained after chromatographic separation of the reaction mixture.



V, VI, VII a R^1=R^2=R^3=H; b R^1=CH$_3$, R^2=R^3=H; c R^2=CH$_3$, R^1=R^3=H; d R^2=C$_2$H$_5$, R^1=R^3=H; e R^3=CH$_3$, R^1=R^2=H

The mechanism of this transformation is as yet unknown, but it evidently includes solvolysis with opening of the triazole ring, decarboxylation, and oxidative aromatization. According to the available data [1], the latter may take place under the influence of hydrazine hydrate, which is reduced to ammonia in the process.

The characteristics of VI and VII and of their derivatives are presented in Table 1.

The UV spectra of the 5-azacinnolines obtained in this study (Table 2) had absorption maxima identical to those observed for cinnoline [λ_{max} (log ε): 222 (4.57), 276 (3.45), 322 (3.34), and 390 (2.4)] [3] but, as seen from Table 1, had a small hypsochromic shift. The introduction of a hydrazine group in the 4 position leads to a bathochromic shift of the long-wave absorption maximum with a sharp increase in the extinction.

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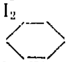
TABLE 1. 5-Azacinnolines and Their Derivatives

Compound	R^1	R^2	R^3	R^4	mp, °C	Empirical formula	Found, %			Calculated, %			M		R_f	Yield, %
							C	H	N	C	H	N	found*	calc.		
VIa	H	H	H	H	89	$C_7H_5N_3$	64,1	3,9	31,9	64,1	3,8	32,1	131	131,1	0,40	14
VIb	CH_3	H	H	H	146	$C_8H_7N_3$	66,1	4,9	29,1	66,2	4,8	29,0	145	145,06	0,36	13
VIc	H	CH_3	H	H	149	$C_8H_7N_3$	66,2	4,9	29,1	66,2	4,8	29,0	145	145,06	0,38	15,5
VId	H	C_2H_5	H	H	80	$C_9H_9N_3$	67,8	5,6	26,5	67,9	5,7	26,1	159	159,08	0,41	16
VIe	H	H	CH_3	H	65—66	$C_8H_7N_3$	66,1	4,9	29,1	66,2	4,8	29,0	145	145,06	0,39	12,5
VIIa	H	H	H	$NHNH_2$	50—51	$C_7H_7N_5$	—	—	43,3	—	—	43,5	161	161,07	0,23	7
VIIb	CH_3	H	H	$NHNH_2$	56—58	$C_8H_9N_5$	—	—	39,8	—		40,0	175	175,09	0,25	5
VIIc	H	CH_3	H	$NHNH_2$		$C_8H_9N_5$	—	—	40,2	—	—	40,0	175	175,09	0,24	6
VIId	H	C_2H_5	H	$NHNH_2$		$C_9H_{11}N_5$	—	—	36,8	—	—	37,0	189	189,1	0,28	5
VIIe	H	H	CH_3	$NHNH_2$		$C_8H_9N_5$	—	—	39,9	—	—	40,0	175	175,09	0,28	4
VIII	H	H	H	NHN = 	Picrate decomposed at 121°	$C_{13}H_{15}N_5$	64,7	6,1	29,1	64,7	6,2	29,1	241	241,13	0,50	90
IX	H	C_2H_5	H	NHN=CH—Ph	220	$C_{14}H_{11}N_5$	67,5	4,4	28,0	67,5	4,4	28,1	249	249,10	0,53	85
X	H	H	H	$NHN{=}C(CH_3)CH_2COCH_3$	227	$C_{12}H_{13}N_5O$	59,1	5,4	—	59,3	5,4	—	243	243,11	0,26	70
XI	H	H	H	3,5-Dimethyl-1-pyrazolyl	198	$C_{12}H_{11}N_5$	—	—	31,0	—	—	31,1	225	225,10	0,46	80
XII	H	H	CH_3	$NHNC(CH_3)_2$	126—128	$C_{10}H_{11}N_5$	59,6	5,4	34,8	59,7	5,5	34,8	201	201,10	0,47	75

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*By mass spectrometry.

TABLE 2. UV Spectra of 5-Azacinnoline Derivatives in Alcohol

	VIa	VIb	VIc	VId	VIe	VIIa	VIIb	VIIc	VIId	VIII	IX	X	XI	XII
λ_{max}, nm (lgε)	262 (3,59) 271 (3,51) 304 (3,60) 316 (3,61) 370 (2,06)	264 (3,76) 300 (3,77) 313 (3,81) 360 (2,43)	252 (3,51) 258 (3,54) 265* (3,46) 310 (3,63) 323 (3,67) 366 (2,34)	252 (3,59) 262 (3,62) 267* (3,58) 313 (3,70) 325 (3,75) 365 (2,41)	265 (3,62) 271* (3,61) 305 (3,59) 317 (3,57) 370 (2,30)	256 (3,83) 262 (3,84) 265 (3,84) 268 (3,83) 283 (3,80) 385 (3,79)	260* (3,82) 265 (3,85) 268* (3,83) 279 (3,82) 292* (3,80) 372 (3,88)	254 (3,76) 294 (3,53) 308 (3,52) 322 (3,48) 370 (3,59)	252 (3,82) 298 (3,61) 312 (3,60) 327 (3,56) 373 (3,68)	259 (4,10) 305 (3,45) 380 (4,04)	213 (4,55) 273 (4,34) 300* (4,48) 330 (4,38) 386 (4,52) 480 (3,66)	255 (4,30) 282 (4,13) 315 (4,32) 442 (4,46) 468 (4,55)	204 (480) 260 (3,57) 268 (3,51) 316 (3,91)	237 (4,12) 305 (3,56) 320* (3,64) 372 (4,08)

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*Inflection.

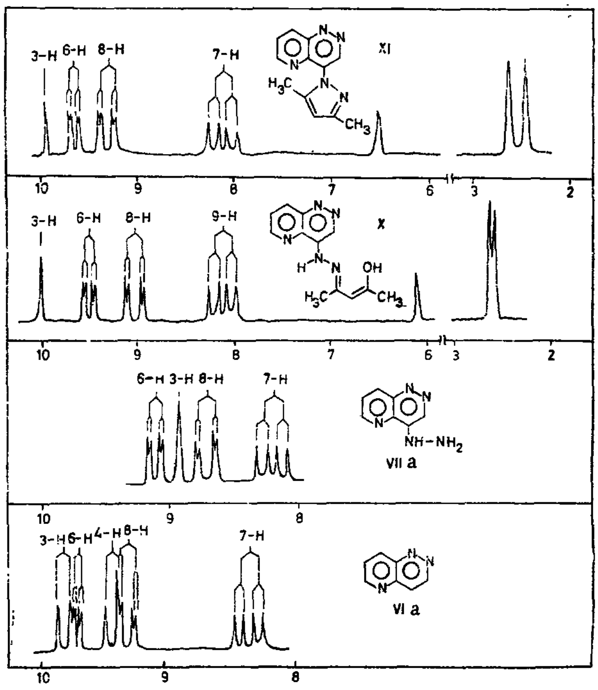
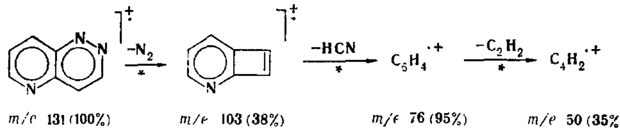


Fig. 1. PMR spectra of VIa, VIIa, X, and XI in trifluoroacetic acid.

The PMR spectra of VIa and VIIa are presented in Fig. 1.

The mass spectra of VI had few lines, the most intense of which was that of the molecular ion; and subsequent fragmentation consisted in the successive elimination of nitrogen and hydrocyanic acid fragments. For example, for VIa



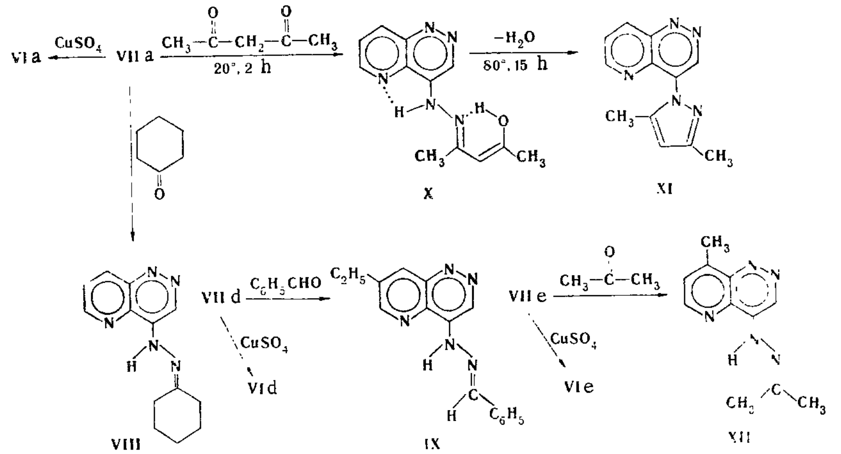
Fragmentation involving the hydrazine groups with splitting out of the elements of NH, NH_2, N_2H_4, and N_2H_3 was observed together with this sort of fragmentation in the spectrum of 4-hydrazino-5-azacinnolines VII.

The IR spectrum of VIIa (in chloroform) had an intense absorption band of the stretching vibrations of an NH group at 3470 cm^{-1}, a doublet of bands at 3380 and 3510 cm^{-1} (NH_2 group), and intense bands of the deformation vibrations of an amino group at 1622 and 1593 cm^{-1} (the latter probably runs together with the aromatic ring absorption). The IR spectra of VIIb-e are similar.

As one should have expected, hydrazines VIIa-e are readily oxidized in the air. They undergo complete conversion to 5-azacinnolines when they are refluxed in alcohol with copper sulfate; this corresponds to conversion of phenylhydrazine to benzene or of III to cinnoline IV [1].

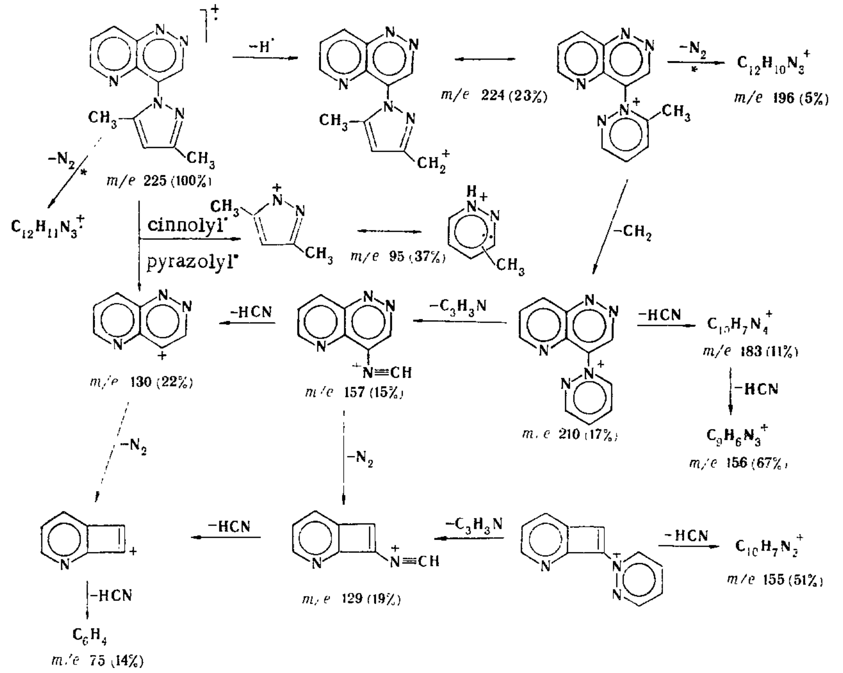
The corresponding hydrazones (VIII, IX, and XII) are formed in the reaction of hydrazine VIIa with cyclohexanone, VIId with benzaldehyde, and VIIe with acetone at room temperature. Compound VIIa reacts with acetylacetone to give hydrazone X, which is stable even in trifluoroacetic acid. It is converted to 4-(3.5-dimethyl-1-pyrazolyl)-5-azacinnoline (XI) only on prolonged heating in benzene. The PMR spectra of X and XI are presented in Fig. 1

Compound X evidently exists entirely in the enol form, since its IR spectrum does not contain the absorption of a carbonyl group, and a singlet of an olefinic proton at 6.2 ppm is observed in its PMR spectrum (see Fig. 1). The high stability of hydrazone X is probably explained by stabilization due to the formation of intramolecular hydrogen bonds. In fact, on reaction with solutions of copper, cobalt, and nickel salts, it readily forms intensely colored complexes that are soluble in organic solvents.



Compounds X and XI behave very similarly under the influence of electron impact. In the first case one observed only mass spectrometric splitting out of a water molecule, and the subsequent fragmentation proceeds via two pathways: The first is characteristic for the fragmentation of 5-azacinnoline (see above), and the second is characteristic for the fragmentation of 3,5-dimethylpyrazole [4] (see the fragmentation diagram).

Diagram of the fragmentation of the molecular ion of 4-(3.5-dimethyl-1-pyrazolyl)-5-azacinnolineXI



Thus, in contrast to the adducts (I) of α-phenylstyrene with dimethyl azodicarboxylate, V undergoes conversion with retention of the 5-azacinnoline ring under the influence of hydrazine hydrate. However, rearrangement processes are not observed.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of chloroform solutions were recorded with IKS-22 and UR-20 spectrometers. The UV spectra of methanol solutions were recorded with a Pye-Unicam-8000 spectrophotometer. The PMR spectra of trifluoroacetic acid solutions were recorded with a T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were recorded with MKh-1303 and Gnom MAT-111 spectrometers with introduction of the substances into the ionization region at ionizing-electron energies of, respectively, 50 and 80 eV. Preparative chromatography was accomplished on activity II (Brockmann classification) Al_2O_3 (with a layer thickness of 1 mm) in a benzene–methanol system (10 : 1).

5-Azacinnolines (VI). These compounds were obtained by the following general method. A solution of 0.01 mole of V in 20 ml of hydrazine hydrate was refluxed for 7 h, after which the excess hydrazine hydrate was removed by distillation. The residue was extracted repeatedly with cold methanol, and azacinnolines VI were isolated preparatively from the combined extracts and purified by vacuum sublimation.

4-Hydrazino-5-azacinnolines (VII). These compounds were isolated similarly from the band with the R_f value indicated in Table 1. Prolonged vacuum drying gave red-brown crystals of hydrazines VII.

Acetylacetone (5-Aza-4-cinnolyl)hydrazone (X). A solution of 95 mg (0.6 mmole) of hydrazine VIIa and 0.5 ml of acetylacetone in 50 ml of methanol was allowed to stand at room temperature for 24 h, after which the methanol and excess acetylacetone were removed by distillation, and the residue was separated preparatively on Al_2O_3. Workup of the band with R_f 0.18-0.3 yielded hydrazone X as a crystalline red-brown substance. The product was recrystallized from methanol to give 100 mg of X.

Cyclohexanone (5-Aza-4-cinnolyl)hydrazone (VIII). Cyclohexanone [100 mg (1 mmole)] was added to a solution of 80 mg (0.5 mmole) of hydrazine VIIa in 3 ml of methanol, and the mixture was allowed to stand at room temperature for 6 h. The methanol was evaporated, and the residue was separated preparatively. Workup of the band with R_f 0.47-0.53 yielded hydrazone VIII. Recrystallization of the product from benzene gave 109 mg of VIII.

Benzaldehyde (7-Ethyl-5-aza-4-cinnolyl)hydrazone (IX). Benzaldehyde [106 mg (1 mmole)] was added to a solution of 95 mg (0.5 mmole) of hydrazine VIId in 2 ml of methanol, and the mixture was allowed to stand for 1 h. The resulting precipitate was then removed by filtration and recrystallized from methanol to give 106 mg of IX.

Acetone (8-Methyl-5-aza-4-cinnolyl)hydrazone (XII). An 85-mg (0.5 mmole) sample of hydrazine VIIe was dissolved in 5 ml of acetone, and the solution was allowed to stand at room temperature for 5 h. The acetone was evaporated, and the residue was separated preparatively. Workup of the band with R_f 0.44-0.50 yielded hydrazone XII. Recrystallization from hexane gave 75 mg of XII.

4-(3,5-Dimethyl-1-pyrazolyl)-5-azacinnoline (XI). A solution of 80 mg (0.33 mmole) of hydrazone X in 10 ml of benzene was refluxed for 15 h, after which the benzene was removed by distillation. The residue was separated preparatively. Workup of the band with R_f 0.42-0.5 gave greenish crystalline XI, which was purified by vacuum sublimation to give 60 mg of XI.

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