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SYNTHESIS OF 2,6-DISUBSTITUTED 3,3,5,5-TETRACYANOPIPERIDINES BY THE REACTION OF 1,1,3,3-TETRACYANOPROPANE WITH 2,4-DIAZAPENTANE-1,4-DIENES

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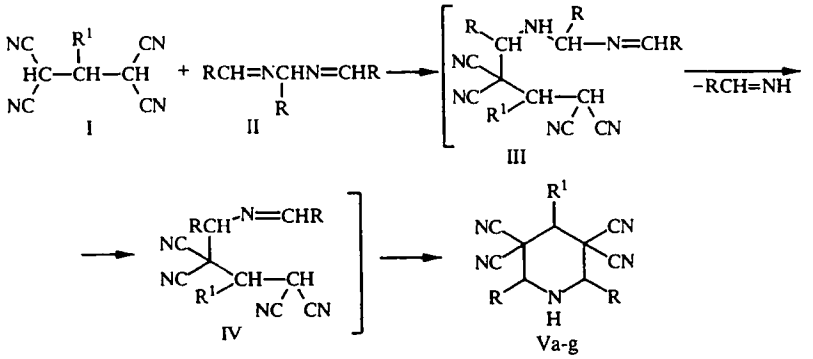
The 3:2 ratio of 1,1,3,3-tetracyanopropane and 1,3,5-trisubstituted 2,4-diazapentane-1,4-dienes in an alcoholic medium led to the synthesis of 2,6-di-R-4-R^1-3,3,5,5-tetracyanopiperidines, the low reactivity of which is explained by their structural features.

In the investigation of the properties of a dibasic acid such as 1,1,2,2-tetracyanoethane, two directions of the interaction with azomethine compounds were found. Thus, heterocyclization with azines proceeds due to one active center and the cyano group [1], and both CH-acid centers participate in the heterocyclization with hydrobenzamide and its derivatives. This results in the formation of 3,3,4,4-tetracyanopyrrolidines [2], which were found to be very reactive compounds. On the basis of these data, we proposed the possibility of synthesizing polynitriles of the piperidine series based on hydrobenzamide and its derivatives. For this purpose, the reaction of the corresponding 2,4-diazapentane-1,4-dienes (II) with the 1,1,3,3-tetracyanopropanes (I) was carried out. When they are mixed in isopropyl alcohol at room temperature, the complete solution of the reagents occurs, and a copious residue is isolated after 15-20 min.

The reaction is probably accomplished with the addition by the CH-acidic center of the propane (I) at one of the CH bonds. The elimination of the aldimine occurs in the resulting adduct (III), as in the case of the reaction with 1,1,2,2-tetracyanoethane [2, 3], which conforms with the data of [4].



Further, intramolecular cyclization in the azomethine (IV) occurs by addition at the resulting C=N bond with the formation of 2,6-disubstituted 3,3,5,5-tetracyanopiperidines (Va-g) (Table 1). The aldimine which is isolated in the course of the reaction is probably trimerized to the initial diene (II) [5], which allows the reaction to be accomplished utilizing the reagents (I) and (II) in the ratio of 3:2 [except for the aliphatic derivatives (II)].

The symmetry of the structures of the piperidines (V) synthesized is indicated by the data of the ^{13}C NMR spectrum of compound (V). Besides the set of signals of the p-methoxyphenyl substituent at 128.22-161.8 and 55.59 ppm (OCH_3), only three signals attributed to the carbon atoms of the heterocycle at 38.28 ppm for $C_{(4)}$, 38.92 ppm for $C_{(3)}$ and $C_{(5)}$, and 66.76 ppm for $C_{(2)}$ and $C_{(6)}$ and the signal of the carbon atom of the cyano group with the δ = 113.14 ppm are observed in the spectrum. The structures of the remaining piperidines (Va,c-g) were confirmed by the comparison of their IR spectra (Table 2), and their composition was confirmed by the data of the elemental analysis.

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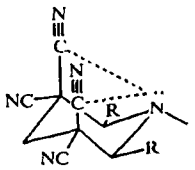
TABLE 1. Properties of the Compounds (Va-g), (VI), and (VII)

Compound	R	R^1	mp, °C	Empirical formula	Found, % / Calculated, %			Yield, %
					C	H	N	
Va	C_6H_5	H	204...205	$C_{21}H_{15}N_5$	74,65 74,76	4,57 4,48	20,88 20,76	96
Vb	4-$CH_3OC_6H_4$	H	157...158	$C_{23}H_{19}N_5O_2$	69,39 69,51	4,96 4,82	17,77 17,62	78
Vc	2-$CH_3OC_6H_4$	H	96...98	$C_{23}H_{19}N_5O_2$	69,37 69,51	4,93 4,82	17,53 17,62	81
Vd	2-Fu	H	163...164 (decomp.)	$C_{17}H_{11}N_5O_2$	64,48 64,35	3,54 3,49	22,19 22,07	34
Ve	4-$CH_3C_6H_4$	H	155...156 (decomp.)	$C_{23}H_{19}N_5$	75,44 75,59	5,40 5,24	19,28 19,16	48
Vf	*i*-C_3H_7	H	142...143	$C_{15}H_{19}N_5$	66,74 66,89	7,03 7,11	26,13 26,00	15
Vg	C_6H_5	CH_3	165...166	$C_{22}H_{17}N_5$	75,28 75,19	4,93 4,88	20,07 19,93	43
VIa	C_6H_5	H	113...114	$C_{19}H_{13}N_3$	80,67 80,54	4,74 4,62	14,71 14,83	80
VIb	4-$CH_3OC_6H_4$	H	111...112	$C_{21}H_{17}N_3O_2$	73,56 73,45	5,07 4,99	12,15 12,24	76
VIIa	C_6H_5	CN	123...124	$C_{17}H_{13}N_3$	78,88 78,74	5,19 5,05	16,07 16,20	68
VIIb	C_6H_5	COOEt	176...177	$C_{18}H_{18}N_2O_2$	73,56 73,45	6,25 6,16	9,41 9,52	33

The mass spectra of the compounds (V) are characterized by molecular ion peaks of low intensity (they are absent in some cases), the decomposition of which is mainly characterized by the formation of the fragments $RCH{=}N^+{=}CHR$, $R{-}C{\equiv}N^+H$, $R{-}CH{=}C(CN)_2$, and $H_2C{=}C(CN)_2$.

The piperidines (V) synthesized were found to be chemically inactive. They could not even be acylated as secondary amines. Such low reactivity is probably associated with their structural features. In the molecule of the compounds (V), the unshared pair of electrons is probably situated in direct proximity to the carbon atoms of the axially disposed cyano groups. Such coordination reduces the basic properties of the nitrogen atom and should simultaneously decrease the activity of the cyano groups to nucleophilic agents, which is also observed in fact. We did not manage to isolate adducts of the interaction of nucleophiles with the compounds (V) in the presence of bases by standard methods. Under drastic conditions, the addition possibly proceeds at the equatorial cyano groups. However, these reactions lead to the complete decomposition of the initial compounds and the formation of unidentified resin-forming reaction masses.



We managed to carry out, with some difficulty, the thermal dehydrocyanation of the tetracyanopiperidines (Va,b) with the formation of 2,6-diaryl-3,5-dicyano-1,4-dihydropyridines (VIa,b). The IR spectra of these compounds contain absorption bands of the stretching vibrations of the N–H bond at 3310-3325 cm^{-1}, the conjugated cyano groups at 2220-2235 cm^{-1}, and the C=C bonds at 1630-1635 cm^{-1}. The composition of the compounds (VIa,b) agrees with the data of the elemental analysis (Table 1).

Starting from the proposed scheme of interaction of the dibasic CH-acids (I) with the diazadienes (II) we attempted to synthesize cyano-substituted azetidines. In fact, malononitrile and cyanacetic ester react with hydrobenzamide to form the corresponding 2,4-diphenylazetidines (VIIa,b). Their IR spectra contain the absorption bands of the stretching vibrations of the N–H bond at 3310-3255 cm^{-1} and the unconjugated cyano group at 2255-2265 cm^{-1}. The IR spectrum of ethyl 2,4-diphenyl-3-cyanoazetidine-3-carboxylate (VIIb) contains the absorption band of the C=O bond at 1720 cm^{-1}, which is characteristic of the unconjugated ethoxycarbonyl portion. The composition of these compounds agrees with the data of the elemental analysis.

TABLE 2. IR and Mass Spectra of the Compounds (V), (VI), and (VII)

Compound	IR spectrum, cm^{-1}		Mass spectrum, m/z (relative intensity, %)*
	ν_{NH}	$\nu_{C\equiv N}$	
Va	3385	2260	337(0,5), 194(5), 154(97), 127(55), 105(85), 104(100), 103(56), 78(97), 77(73), 63(10), 51(84)
Vb	3370	2265	397(0,5), 254(6), 184(100), 169(15), 135(80), 134(86), 114(52), 88(13), 78(60), 63(21), 51(45)
Vc	3320, 3275	2270	—
Vd	3320	2270	251(7), 173(65), 144(15), 108(42), 95(100), 94(43), 81(25), 78(44), 68(9), 51(51) †
Ve	3340	2270	—
Vf	3320	2265	269(4), 254(2), 226(3), 191(53), 148(100), 121(20), 107(7), 94(5), 79(9), 70(6), 56(47)
Vg	3385, 3335	2265	259(2), 197(52), 182(4), 154(26), 132(19), 105(100), 104(63), 92(15), 77(29), 51(28) †
VIa	3325	2230 1635‡	194(33), 183(74), 154(26), 118(100), 105(79), 104(70), 91(85), 78(57), 65(17), 51(56)†
VIb	3310	2220, 2230 1630‡	341(1), 286(12), 261(10), 109(100), 181(12), 154(5), 131(22), 104(10), 78(19), 66(8), 52(20)
VIIa	3315	2255	259(0,3), 194(100), 165(8), 154(42), 127(21), 105(35), 104(44), 91(22), 77(22), 66(15), 51(22)
VIIb	3310, 3255	2265 1720**	—

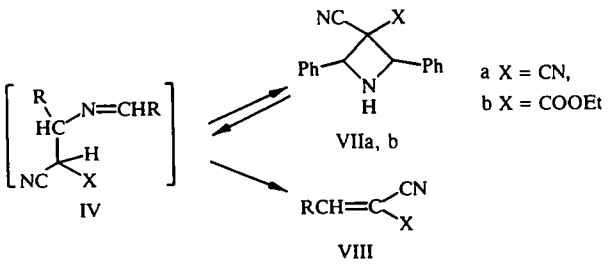
*The peak of the molecular ion and the 10 most intense peaks of the fragment ions are presented.

†Peaks of the molecular ions are absent.

‡C=C.

**C=O.

The utilization of hydrofuramide or the dienes (II) with electron-donor substituents in the aromatic radical in this reaction under analogous conditions leads to the thermodynamically more stable ylidene derivatives (VIII). They were identified with samples synthesized directly from the corresponding aldehydes. The compounds (VII), which occur partially in solution in the linear tautomeric form (IV), are probably readily converted to the corresponding olefins (VIII) under external influences. This route is the main direction of their conversions.



Interaction between the dienes (II), having electron-acceptor groups, and malononitrile or cyanacetic ester is not observed.

EXPERIMENTAL

The IR spectra of the compounds synthesized were taken on the UR-20 instrument using the suspension in mineral oil. The ^{13}C NMR spectrum was obtained on the Gemini-300 spectrometer (Varian) with the working frequency of 75 MHz in deuteroacetone, using HMDS as the internal standard. Monitoring of the course of reactions and the purity of the substances synthesized was accomplished by the method of TLC on plates of Silufol UV-254; the developer comprised UV irradiation and iodine vapor.

2,5-Disubstituted 3,3,5,5-tetracyanopiperidines (Va-g). To the suspension of 20 mmole of 1,3,5-trisubstituted 2,4-diazapentane-1,4-diene (II) in 20 ml of isopropyl alcohol are added, with stirring, 30 mmole of 1,1,3,3-tetracyanopropane in one process. The stirring is continued until the complete solution of the initial substances is effected. After 15-20 min, the isolated residue is filtered off, washed with isopropyl alcohol, and recrystallized from isopropyl alcohol.

2,6-Diaryl-3,5-dicyano-1,4-dihydropyridines (VIa,b). The 2,6-diaryl-3,3,5,5-tetracyanopiperidine (Va,b) (1 mmole) is boiled in 3-5 ml of DMF for 5-7 min. After cooling the solution, it is diluted with water. The isolated residue is filtered off, washed with water, and recrystallized from isopropyl alcohol.

2,4-Diphenyl-3-cyano-3-X-azetidines (VIIa,b). To the solution of 15 mmole of malononitrile [for X = CN in (VIIa)] or cyanacetic ester [for X = COOEt in (VIIb)] in 10 ml of isopropyl alcohol are added 2.98 g (10 mmole) of hydrobenzamide in one process, and the mixture is stirred until complete solution is effected. After 30 min, the resulting residue is filtered off, washed with isopropyl alcohol, and recrystallized from isopropyl alcohol.

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