4,6-DICHLORO-5-ISOCYANATOPYRIMIDINES

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We have previously established [1,2] that on reaction of oxalyl chloride with 4,6dichloro-5-aminopyrimidines stable acid chlorides of N-pyrimidinyl-5-oxamic acids are formed; but in the case of 4,6-dichloro-2-aminopyrimidines, unstable acid chlorides of N-pyrimidinyl-2-oxamic acids. The differing stability of the acid chlorides of the 4,6-dichloropyrimidinyl-5-and 4,6-dichloropyrimidinyl-2-oxamic acids obviously depends on the effect of the two chlorine atoms in the 4 and 6 positions on the -NH-CO-CO-Cl group. The formation of the isocyanates IIa and b probably takes place via a cyclic transition state. Stuart-Briegleb models show that the chlorine atoms hinder the realization of this transition state, which is possible only when the NH group is drawn out of the plane of the ring. In the acid chlorides of the N-pyrimidinyl-2-oxamic acids there is no hindrance to the generation of the transition state, which helps in the formation of isocyanates under milder conditions. The low basicity of the 4,6-dichloro-2- and 4,6-dichloro-5-aminopyrimidines should favor the formation of the isocyanates (pK_a for 4,6-dichloro- and 4,6-dichloro-5-phenyl-2-aminopyrimidine [2] are -1.16 and -1.18; and for IIIa and b, -2.28 and -2.59).

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I, II, III a R=H, b $R=C_6H_5$; IV a R=H, $R'=C_6H_5$; b R=H, R'= cyclohexyl; c $R=R'=C_6H_5$; d $R=C_6H_5$, R'= cyclohexyl; V a R=H, $R''=C_2H_5$; b R=H, $R''=i-C_3H_7$; c $-R=C_6H_5$, $R''=C_2H_5$; d $R=C_6H_5$, $R''=i-C_3H_7$

In the present work we have prepared 4,6-dichloro-5-isocyanatopyrimidines IIa and b in good yield on thermal decomposition of the acid chlorides of 4,6-dichloropyrimidinyl-5oxamic acids Ia and b in o-dichlorobenzene at 170-180°. On reaction of the isocyanates IIa and b with amines or alcohols, their transformation products have been obtained - N,N'substituted ureas (IVa-d) or esters of pyrimidinyl-5-carbamic acids (Va-d). The starting aminopyrimidines IIIa and b are formed as a result of hydrolysis of IIa or b.

The N,N'-pyrimidinylphenylureas IVa and c could not be obtained on reaction of the aminopyrimidines IIIa and b with phenyl isocyanate. Probably the chlorine atoms in the 4 and 6 positions of the pyrimidine ring sterically hinder nucleophilic attack of the phenyl isocyanate and greatly reduce the basicity of the amino group. In distinction from compounds IIIa and b, the unsubstituted 5-aminopyrimidine, VI, gives a urea, VII, with phenyl isocyanate.

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Only a limited number of works are known on ³⁵Cl nuclear quadruple resonance spectroscopy of substituted pyrimidines [3-5]. We have obtained and analyzed the ³⁵Cl NQR spectra of the 4,6-dichloropyrimidines synthesized in this work. Replacement of H by C_6H_5 in the 2 position ought to lead to an increase in the ³⁵Cl $\nu_m^{\ b}$ NQR frequencies due to the inductive effect of this group. However, the observed frequencies are systematically lower than the ν_m^a frequencies ($\Delta > 0$). This indicates an increase in the double bond character of the C-Cl bond on transition from the H- to C_6H_5 -substituted compounds. The greatest effect, with $\Delta = 1$ MHz, is observed for IIIa,b, which is probably caused by a coplanar disposition of the amino group, in distinction from compounds IIa,b, IV, and Va-d, where, according to Stuart-Briegleb models, the isocyanate and amide groups are inclined to the plane of the pyrimidine ring. Therefore their effect is limited to an inductive component. Because of the relation of the substituents in IIa,b, IV, and Va-d, very closely similar ν_m^a frequencies in the range 35.78-35.98 MHz and ν_m^b frequencies from 35.38 to 35.82 MHz are observed in them. Therefore the means with respect to frequency ranges are also less for the C₆H₅-substituted compounds IIa, b, IV, and Va-d, and their difference is 0.28 MHz. This is considerably lower than the $\Delta = 1$ MHz value for compounds IIIa, b, which indicates an activating effect of the amino group on the redistribution of electron density in the pyrimidine ring upon substitutior in the 2 position.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in CCl₄, benzene, or KBr disks. The ³⁵Cl NQR spectra at 77°K were obtained on an ISSh-1-13 impulse spectrometer. Basicity constants of compounds IIIa and b were determined by the method of [2]. Purity of compounds was checked by thin-layer chromatography on a bonded layer of silica gel in the solvent system chloroform-methanol (80:1); the chromatograms were developed in an atmosphere of gaseous chlorine, and then were sprayed with an iodide-starch solution. Compounds Ia and Ib were prepared by the method of [1].

<u>4,6-Dichloro-5-isocyanatopyrimidine (IIa)</u>. A solution of 3.4 g (13.4 mmole) of Ia in 50 ml of o-dichlorobenzene was heated at 170-175° for 1 h, then at 190° for 15 min, until evolution of hydrogen chloride and carbon monoxide ceased. The reaction mixture was filtered without contact with atmospheric moisture, the mother liquor was evaporated, and the syrupy residue of IIa crystallized. The yield of IIa was 2.28 g (90%). It formed colorless crystals, bp 46-48° (0.15 mm); mp 38-40°. Found: C 32.0; H 0.9; Cl 37.1; N 22.2%. $C_5HCl_2N_3O$. Calculated: C 31.6, H 0.5, Cl 37.3, N 22.1%. IR frequencies (in absolute benzene): 2275 cm⁻¹ (NCO).

<u>4,6-Dichloro-5-isocyanato-2-phenylpyrimidine (IIb)</u> was obtained from 4.57 g (13.9 mmole) of Ib in 50 ml of o-dichlorobenzene analogously to IIa. The yield of isocyanate IIb was 3.48 g (94%). The product was purified by sublimation at 140-150° (0.025 mm), mp 140-142.5°. Found: C 49.8; H 1.8; Cl 26.8; N 16.0%. $C_{12}H_5Cl_2N_3O$. Calculated: C 49.6; H 1.9; Cl 26.7; N 15.8%. IR frequencies (in CCl₄): 2270 cm⁻¹ (NCO).

Hydrolysis of Isocyanate IIa. To a solution of 1.08 g (5.7 mmole) of IIa in 20 ml of acetone was added 0.5 ml of water, and the mixture was allowed to stand for 24 h at 20°. The solvent was distilled off under vacuum, and there was obtained 0.93 g (99%) of IIIa having a mp of 144-146° (from heptane), a mixed mp with a known specimen gave no depression.

<u>Hydrolysis of isocyanate IIb</u> was carried out with 0.98 g (3.7 mmole) of IIb in 30 ml of acetone, analogously to that of IIa. There was obtained 0.84 g (95%) of IIIb, having a mp of $139-141.5^{\circ}$ (from aqueous ethanol). The substance does not give a depression in a mixed melting point test with a known specimen.

<u>N-(4,6-Dichloro-2-substituted-5-pyrimidiny1)-N'-substituted Ureas (IVa-d)</u>. To 0.01 mole of IIa or b in 50 ml of absolute benzene was added 0.01 mole of amine in 20 ml of absolute benzene. The mixture was allowed to stand overnight at 20°. The precipitate which settled out was filtered off and the benzene filtrate was evaporated to dryness. The residue was combined with the filtered solid and was recrystallized. Compounds Iva-d are needle-like crystals (Table 1). IR frequencies (in KBr): 1700 (C=0), 3100-3400 cm⁻¹ (N-H).

Esters of N-(4,6-dichloro-2-substituted-5-pyrimidinyl)-carbamic Acids (Va-d). To 0.01 mole of IIa or b in 50 ml of absolute benzene was added a solution of 0.01 mole of absolute alcohol (or isopropyl alcohol) in 10 ml of benzene. The reaction mixture was allowed to

TABLE 🛛	1. C	haracterist	ics c	f C	compound	s Sj	ynthesized	1
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Com- pound	mp, °C ^a	Found, %				Empirical	Calculated, %				Vield
		с	н	Cl	N	formula	с	н	CI	N	%
IVa IVb IVc IVd Va Vb Vc Vd	203-205b 185-187 238-239 227-228b 113-116 135-137 170c 192-194 ^c	46,9 45,4 56,7 56,0 35,7 38,2 50,2 51,3	3,0 5,0 3,2 5,0 3,4 3,9 3,6 4,3	25,6 24,2 19,6 19,3 30,3 28,5 22,9 21,6	19,7 19,2 15,7 15,4 18,1 17,1 13,5 12,9	$\begin{array}{c} C_{11}H_8Cl_2N_4O\\ C_{11}H_{14}Cl_2N_4O\\ C_{17}H_{12}Cl_2N_4O\\ C_{17}H_{12}Cl_2N_4O\\ C_{7}H_7Cl_2N_3O_2\\ C_8H_9Cl_2N_3O_2\\ C_8H_9Cl_2N_3O_2\\ C_{13}H_{11}Cl_2N_3O_2\\ C_{14}H_{13}Cl_2N_3O_2 \end{array}$	46.7 45,7 56,8 55,9 35,6 38,4 50,0 51,5	2,9 4,9 3,4 5,0 3,6 3,6 3,5 4,0	25,1 24,5 19,7 19,4 30,0 28,4 22,7 21,7	19,8 19,4 15,6 15,3 17,8 16,8 13,5 12,9	96 95 93 96 91 91 93 97

^aCompound IVa was crystallized from dichloroethane; IV b and d, from ethanol; IVc, from a mixture of dimethylformamide and water; Va-d, from petroleum ether. ^bWith decomposition. ^cVc melts on introduction of the capillary into a block which has been preliminarily heated to 169°; Vd, when it has been preheated to 191°.

TABLE 2. ³⁵Cl Nuclear Quadrupole Resonance Frequencies (at 77°K) of Substituted 4,6-Dichloropyrimidines (II, IIIa,b, IV, Va-d)

	н		C ₆			
Compound	v ^a . MHz	v ^a m, MHz	ν ^b , MHz	vb, MHz	∆, MHz	
IIa, b	36,091	35.80	35,830	35.60	0,20	
	35 312	00,00	00,011	00,00		
IIIa, b	35,010	35,01	$34,180 \\ 33,829$	34,01	1,00	
IVa, c	36,046 35,943	35,84	36,068 35,581	35,82	0,02	
ivh d	35,685 36 254		35.894			
, (D, C	35,296	35.78	34,963	35,43	0,35	
Va,c	35,982	35,98	35,607 35,069	35,38	0,60	
Vb, d	36,202 35,751	35,98	35,596 35,461	35,53	0,45	

stand overnight at 20°, the solvent was distilled off under vacuum, and the residue was purified by recrystallization. Va is needle-like crystals; Vb-d are prisms (Table 1). IR frequencies (in KBr): 1630 (C=O), $3100-3400 \text{ cm}^{-1}$ (N-H).

Reaction of Aminopyrimidine IIIa with Phenyl Isocyanate. To a solution of 3.28 g (0.02 mole) of IIIa in 40 ml of chloroform was added 2.38 g (0.02 mole) of phenyl isocyanate in 10 ml of chloroform. The mixture was allowed to stand for 24 h at 20°. It was boiled for 2 h and evaporated to dryness. The starting aminopyrimidine IIIa was recovered unchanged.

<u>N-(5-Pyrimidinyl)-N'-phenylurea (VII)</u>. To a solution of 0.92 g (9.7 mmole) of VI in 200 ml of absolute benzene at 50-60° was added 1.16 g (9.7 mmole) of phenyl isocyanate in 15 ml of absolute benzene, over a 20-min period. The mixture was allowed to stand for 48 h at 20°. The precipitate which separated was filtered off, and the benzene filtrate was evaporated to dryness. There was obtained 1.39 g (67%) of needle-like crystals of VII, mp 199-201° (dec., from dichloroethane). Found: C 61.5; H 4.6; N 26.0%. $C_{11}H_{10}N_{4}O$. Calculated: C 61.7; H 4.7; N 26.1%. IR frequencies (in KBr): 1690 (C=O); 3100-3400 cm⁻¹ (N-H).

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