RECYCLIZATION OF 1-AMINO-3,5-DIARYL-2,6,6-TRICYANOCYCLOHEXA-1,3,-DIENES TO PYRIDINE DERIVATIVES

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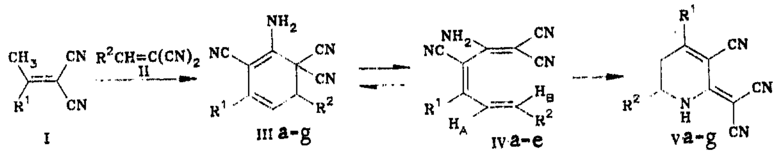
The base-catalyzed recyclization of 1-amino-3,5-diaryl-2,6,6-tricyanocyclohexa-1,3-dienes to 2,4-diaryl-5-cyano-6-dicyanomethylene-1,2,3,6-tetrahydropyridines, 4,6-diaryl-3-cyano-2-dicyanomethylene-1,2-dihydropyridines, and 4,6-diaryl-3-cyano-2-dicyanomethylpyridines has been investigated. The intermediate products of this reaction — cis,trans-2-amino,4,6-diaryl-1,1,3-tricyanohexa-1,3,5-trienes — have been isolated; on heating these are transformed reversibly into the initial cyclohexadienes or they isomerize irreversibly into trans,trans-hexatrienes, while in the presence of a base (piperidine, diethylamine, triethylamine, KOH), they cyclize to form the above-mentioned pyridine derivatives.

It has been established previously that the products of the cross-dimerization of 3-aryl-2-cyanobut-2-enonitriles (I) and of 3-aryl-2-cyanopropenonitriles (II) — 1-amino-3,5-diaryl-2,6,6-tricyanocyclohexa-1,3-dienes (III) — recyclize to form the pyridine derivatives (Va-g) [1, 2]. In the present investigation, this reaction has been studied in more detail.



III—V a,c,e $R^1=C_6H_5$, b $R^1=4\text{-}ClC_6H_4$, d $R^1=4\text{-}CH_3C_6H_4$; a, b, d $R^2=C_6H_5$, c $R^2=$ $=4\text{-}ClC_6H_4$, e $R^2=4\text{-}FC_6H_4$; V f, g $R^1=4\text{-}ClC_6H_4$; f $R^2=4\text{-}ClC_6H_4$, g $R^2=4\text{-}FC_6H_4$

We have shown that the thermally unstable cyclohexadienes (IIIa-g) [1] readily undergo an electrocyclic transformation with the opening of the ring at the $C_{(5)}-C_{(6)}$ bond and the formation of the cis-hexatrienes (IVa-e).

In the PMR spectrum (acetone-d_6) of the cyclohexadiene (IIIa), an AB system of protons was observed with chemical shifts of 5.73 and 4.52 ppm and SSCC $^3J_{AB}$ = 4 Hz [1, 2]. Under these conditions the protons of the cis-hexatriene (IVa) also formed an AB system, but with signals at 7.36 and 6.65 ppm ($^3J_{AB}$ = 16 Hz, Table 1). The substantial difference between the SSCCs of the protons of compounds (IIIa) and (IVa) has permitted their interconversion to be recorded by the PMR method. For example, the heating in sealed tubes to 100°C of solutions both of the cyclohexadiene (IIIa) and of the cis-hexatriene (IVa) led to the formation of mixtures of them in ratios of 1:5 (in deuteroacetone) and 2:3 (in deuterochloroform). It has been established preparatively that the ratio of the concentrations of these compounds in xylene is 1:1 (100°C). Consequently, the position of the equilibrium (IIIa) $\rightleftarrows$ (IVa) depends appreciably on the polarity of the medium. We may note that the electrocyclic transformations of substituted cyclohexadienes and noncyclic hexatrienes have been widely studied and have already become classical. The opening of the ring and cyclization on heating take place in disrotatory fashion and reversibly [3], but they have not hitherto been observed in the enaminonitrile series.

The prolonged heating of xylene solutions both of the cyclohexadiene (IIIa) and of the cis-hexatriene (IVa) at 100°C led to the formation of the stable trans-hexatriene (VIa), which no longer cyclized into the cyclohexadiene (IIIa). The invariability of the SSCCs of

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TABLE 1. PMR Spectra (acetone-d_6) of Compounds (IVa-d) and (VIa), δ, ppm

Compound	NH_2	Ar,m	A—H, d	B—H, d	$^3J_{AB}$,Hz
IVa	8,34; 8,10	7,40	7,36	6,65	16,0
IVb	8,38, br.s	7,40	*	6,76	16,5
IVc	8,39, br.s	7,40	*	6,70	16,0
IVd	8,22; 8,05	7,40	7,29	6,65	15,5
VIa	8,04, br.s	7,41	7,63	6,80	16,0

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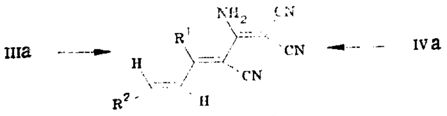
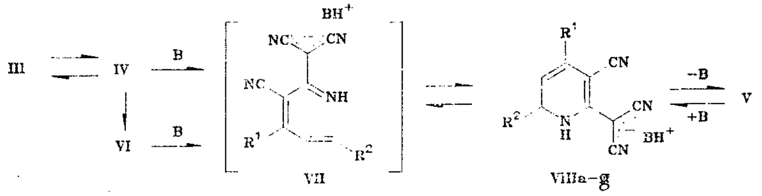
*Overlapping with the multiplet of the aromatic protons.

the A—H and the B—H protons as the result of the conversion of the triene (IVa) into (VIa) indicated the isomerization of compound (IVa) relative to just the $C_{(3)}$—$C_{(4)}$ double bond, since the trans configuration of the $C_{(5)}$—$C_{(6)}$ double bond was retained, and the presence of two identical substituents (nitrile groups) at the $C_{(1)}$ carbon atom excluded such a possibility for the $C_{(4)}$—$C_{(2)}$ double bond.



VI a $R^1=R^2=C_6H_5$

The result of heating ethanol solutions of the trienes (IV) and (VIa) with an excess of a base (diethylamine, piperidine, triethylamine, KOH) was the formation in high yields of the salts (VIIIa-g), which, under the action of acids, were converted reversibly into the corresponding tetrahydropyridines (V). Compounds (VIIId-g) were also obtained at room temperature by treating the cyclohexadienes (IIIa-g) with 2 N ethanolic KOH. The recrystallization of the cyclohexadienes (III) into the tetrahydropyridines (V) apparently took place with the intermediate formation of the hypothetical compounds (VII) which underwent electrocyclization to compound (VIII) under the reaction conditions.



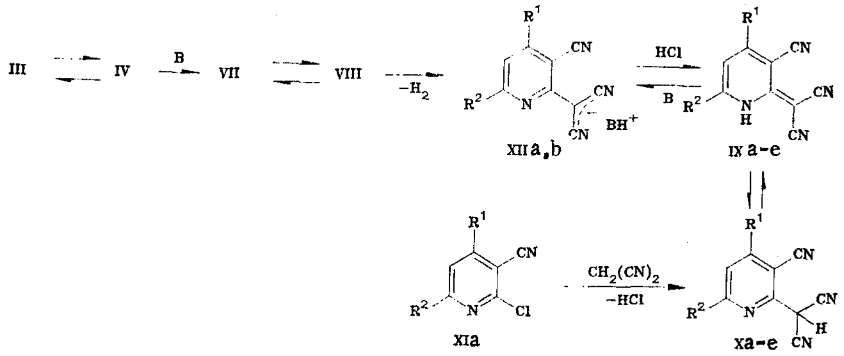
VIII a—f $R^1=C_6H_5$, g $R^1=4\text{-}CH_3C_6H_4$; a—d, g $R^2=C_6H_5$, e $R^2=4\text{-}FC_6H_4$, f $R^2=4\text{-}ClC_6H_4$; a $B=(C_2H_5)_3N$, b $B=(C_2H_5)_2NH$, c B=piperidine, d-g B=KOH

In the IR spectra of the tetrahydropyridines (Va-g) strong absorption bands in the 2220-2190 cm^{-1} corresponded to conjugated nitrile groups. An absorption band at 3260 cm^{-1} was due to the stretching vibrations of an NH group bound by a hydrogen bond. The formation of the salts (VIII) led to a lowering of the frequency of the stretching vibrations of the nitrile group to 2150-2000 cm^{-1} and to a broadening of these absorption bands. The absorption band of the NH group was, as a rule, shifted into the region of higher frequencies (Table 2).

When xylene solutions of the cyclohexadienes (III) were heated to boiling for 1 h with an excess of an organic base and were then cooled and were treated with concentrated hydrochloric acid, mixtures of the pyridines (IXa-e) and (Xa-e) were obtained. Their structures were confirmed by spectral methods and by independent synthesis — in particular, by the reaction of 2-chloro-3-cyano-4,6-diphenylpyridine (XIa) with malonodinitrile in DMFA in the presence of sodium hydride.

TABLE 2. IR Spectra of Compounds (Va-g) and (VIIIa-g)

Compound	ν, cm^{-1}		Compound	ν, cm^{-1}	
	NH	CN		NH	CN
Va	3250	2220, 2200	VIIIa	3280	2180, 2140
Vb	3270	2210, 2190	VIIIb	3240	2200, 2170, 2140
Vc	3250	2210, 2190	VIIIc	3260	2200, 2180, 2140
Vd	3250	2220, 2220	VIIId	3340	2200, 2160
Ve	3240	2210, 2190	VIIIe	3300	2200, 2160
Vf	3260	2210, 2190	VIIIf	3300	2200, 2160
Vg	3270	2220, 2200	VIIIg	3320	2200, 2150



IX—XIIa, IX, Xd e $R^1=C_6H_5$, IX, X, XIIb $R^1=4\text{-}CH_3C_6H_4$, IX, Xc $R^1=4\text{-}ClC_6H_4$; IX, Xa–c, XIa, XIIa,b $R^2=C_6H_5$, IX, Xd $R^2=4\text{-}FC_6H_4$, e $R^2=4\text{-}ClC_6H_4$; XIIa,b B=KOH

In the IR spectra of the majority of pyridines (IX) and (X), only weak broad absorption bands were observed in the 3250-3220 cm^{-1} region which it is difficult to assign unambiguously to the vibrations of a NH group. An exception was the pyridine (IXb), in the IR spectrum of which a strong absorption band was observed at 3350 cm^{-1} corresponding to the stretching vibrations of a NH bond. In the Raman spectra of pyridines (IXa) and (Xa) absorption bands were observed at (cm^{-1}) 2260 (m.br.), 2220 (s), 2204 (m), and 2175 (s), which are characteristic for conjugated and nonconjugated nitrile groups. The pyridines (IX) and (X) apparently existed in solutions and crystallized from them as mixtures of the two forms [(IX) $\rightleftarrows$ (X)]. These compounds were also readily converted into the high-melting crystalline salts (XIIa, b) in a 2 N ethanolic solution of KOH.

EXPERIMENTAL

IR spectra were taken on UR-10 and Perkin-Elmer 457 instruments (in KBr tablets), and Raman spectra on a Coderg T-800 instrument using the 5145 Å green line of an argon laser for excitation. Mass spectra were measured on a LKB-2091 instrument (under standard conditions). PMR spectra were recorded on Tesla BS-4870 and Bruker XH-90E instruments (80 MHz and 90 MHz, respectively) using 10% solutions in $(CD_3)_2CO$, with TMS as internal standard. Chromatograms of solutions of the substances were obtained on Kavalier light-sensitive plates in acetone–hexane (3:4) and tetrahydrofuran–hexane (2:1) solutions.

The characteristics of the compounds synthesized are given in Tables 1-3.

2-Amino-4,6-diaryl-1,1,3-tricyano-1,cis-3,trans-5-hexatrienes (IVa-e). A mixture of 0.01 mole of a cyclohexadiene (III) [1, 2] and 30 ml of xylene was heated to boiling. After 10 min, a pale yellow precipitate deposited from the boiling solution, and this was filtered off and washed with hot xylene and with hexane. In this way the analytically pure trienes (IVa-e) were obtained with a yield of 50%. The initial compounds (III) remained in the mother solutions. The solutions were boiled again for a few minutes, giving an additional 25-30% of the trienes (IV) containing the trienes (VI) as an impurity.

2,4-Diaryl-5-cyano-6-dicyanomethylene-1,2,3,6-tetrahydropyridines (Va-g). A. A mixture of 0.01 mole of a diene (III) and 10 ml of 2 N ethanolic KOH was heated to boiling. After

TABLE 3. Characteristics of the Compounds Synthesized

Compound	T_{mp},* °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IVa	205	78,4	4,1	17,1	$C_{21}H_{14}N_4$	78,2	4,4	17,4	50
IVb	218—220	70,9	3,9	15,8	$C_{21}H_{13}ClN_4$	70,7	3,7	15,7	50
IVc	246	70,7	3,7	15,8	$C_{21}H_{13}ClN_4$	70,7	3,7	15,7	50
IVd	215	78,2	5,0	16,7	$C_{22}H_{16}N_4$	78,6	4,8	16,7	50
IVe	209—212	74,2	3,7	16,4	$C_{21}H_{13}FN_4$	74,1	3,9	16,5	50
Va	238—240	78,3	4,0	17,2	$C_{21}H_{14}N_4$	78,2	4,4	17,4	76
Vb	199—200	70,7	3,7	15,5	$C_{21}H_{13}ClN_4$	70,7	3,7	15,7	—
Vc	246—247	70,5	3,6	15,1	$C_{21}H_{13}ClN_4$	70,7	3,7	15,7	57
Vd	175—177	—	—	16,7	$C_{22}H_{16}N_4$	—	—	16,7	46
Ve	241—242	74,1	3,8	16,2	$C_{22}H_{13}FN_4$	74,1	3,9	16,5	86
Vf	220—222	64,5	3,2	14,3	$C_{21}H_{12}Cl_2N_4$	64,5	3,1	14,3	43
Vg	226	67,2	3,5	15,1	$C_{21}H_{12}ClFN_4$	67,3	3,5	15,0	70
VIa	219—221	78,3	4,2	17,6	$C_{21}H_{14}N_4$	78,2	4,4	17,4	50
VIIIa	127—130	76,1	6,6	16,3	$C_{27}H_{29}N_5$	76,3	6,9	16,5	50
VIIIb	147—149	75,8	6,2	17,6	$C_{25}H_{25}N_5$	76,0	6,3	17,7	75
VIIIc	151—152	76,6	6,2	17,3	$C_{25}H_{23}N_5$	76,5	6,2	7,2	78
VIIId	181—184	67,8	4,5	13,7	$C_{21}H_{15}KN_4O$	66,6	4,0	14,8	80
VIIIe	175	—	—	—	$C_{21}H_{14}FKN_4O$	—	—	—	77
VIIIf	185	—	—	—	$C_{21}H_{14}ClKN_4O$	—	—	—	78
VIIIg	202—204	68,3	4,1	15,5	$C_{22}H_{17}KN_4O$	67,4	3,8	14,3	62
IXb	251—253	—	—	16,9	$C_{22}H_{14}N_4$	—	—	16,8	48
Xa	252	—	—	17,1	$C_{21}H_{12}N_4$	—	—	17,5	40
Xc	250	—	—	15,7	$C_{21}H_{11}ClN_4$	—	—	15,8	48
Xd	243	—	—	16,6	$C_{21}H_{11}FN_4$	—	—	16,7	45
Xe	220—222	—	—	15,8	$C_{21}H_{11}ClN_4$	—	—	15,8	22
XIIa	>300	—	—	15,6	$C_{21}H_{13}KN_4O$	—	—	14,9	82
XIIb	>300	67,6	4,1	15,0	$C_{22}H_{15}KN_4O$	67,8	3,6	14,4	78

*Compounds (IVa-e) were crystallized from xylene; (Va, c, e, g) from chlorobenzene; (Vb, f) and (IXb) from acetic acid; (Vd) from toluene; (VIa) and (Xa, d, e) from nitromethane; (VIIa, d-g) and (XIIa) from ethane [sic]; (VIIIb) from methanol; (VIIIc) and (XIIb) from acetonitrile; and (Xc) from nitromethane–toluene.

5 min, it was cooled and was acidified with concentrated hydrochloric acid, and the precipitate was filtered off and was washed successively with water, ethanol, and hexane to give one of the pyridines (Va-g).

B. A mixture of 0.01 mole of a triene (IV) and 2 ml of diethylamine (or piperidine) in 10-15 ml of ethanol was heated to boiling for 10 min. Then it was cooled and was treated with an excess of concentrated hydrochloric acid, and the resulting yellow precipitate was filtered off and was washed by method A, giving the corresponding pyridine (Va-g).

C. A suspension of 0.01 mole of one of the salts (VIIIa-g) in 10 ml of ethanol was acidified with hydrochloric acid. The corresponding pyridine (V) was obtained, and this was isolated by method A. Mass spectrum of the pyridine (Va): 322 (34.0; M^+),* 295 (7.0), 220 (18.0), 217 (6.0), 206 (11.5), 191 (8.0), 135 (6.5), 116 (67.0), 93 (6.0), 91 (10.0), 83 (5.0) 81 (5.0), 78 (7.0), 77 (17.0), 71 (6.0), 69 (7.5), 57 (9.5), 55 (11.5).

2-Amino-1,1,3-tricyano-4,6-diphenyl-1,trans-3,trans-5-hexatriene (VIa). A mixture of 0.01 mole of the diene (IIIa) and 30 ml of xylene was heated to boiling for 3 h and was cooled, and the precipitate was filtered off and recrystallized from nitromethane. This gave the yellow crystalline triene (VIa).

Salts of 2,4-Diaryl-5-cyano-6-dicyanomethylene-1,2,3,6-tetrahydropyridines with Bases (VIIIa-g). A. A mixture of 0.1 mole of the triene (VIa) and 2 ml of diethylamine, piperidine, or triethylamine in 10-15 ml of ethanol was boiled for 10 min. Then it was cooled and the resulting precipitate was filtered off, washed with ethanol and then with hexane, and recrystallized from the appropriate solvent, giving the salt (VIIIa, b, or c).

B. A mixture of 0.01 mole of diene (III) in 10 ml of 2 N ethanolic KOH was boiled for 5-10 min. Then it was cooled and the resulting white precipitate was filtered off, washed with 2 N ethanolic KOH, and dried in vacuum. This gave the corresponding salt (VIIId-g), which

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*Here and below the mass spectra are given the values of m/z (intensity in % relative to the maximum ion peak).

it was difficult to recrystallize, and therefore in some cases, the characteristics of these salts are given in Table 3 without their elementary analyses.

C. A mixture of 0.01 mole of a pyridine (V) and 10-15 ml of ethanol was boiled with an excess of a base and, after cooling, the corresponding salt (VIIIa-g) was isolated by methods A and B.

4,6-Diaryl-3-cyano-2-dicyanomethylpyridines (IX, Xa-e). A. A mixture of 0.01 mole of a diene (III) and 20 ml of xylene was boiled for 10 min, and then 2 ml of triethylamine was added and boiling was continued for another 1 h. The reaction mixture was cooled, the upper, xylene, layer was decanted off, and the resinous precipitate was triturated in concentrated hydrochloric acid until it solidified and was then filtered off. The residue was washed successively with water, ethanol, and hexane and was recrystallized from a suitable solvent. The pyridines (IX), and (Xa-e) were obtained in this way.

B. A mixture of 1 mmole of the pyridine (IXa), 2 mmoles of sodium hydride, and 2 mmoles of malononitrile in 10 ml of absolute DMFA was stirred in a current of argon for 1 h. Then it was heated to 100°C and was stirred at this temperature for another 1 h. The reaction mixture was diluted with water and was treated with an excess of hydrochlorid acid and the resulting precipitate was filtered off and washed with water, ethanol, and hexane and recrystallized from nitromethane. This gave the pyridine (Xa) with a yield of 38%, mp 252°C. Mass spectrum: 321 (100), 320 (96; M^+), 293 (10.0), 294 (10.0), 295 (10.0), 266 (5.5), 255 (11.0), 228 (7.0), 228 (14.0), 165 (5.0), 149 (9.0), 135 (9.0), 133 (12.5), 123 (10.0), 119 (10.5), 105 (15.0), 94 (13.5), 90 (15.0), 83 (12.0), 81 (12.8), 79 (15.0), 77 (32.5), 69 (18.5), 68 (12.0), 55 (35.0).

Hydrates of the Potassium Salts (XIIa, b). With stirring 10 mmoles of one of the mixtures of the pyridines (IX, Xa, b) in 15-20 ml of 2 N ethanolic KOH was heated to boiling for a few minutes. The bright orange coloration of the initial compounds disappeared almost instantaneously and a light yellow precipitate was formed which was filtered off and was washed with 2 N ethanolic KOH, with a small amount of ethanol, and with hexane. This gave the corresponding salt (XIIa, b) crystallizing poorly from ethanol and acetonitrile.

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