REACTION OF TETRACHLORO-3-CYANOPYRIDINE WITH ANILINES

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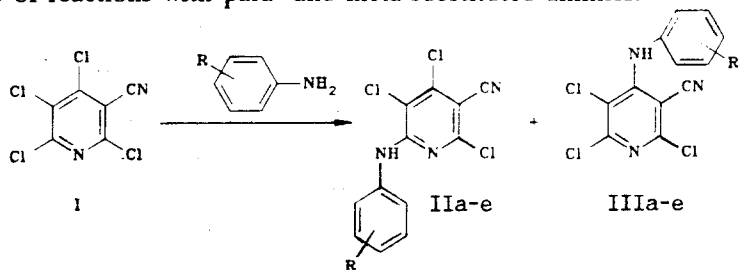
It was determined by ^{13}C NMR spectroscopy that the reaction of tetrachloro-3-cyanopyridine with anilines occurs with the formation of isomeric 6- and 4-(arylamino)trichloro-3-cyanopyridines. It was shown that the nucleophilic properties of the anilines do not affect the ratio of the isomers that are formed in the reaction.

The presence of three reactive electrophilic centers in the pyridine ring of tetrachloro-3-cyanopyridine makes this compound promising from the standpoint of the preparation of a wide range of pyridine derivatives. At the same time, nucleophilic substitution reactions in tetrachloro-3-cyanopyridine have been studied comparatively little, and the available publications contain contradictory data on the possible directions of substitution in the pyridine ring [1, 2]. In the present paper, we studied the characteristics of nucleophilic substitution in tetrachloro-3-cyanopyridine for the case of reactions with para- and meta-substituted anilines.



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

The reaction of compound I with anilines was carried out in ethanol at room temperature for 4-6 h. The only exception was the reaction with m-nitroaniline, for which prolonged (10-12 h) heating was required, apparently because of the weak nucleophilicity of m-nitroaniline. In each case, we obtained two isomeric compounds which, according to the data of IR and PMR spectroscopy and also according to the data of elemental analysis (Table 1), were products of substitution of one of the chlorine atoms by an aniline fragment. A traditionally complex question in the study of nucleophilic substitution reactions in polyhalopyridines is the determination of the position of the substituents in the reaction products. To solve this problem, we compared the ^{13}C NMR spectra of the recovered isomers (Table 2) and three possible NHAr-substituted trichloro-3-cyanopyridines (Table 3) calculated on the basis of known increments of substituents with the general formula NHAr for the α and γ positions of the pyridine ring and the ^{13}C NMR spectrum of compound I used as a standard [3]. In comparing the data of Tables 2 and 3, it is evident that the characteristic signals correspond most optimally to the calculated spectral characteristics of 6- and 4-NHAr-substituted trichloro-3-cyanopyridines. Therefore, the products of the reaction of compound I with anilines are 6-(arylamino)-2,4,5-trichloro-3-cyanopyridines (IIa-e) and 4-(arylamino)-2,5,6-trichloro-3-cyanopyridines (IIIa-e). Some differences between the experimentally determined and calculated values of the chemical shifts for compounds IIa-e and IIIa-e are apparently due to the specifics of bonding of the aniline fragment to the pyridine ring in these compounds in comparison with 2- and 4-NHAr-substituted tetrachloropyridines, for which the increments of the NHAr group were originally determined [3].

Taking into account the corresponding difficulties in determining the position of the substituents in polyhalopyridines, we consider it important to note the characteristic differences in the UV and PMR spectra of isomers IIa-e and IIIa-e. Thus, unlike the analogous spectra of compounds IIIa-e, the UV spectra of compounds

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TABLE 1. Spectral Characteristics* of Compounds IIa-e and IIIa-e

Compound	Empirical formula	mp, °C	R_f	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm		Yield, %
					NH	C=N	C=C, C=N	NH	Ar	
IIa	$C_{13}H_8Cl_3N_3O$	208...209	0,57	323 (4,20), 305 sh (4,14), 214 (4,38)	3330	2230	1620, 1595, 1570	7,38	3,83 (OCH_3); 6,90...7,40 (4H, m)	64
IIb	$C_{13}H_8Cl_3N_3$	185...186	0,72	323 (4,26), 305 sh (4,24), 212 (4,52)	3330	2235	1600, 1570	7,43	2,35 (CH_3); 7,20...7,41 (4H, m)	63
IIc	$C_{12}H_6Cl_3N_3$	168...169	0,77	325 sh (4,26), 305 (4,27), 212 (4,43)	3305	2225	1595, 1570	7,50	7,21...7,58 (5H, m)	63
IId	$C_{12}H_5BrCl_3N_3$	220...221	0,73	326 (4,34), 307 (4,34), 213 (4,53)	3315	2230	1595, 1570	7,40	7,45...7,55 (4H, m)	65
IIe	$C_{12}H_5N_4O_2$	224...225	0,49	326 (4,30), 294 (4,31), 210 (4,50)	3260	2240	1610, 1590, 1570	7,65	7,59...8,5 (4H, m)	68
IIIa	$C_{13}H_8Cl_3N_3O$	182...183	0,51	321 sh (3,63), 285 sh (3,92), 237 (4,51)	3290	2220	1605, 1585, 1570	7,12	3,84 (OCH_3); 6,90...7,18 (4H, m)	26
IIIb	$C_{13}H_8Cl_3N_3$	199...200	0,57	315 sh (3,67), 284 sh (3,89), 239 (4,53)	3345	2230	1600, 1570	7,17	2,37 (CH_3); 7,10...7,23 (4H, m)	26
IIIc	$C_{12}H_6Cl_3N_3$	191...192	0,57	315 sh (3,62), 287 sh (3,89), 239 (4,47)	3325	2210	1570	7,21	7,24...7,46 (5H, m)	24
IIId	$C_{12}H_5BrCl_3N_3$	175...176	0,60	315 sh (3,70), 287 (4,01), 241 (4,48)	3315	2230	1570	7,12	7,01...7,58 (4H, m)	24
IIIe	$C_{12}H_5N_4O_2$	230...231	0,42	320 (3,82), 243 (4,49)	3300	2230	1580	9,28**	7,44...7,97 (4H, m)	20

*The UV spectra (sh denotes shoulder) were recorded in methanol, the IR spectra in white mineral oil, and the PMR spectra (m denotes multiplet) in $CDCl_3$.

**DMFA-D_7.

TABLE 2. Carbon-13 NMR Spectra of Compounds IIa-e and IIIa-e

Compound	Chemical shifts, δ (in $CDCl_3$), ppm*						
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	C=N	Ar
IIa	152,09	100,97	145,13	113,95	153,31	113,16	158,30 ($C_{(4')}$); 130,33 ($C_{(1')}$); 124,35 ($C_{(3')}$, $C_{(5')}$); 115,00 ($C_{(2')}$, $C_{(6')}$); 55,79 (OCH_3)
IIb	151,15	100,66	144,40	113,30	152,23	112,76	135,51 ($C_{(1')}$); 134,19 ($C_{(4')}$); 129,75 ($C_{(3')}$, $C_{(5')}$); 121,53 ($C_{(2')}$, $C_{(6')}$); 21,24 (CH_3)
IIc	151,90	101,56	145,35	113,80	152,93	113,57	137,58 ($C_{(1')}$); 129,90 ($C_{(3')}$, $C_{(5')}$); 126,13 ($C_{(4')}$); 122,06 ($C_{(2')}$, $C_{(6')}$)
IId	150,29	100,40	144,50	114,00	153,64	113,67	137,04 ($C_{(1')}$); 131,05 ($C_{(3')}$, $C_{(5')}$); 125,30 ($C_{(2')}$, $C_{(3')}$); 117,05 ($C_{(4')}$)
IIe	150,31	101,52	145,11	114,70	153,69	113,79	148,86 ($C_{(3')}$); 140,13 ($C_{(1')}$); 130,37 ($C_{(5')}$); 129,17 ($C_{(6')}$); 119,78 ($C_{(4')}$); 117,70 ($C_{(2')}$)
IIIa	151,14	93,76	153,40	115,70	153,46	112,37	160,96 ($C_{(4')}$); 129,43 ($C_{(1')}$); 129,30 ($C_{(3')}$, $C_{(5')}$); 115,31 ($C_{(2')}$, $C_{(6')}$); 55,76 (OCH_3)
IIIb	150,46	93,73	152,13	115,49	152,47	111,73	139,08 ($C_{(1')}$); 133,47 ($C_{(4')}$); 130,21 ($C_{(3')}$, $C_{(5')}$); 126,47 ($C_{(2')}$, $C_{(6')}$); 21,24 (CH_3)
IIIc	151,44	94,52	152,74	116,38	153,25	112,28	136,88 ($C_{(1')}$); 130,45 ($C_{(3')}$, $C_{(5')}$); 129,64 ($C_{(4')}$); 127,03 ($C_{(2')}$, $C_{(6')}$)
IIId	151,47	94,00	152,13	116,49	152,89	112,11	135,80 ($C_{(1')}$); 133,20 ($C_{(3')}$, $C_{(6')}$); 128,05 ($C_{(2')}$, $C_{(6')}$); 122,60 ($C_{(4')}$)
IIIe	150,90	97,12	151,70	118,88	153,31	113,33	148,98 ($C_{(3')}$); 140,72 ($C_{(1')}$); 131,21 ($C_{(6')}$); 130,92 ($C_{(5')}$); 121,36 ($C_{(4')}$); 119,63 ($C_{(2')}$)

*The spectra of compound IId were obtained in a 1:1 DMFA-D_7—$CDCl_3$ mixture; those of compounds IIe and IIIe were obtained in DMFA-D_7.

TABLE 3. Carbon-13 NMR Spectra of NHAr-Substituted Trichloro-3-cyanopyridines with Respect to ^{13}C NMR spectrum of Compound I*

Position of NHAr substituent	δ, ppm				
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$
2	151.1	96.0	145.8	118.5	150.9
6	148.2	101.0	145.8	113.5	153.8
4	149.7	101.1	150.4	118.6	152.4

*The ^{13}C NMR spectrum of compound I and the increments of the NHAr substituents are given in [3].

TABLE 4. Ratio of Isomers II and III in Reaction Mixture

Isomer	R, %				
	p-OCH_3	p-CH_3	H	p-Br	m-NO_2
II	70	73	75	75	74
III	30	27	25	25	26

IIa-e (Table 1) are characterized by the presence of two rather intense (ε 14,000-22,100) absorption bands in the region of 294-326 nm, apparently because of more complete bonding of the aniline fragment to the pyridine ring in these isomers [3]. In the PMR spectra of compounds IIa-e and IIIa-e, the signals corresponding to protons of the NH group of compounds IIa-e are shifted to the weak-field region by 0.26-0.29 ppm in comparison with the corresponding signals of compounds IIIa-e.

Thus, not only the ^{13}C NMR spectra, but also the UV and PMR spectra, can be sufficiently informative for identification of α- and γ-NHAr-substituted polyhalopyridines.

The effect of the nucleophilicity of the anilines on the ratio of the isomers II and III formed in the reaction was studied by microcolumn liquid chromatography. In addition, it was determined that for the considered series of anilines this ratio remains practically constant [II/III = ~(3:1); see Table 4].

EXPERIMENTAL

The IR spectra were recorded on a Specord IR-75 instrument. The UV spectra were recorded on a Beckman DU-7 HS instrument. The PMR spectra were obtained on a Bruker AM-400 instrument (400 MHz). The internal standard was TMS, and the ^{13}C NMR spectra were obtained on a Bruker AM-400 spectrometer (100.6 MHz). The mass spectra were obtained on an MKh-1303 mass spectrometer with direct feed of the substance into the ion source, the energy of the ionizing electrons was 50 eV, the emission current was 60 μA, and the temperature was 150°C. The reaction mixture was analyzed on a Milikhrom-1 microcolumn liquid chromatograph, the sorbent was silica gel Sinasorb-600, and the eluent was benzene. Silica gel L 40/100 was used for column chromatography. The purity of the substances was monitored by thin-layer chromatography in a 1:9 ethyl acetate—benzene system on Silufol UV-254 plates.

The data of elemental analysis for C, H, and N for compounds IIa-e and IIIa-e corresponded to the calculated values.

Arylaminotrichloro-3-cyanopyridines (IIa-e and IIIa-e). General Method. To a solution of 2.42 g (10 mmoles) of compound I in 150 ml of ethanol was added 20 mmoles of the corresponding aniline, and the reaction mixture was stirred at room temperature for 4-6 h. After completion of the reaction, the precipitated isomer IIa-e was filtered from the solution, the solvent was driven off, and the residue was chromatographed on the column. Isomer IIIa-e and an additional amount of isomer IIa-e were obtained. Compounds IIa-e and IIIa-e were recrystallized from ethanol.

Determination of Ratio of Isomers IIa-e and IIIa-e in Reaction Mixture. General Method. To a boiling solution of 0.24 g (1 mmole) of compound I in 50 ml of ethanol was added a solution (brought to boiling) of 2 mmoles of the appropriate aniline in 10 ml of ethanol. The reaction mixture was boiled for 12 h, after which 10 μliters of the solution was analyzed chromatographically. The quantitative ratio of the isomers (see Table 4) in the

mixture was determined from UV chromatograms according to the peak intensity of the band at λ 224 nm with allowance for the fact that the extinction coefficient ε_{224} was 18,200 for compounds IIa-e and 22,900 for compounds IIIa-e. Each experiment was run three times. The reproducibility of the results was ±2%.

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CYCLIZATION REACTIONS OF NITRILES.

50.* REGIOSELECTIVITY IN THE REACTIONS OF QUATERNIZED PYRIDIN-3-YLIDENE MALONITRILE AND CYANOACETATE ESTER DERIVATIVES WITH 1,3-DICARBONYL COMPOUNDS. CRYSTAL STRUCTURE OF 2-AMINO-3,5-DICARBOETHOXY-6-METHYL-4-(1-METHYLPYRIDINIUM-3-YL)-4H-PYRAN IODIDE

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The reaction of quaternized pyridin-3-ylidene malonitrile and cyanoacetate ester derivatives with 1,3-dicarbonyl compounds proceeds highly regioselectively to give substituted 2-amino-4-(1-methylpyridinium-3-yl)-4H-pyran iodides. The structure of 2-amino-3,5-dicarboethoxy-6-methyl-4-(1-methylpyridinium-3-yl)-4H-pyran iodide has been investigated by x-ray structural analysis.

Reaction studies of arylmethylenemalononitriles and arylmethylenecyanoacetate esters with carbonyl and 1,3-dicarbonyl compounds are related to research into biologically active substances [2-9]. These reactions have been found to proceed highly regioselectively to give substituted 2-amino-4-aryl-4H-pyrans [3-6, 8, 9]. The reaction pathway is not altered when hetarylmethylenemalononitriles or heterocyclic carbonyl compounds, such as pyrazol-5-one, barbituric acid, or thiohydantoin derivatives are used as substrates [2, 4-6, 9]. The high regioselectivity observed in these reactions can be explained in terms of the formation of Michael adducts [4, 8], and their subsequent cyclization (thermally or upon treatment with base) to give substituted 2-amino-4H-pyrans. Electronic and steric factors appear to be the controlling or determining factors (in the observed regioselectivity) [2, 5]. However, the principal aspects of this problem have not yet been clarified, and elucidating the factors responsible for the regioselectivity in the reactions of unsaturated nitriles with carbonyl compounds remains an important problem with both practical and theoretical implications. For example, in [7] the authors erroneously attributed the reaction of arylmethylenemalononitriles with 3-methyl-4-phenylpyrazol-5-one to result from nucleophilic addition

*See [1] for communication No. 49.

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