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SYNTHESIS AND PROPERTIES OF AZIDO DERIVATIVES OF 2- AND 4-ARYLAMINO-5-CYANOCHLOROPYRIDINES

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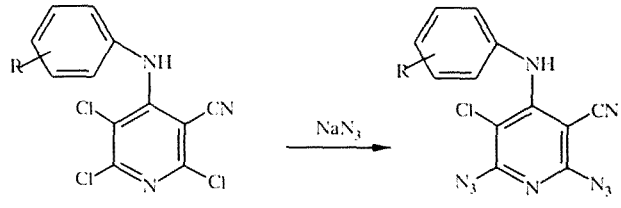
Reaction of 2- and 4-arylaminotrichloro-5-cyanopyridines with sodium azide gives 6-azido-2-arylamino-3,4-dichloro-5-cyanopyridines and 2,6-diazido-4-arylamino-3-chloro-5-cyanopyridines respectively. It is shown that the azide group of the monoazidopyridines synthesized, readily undergoes cycloaddition with norbornene, whereas the azide groups of the diazidopyridines are unreactive towards this dipolarophile.

Because of the presence of three reactive electrophilic sites in the pyridine ring of 5-cyanotetrachloropyridine, this compound is of potential importance for the preparation of a wide range of pyridine derivatives. However, in reactions with aniline and hydrazine, the replacement of the chlorine atoms in the pyridine ring of 5-cyanotetrachloropyridine by electron-donating nitrogen-containing groups stops at the stage where the corresponding monosubstituted derivatives of this compounds re-formed [1, 2]. At the same time all three chlorine atoms in the 2-, 4-, and 6-positions of the pyridine ring in 5-cyanotetrachloropyridine are readily replaced in the reaction with sodium azide [3]. In turn, the ability of the azide groups readily to undergo different reactions with the formation of other nitrogen-containing functional groups [4], can be utilized in the synthesis of compounds whose preparation is impossible by successive substitution of the chlorine atoms in the pyirdine ring of 5-cyanotetrachloropyridine.

As the nucleophilic substitution of 5-cyanotetrachloropyridine by sodium azide is highly efficient [3], it was of interest to study the nucleophilic substitution by sodium azide of the chlorine atoms in the pyridine ring of monoaminated derivatives of this compound. We selected the series of previously obtained 2- and 4-arylamino-5-cyanotrichloropyridines (Ia-e and Va-e) [1] as substrates for this study.

The reactions of Ia-e with excess sodium azide were carried out in aqueous acetone at room temperature in the dark. It was shown that all compounds Ia-e readily undergo nucleophilic substitution of the two chlorine atoms at the 2- and 6-positions of the pyridine ring to give the diazidopyridines IIa-e.



I a-e IIa-e

I, II a R = *p*-OCH_3, b R = *p*-CH_3, c R = H, d R = *p*-Br, e R = *m*-NO_2

The structure of compounds IIa-e was fully supported by the elemental analysis data and by UV, IR, PMR, and ^{13}C NMR spectroscopy.

It is clear from Tables 1 and 2 that the substituent in the benzene ring of compounds IIa-e has hardly any effect on the spectroscopic properties of these compounds. At the same time, by comparing the results of UV, IR, and PMR spectroscopy for compounds IIa-e (Table 1) with the corresponding data for the initial compounds Ia-e [1], it is possible to detect a

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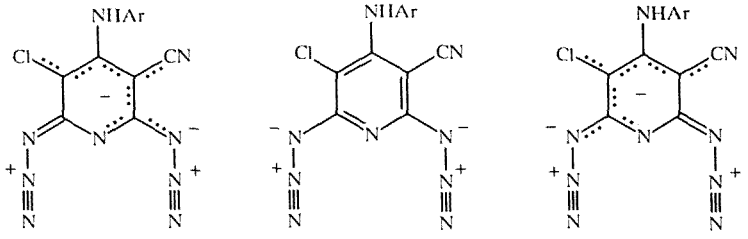
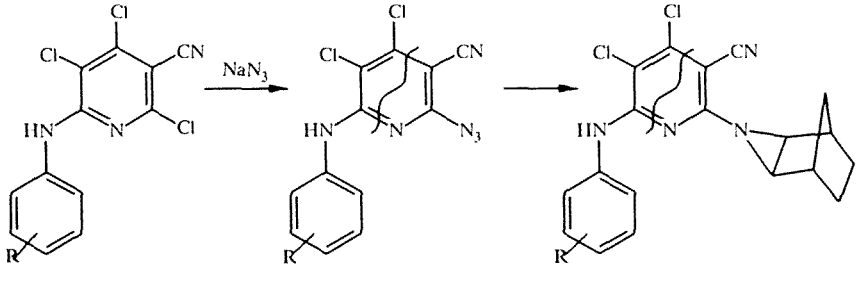
number of general trends in the spectroscopic properties of 4-arylamino-5-cyanopyridines relating to the replacement of two chlorine atoms in the pyridine ring of these compounds by azide groups. Thus, when comparing the UV spectra of compounds IIa-e, it is clear that replacement of two chlorine atoms by azide groups in the pyridine ring of 4-arylamino-5-cyanopyridines gives rise to a slight bathochromic shift (7-11 nm) of the long-wavelength absorption at 323-328 nm while at the same time increasing the intensity of this band by a factor of 1.5-2. A similar comparison of the PMR spectra indicates a 0.21-0.25 ppm upfield shift in the signals due to the NH protons. The C≡N group absorption bands in the IR spectra are shifted to lower frequency by 5-25 cm^{-1}.



III II IV

It may be concluded from these findings that the presence of the two azide groups in compounds IIa-e is responsible for additional conjugation of the C≡N group with the pyridine ring and the two azide groups (resonance structures III and IV) while weakening conjugation between the pyridine ring and the ArNH residue [1]. This is also reflected in the chemical behavior of compounds IIa-e. Thus, it is known that α-azidopyridines can participate in azide–tetrazole tautomerism [4]. The presence of the electron-donating arylamino group at the para position relative to the pyridine nitrogen atom should in theory assist in displacing the azide–tetrazole equilibrium in favor of the tetrazole form [5]. Formation of the tetrazole form can be observed in the ^{13}C NMR spectra of α-azidopyridines from the significant upfield shift (130-120 ppm) of the signal of the C(α) pyridine atom that is not involved in the formation of the tetrazole ring [5, 6]. At the same time, study of the ^{13}C NMR spectra of compound IIc in different solvents ($CDCl_3$, DMSO-d_6) over the temperature range −20 to 50°C has shown that the signals from the $C_{(2)}$ and $C_{(6)}$ atoms of its pyridine ring are hardly affected at all by a change in temperature or solvent and they appear exclusively in the region 150-154 ppm (Table 2), which suggests that compound IIc exists solely in the azide form. Another characteristic of compounds IIa-e is their inertness towards reaction with a strong dipolarophile such as norbornene [7]. All our attempts to obtain cycloaddition products of norbornene with diazidopyridines IIa-e proved unsuccessful, regardless of the wide variation in reaction conditions (time, temperature, solvent). It is interesting to note that 4-azidopyridines that have two substituents at the ortho position relative to the azido group readily form cycloadducts on reaction with norbornene [3, 8]. This is probably related to steric factors which inhibit strong conjugation of this azide group with the pyridine ring and reduction of the negative charge on the N(α) atom of this azide group, which is necessary for cycloaddition to occur successfully [7].

The reactions of compounds Va-e with excess sodium azide were carried out under conditions similar to those involving compounds Ia-e. It transpired that, in contrast to compounds Ia-e, compounds Va-e undergo reaction with sodium azide with replacement of only one chlorine atom — at the 6-position of the pyridine ring — to give the monoazidopyridines VIa-e in 86-92% yield.



Va-e VIa-e VII

V, VIa R = *p*-OCH_3, b R = *p*-CH_3, c R = H, d R = *p*-Br, e R = *m*-NO_2

TABLE 1. Properties of Compounds IIa-e, VIa-e, and VII

Compound	Empirical formula	mp, °C (dec.)	UV spectrum, λ, nm (log ε)	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, (in $CDCl_3$)*, ppm		Yield, %
				NH	C ≡ N	N_3	NH	Ar/Alk	
IIa	$C_{13}H_8ClN_9O$	205...206	328 (3,81) 259 (4,62)	3300	2210	2150 2120	9,17	3,75 (OCH_3); 6,94...7,26 (4H, m)	90
IIb	$C_{13}H_8ClN_9$	218...220	323 (3,86) 261 (4,56)	3300	2210	2150 2120	6,95	2,37 (CH_3); 6,90...7,23 (4H, m)	84
IIc	$C_{12}H_6ClN_9$	215...217	326 (3,87) 263 (4,63)	3300	2205	2140 2120	7,00	7,22...7,43 (5H, m)	88
IId	$C_{12}H_5BrClN_9$	230...233	323 (3,99) 266(4,70)	3300	2205	2160 2130	6,87	7,08...7,54 (4H, m)	84
IIe	$C_{12}H_5ClN_{10}O_2$	204...206	327 (4,07) 267 (4,74)	3350	2205	2150 2125	9,20	7,44...7,96 (4H, m)	78
VIa	$C_{13}H_8Cl_2N_6O$	154...156	328 (4,17)	3320	2210	2110	9,51	3,77 (OCH_3); 6,91...7,17 (4H, m)	84
VIb	$C_{13}H_8Cl_2N_6$	141...142	336 (4,23) 315(4,25)	3305	2210	2110	7,38	2,35 (CH_3); 7,14...7,40 (4H, m)	80
VIc	$C_{12}H_6Cl_2N_6$	165...167	336 (4,25) 303(4,31)	3300	2205	2100	7,50	7,19...7,55 (5H, m)	88
VId	$C_{12}H_5BrCl_2N_6$	184...186	336 (4,27) 309(4,28)	3310	2220	2110	7,40	7,45...7,55 (4H, m)	85
VIe	$C_{12}H_5Cl_2N_7O_2$	203...205	328 (4,27) 295(4,29)	3300	2220	2110	7,63	7,59...8,05 (4H, m)	82
VII	$C_{19}H_{16}Cl_2N_4$	170...171	321 (4,14) 305(4,18)	3300	2205	–	7,23	7.11...7.57 (5H, m); 2.84 (2H, s, NCH); 2.71 (2H, s, CH); 1.55 (2H, d, 6- and 7-H_{eq}, J = 8.7 Hz); 1.41 (1H, d, 8-H_{exo}, J = 10.4 Hz); 1.21 (2H, d, 6- and 7-H_{ax}, J = 7.5 Hz); 0.92 (1H, d, 8-H_{endo}, J = 10.2 Hz).	88

*PMR spectra of compounds IIa and VIa, e obtained in DMF-d_7.

TABLE 2. ^{13}C NMR Spectra of Compounds IIe, VIa-e, and VII*

Compound	Chemical shifts, δ (in $CDCl_3$), ppm**						
	C-2	C-3	C-4	C-5	C-6	C ≡ N	Ar/Alk
IIe	152,3	103,7	155,4	83,5	151,6	113,2	147,9 (C'-3); 140,3 (C'-1); 130,2 (C'-6); 129,6 (C'-5); 119,7 (C'-4); 117,7 (C'-2)
VIa	153,5	105,9	147,0	93,7	152,8	112,3	158,2 (C'-4); 130,5 (C'-1); 124,2 (C'-3, C'-5); 114,9 (C'-2, C'-6); 55,8 (OCH_3)
VIb	153,5	105,9	147,1	93,9	152,7	113,1	135 (C'-1); 135,0 (C'-4); 130,4 (C'-3, C'-5); 122,1 (C'-2, C'-6); 20,9 (CH_3)
VIc	152,2	108,0	147,3	94,3	152,7	113,0	137,8 (C'-1); 129,9 (C'-3, C'-5); 126,0 (C'-4); 121,9 (C'-2, C'-6)
VId	152,9	105,8	147,5	94,0	152,7	113,0	136,8 (C'-1); 132,9 (C'-3, C'-5); 123,5 (C'-2, C'-6); 118,7 (C'-4)
VIe	153,0	106,8	147,5	93,6	150,4	112,9	148,0 (C'-3); 139,6 (C'-1); 130,0 (C'-5); 128,7 (C'-6) 119,1 (C'-4); 117,0 (C'-2)
VII	151,9	102,8	151,2	93,0	157,5	114,4	137,9 (C'-1); 129,0 (C'-3, C'-5); 124,3 (C'-4); 120,8 (C'-2, C'-6); 43,9 (NCH); 36,8 (CH); 28,7 (CH_2CH_2); 25,8 (CH_2)

*Spectra of compounds IIa-d were not obtained because of the low solubility of these compounds in all organic solvents.

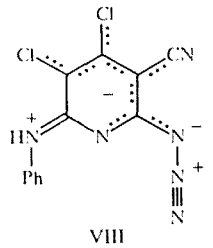
**Spectra of compounds IIe and VIe obtained in DMSO-d_6.

The structure of compounds VIa-e was fully supported by the elemental analysis data and by UV, IR, PMR, and ^{13}C NMR spectroscopy.

The low reactivity of the chlorine at the 4-position in compounds Va-e in reactions with sodium azide correlates well with the ^{13}C NMR data for these compounds [1], according to which the signals from the $C_{(4)}$ atoms of the pyridine ring in compounds Va-e appear at 144.4-145.4 ppm, whereas the signals from the $C_{(6)}$ atoms occur at 150.3-152.1 ppm.

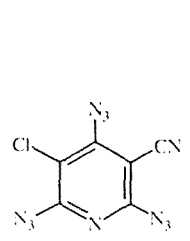
In contrast to diazidopyridines IIa-e, azidopyridines VIa-e readily undergo cycloaddition with norbornene. Thus, when azide VIc is reacted with norbornene in ether at room temperature, the aziridine cycloadduct VII is formed in 88% yield. As in the case of the aziridine cycloadduct in the reaction of 2,4,6-triazido-3-chloro-5-cyanopyridine with norbornene [3], cycloadduct VII assumes the most favorable exo conformation, which follows from the absence of a spin–spin interaction between the protons of the aziridine ring and the CH protons on the bridgehead of the carbocyclic residue, which appear as a singlet at 2.84 and 2.71 ppm respectively.

Comparison of the spectroscopic properties of the initial compounds Va-e [1] and their azide derivatives VIa-e (Table 1) shows that replacement of the chlorine atom at the 6-position of 2-arylamino-5-cyanopyridines by an azide group leads to virtually no change in the degree of conjugation of the ArNH residue with the pyridine ring. For both series of compounds Va-e and VIa-e, the long-wavelength absorption bands have approximately the same intensities in their UV spectra and approximately the same chemical shifts of the NH protons in their PMR spectra. It may be assumed from this that the high reactivity of the α-azide group of compounds IIa-e towards cycloaddition with norbornene are due to the varying degree of conjugation of the α-azide groups in these compounds. Thus, the predominant effect for azidopyridine VIc is likely to the conjugation between the PhNH group and the pyridine ring (resonance structure VIII), with the consequence that a negative charge density is retained on the N(α) atom of the azide group which is sufficiently high for cycloaddition to occur successfully [7].

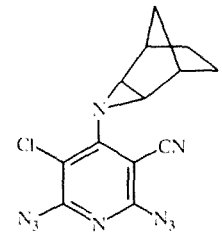


VIII

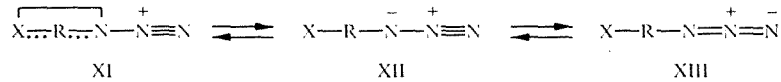
This assumption is borne out by analysis of the IR spectra of azidopyridines IIa-e, VIa-e, and compounds IX and X, which we obtained previously [3].



IX



X



XI XII XIII

Thus, the absorption band of the least conjugated azide group at the 4-position of the pyridine ring in the triazidopyridine IX appears at 2070 cm^{-1}, suggesting that resonance structures XII and XIII predominate in a representation of the state of this group [3]. The contribution of the resonance structures XI starts to predominate for the α-azide groups of compound IX, which are more involved in resonance with the pyridine ring, and this is reflected in the higher absorption frequency of these groups— at 2140 and 2120 cm^{-1} respectively. A more significant share of resonance structure XI is also retained for the diazidopyridines IIa-e and X, the α-azide groups of which in the IR spectrum give two intense absorption bands – at 2160-2140 cm^{-1} and 2130-2120 cm^{-1} for compounds IIa-e (Table 1) and at 2150 and 2130 cm^{-1} for compound X [3]. On the other hand, the absorption band of the α-azide group in the IR spectra of compounds VIa-e are displaced to lower frequency (2110-2100 cm^{-1}, Table 1), which is probably due to the more pronounced contribution of structures XII and XIII rather than structures XI, and, as a consequence of this, the ability of the azide groups to undergo cycloaddition with norbornene.

All the azidopyridines IIa-e and VI-e prepared in this study are compounds that are fairly stable towards impact and heat. A characteristic feature of diazidopyridines IIa-e is their extremely low solubility in most organic solvents. As a result we were not able to obtain ^{13}C NMR spectra for IIa-d. Another characteristic of diazidopyridines IIa-e is their relatively low sensitivity to light. All the diazidopyridines IIa-e are colorless crystalline compounds which on standing in daylight slowly change to a violet color. On the other hand, the monoazidopyridines VIa-e are fairly readily soluble in most organic solvents and are quite sensitive to light, with the result that a short exposure of these compounds to daylight causes them to become highly colored. It is interesting to not that the substituents in the benzene ring of monoazidopyridines VIa-e have a more significant effect on the light sensitivity of these compounds than for diazidopyridines IIa-e (Table 1). This is probably due to the more pronounced conjugation of the ArNH residue with the pyridine ring of these compounds and the more significant contribution from resonance structure VIII.

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 instrument while the UV spectra were recorded in methanol on a Beckman DU-7 HS instrument. The PMR spectra were obtained on a Bruker AM-400 instrument (400 MHz) with TMS as the internal standard. The ^{13}C NMR spectra were obtained on a Bruker AM-400 instrument (100.6 MHz). The purity of the compounds was monitored by TLC in any ethyl acetate–benzene (1:3) system on Silufol UV-254 plates.

The general method for preparing the starting compounds Ia-e and Va-e is described in [1].

The elemental analysis data for C, H, and N for compounds IIa-e, VIa-e, and VII correspond to the calculated values.

2,6-Diazido-4-arylamino3-chloro-5-cyanopyridines (IIa-e); General Method. To a solution of 1 mmole of compound Ia-e in 50 ml of aqueous acetone (10% water) was added 0.195 g (3 mmole) of sodium azide. The reaction mixture was agitated at room temperature in the dark for 6 h, the solvent was then distilled off under reduced pressure, and 50 ml of water was added to the residue. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

The properties of compounds IIa-e are given in Tables 1 and 2.

6-Azido-2-arylamino-3,4-dichloro-5-cyanopyridines (VIa-e); General Method. To a solution of 1 mmole of compound Va-e in 50 ml of aqueous acetone (10% water) was added 0.195 g (3 mmole) of sodium azide. The reaction mixture was agitated at room temperature in the dark for 6 h, the solvent was then distilled off under reduced pressure, and 50 ml of water was added to the residue. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

The properties of compounds VIa-e are given in Tables 1 and 2.

3-(4,5-Dichloro-3-cyano-6-phenylamino-2-pyridyl)-3-azatricyclo[3.2.1.0]octane (VII). To a solution of 0.305 g (1 mmole) of compound VIc in 100 ml of dry diethyl ether was added 0.188 g (2 mmole) of norbornene in 10 ml of ether. The reaction mixture was kept at room temperature in the dark for 2 weeks, the solvent was then distilled off under reduced pressure, and the residue was recrystallized from an ethanol–water mixture.

The properties of compound VII are given in Tables 1 and 2.

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