# REACTION OF 5-SUBSTITUTED 4,6-DICHLORO-2-AMINOPYRIMIDINES WITH OXALYL CHLORIDE

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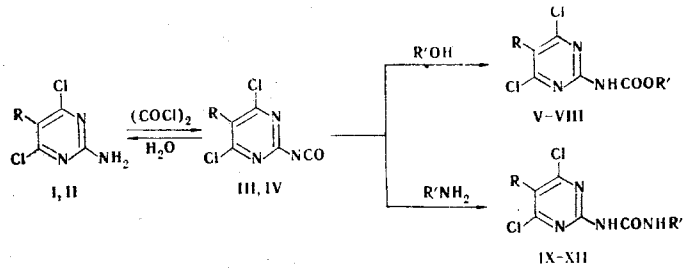
The reaction of 5-substituted 4,6-dichloro-2-aminopyrimidines with oxalyl chloride gives 2-isocyanatopyrimidines, the structures of which were proved by chemical means and the IR, PMR, and $^{35}Cl$ nuclear quadrupole resonance spectra. The intermediate pyrimidinyloxamic acid chlorides were not isolated; this is evidently explained by the low basicities of 2-aminopyrimidines.

It has been shown [1] that stable N-pyrimidinyl-5-oxamic acid chlorides are formed in the reaction of 4,6-dichloro-5-aminopyrimidines with excess oxalyl chloride.

In the present research we found that 2-isocyanatopyrimidines (III, IV) are formed in high yields when 2-aminopyrimidines (I, II) are refluxed with oxalyl chloride in benzene.

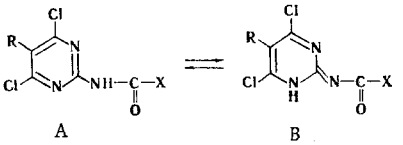



I R=H; II R=$C_6H_5$; III R=H; IV R=$C_6H_5$; V R=H, R'=$CH_3$; VI R=H, R'=2-naphthyl; VII R=$C_6H_5$, R'=$CH_3$; VIII R=$C_6H_5$, R=2-naphthyl; IX R=H, R'=$C_6H_5$; X R=H, R'=1-adamantyl; XI R=R'=$C_6H_5$; XII R=$C_6H_5$, R'=1-adamantyl

We were unable to isolate the intermediately formed N-pyrimidinyl-2-oxamic acid chlorides. The instability of the latter is evidently explained by the low basicities of the starting 2-aminopyrimidines (I and II), which, according to our data, have $pK_a$ values of −1.16 and −1.18, respectively. The presence of an isocyanato group in III and IV was confirmed by chemical transformations. 2-Pyrimidinylcarbamic acid esters (V-VIII) and N,N'-substituted ureas (IX-XII) were obtained by alcoholysis and aminolysis, respectively. Hydrolysis of isocyanates III and IV leads to the formation of starting aminopyrimidines I and II.

The IR spectra of III and IV contain an intense $\nu_{NCO}$ band at 2260 $cm^{-1}$ but do not contain the bands in the $\nu_{NH_2}$ region at 3350-3450 $cm^{-1}$ that are characteristic for starting I and II.

Since V-XII can exist in two tautomeric forms A and B, we investigated their IR, PMR, and $^{35}Cl$ nuclear quadrupole resonance (NQR) spectra.




V-VIII X=OR'; IX-XII X=NHR'

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TABLE 1. Characteristics of the Synthesized Compounds

| Compound | mp, °C | Crystallization solvent | Found, % | | | | Empirical formula | Calculated, % | | | | Chemical shifts[a] | | δH, ppm | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | Cl | N | | C | H | Cl | N | NH (1') | NH (3') | R | R' | |
| V | 134—136 | Petroleum ether | 32,9 | 2,2 | 31,9 | 18,8 | $C_6H_5Cl_2N_3O_2$ | 32,5 | 18,9 | 31,9 | 2,3 | 8,30 | - - | 7,47 | 4,24 | 100 |
| VI | 121—123 | Petroleum ether | 54,1 | 2,7 | 21,0 | 12,4 | $C_{15}H_9Cl_2N_3O_2$ | 53,9 | 12,6 | 21,2 | 2,7 | 8,60 | - - | 7,40 | 7,91 | 93 |
| VII | 163—165 | Carbon tetrachloride, petroleum ether | 48,5 | 2,9 | 23,8 | 14,3 | $C_{12}H_9Cl_2N_3O_2$ | 48,3 | 14,1 | 23,8 | 3,0 | 8,55 | - - | 7,75 | 4,24 | 97 |
| VIII | 176—178 | Ethanol | 61,2 | 3,3 | 17,4 | 10,4 | $C_{21}H_{13}Cl_2N_3O_2$ | 61,5 | 10,2 | 17,3 | 3,2 | 8,60 | - - | 7,75 | 7,91 | 96 |
| IX | 195—197 | Ethanol | 47,0 | 2,7 | 25,2 | 19,6 | $C_{11}H_8Cl_2N_4O$ | 46,7 | 19,8 | 25,1 | 2,8 | 8,50 | 11,00 | 7,35 | 7,75 | 97 |
| X | 218—219 | Petroleum ether | 52,7 | 5,3 | 20,8 | 16,3 | $C_{15}H_{18}Cl_2N_4O$ | 52,8 | 16,4 | 20,8 | 5,3 | 8,73 | 7,92 | 7,27 | β- and γ-H 2,47[b] δ-H 2,09 | 88 |
| XI | 218—220 | Ethanol | 56,9 | 3,5 | 19,8 | 15,5 | $C_{17}H_{12}Cl_2N_4O$ | 56,8 | 15,6 | 19,7 | 3,4 | 8,50 | 11,01 | 7,75 | 7,75 | 92 |
| XII | 249—250 | Methanol | 61,1 | 5,4 | 17,0 | 13,1 | $C_{21}H_{22}Cl_2N_4O$ | 60,4 | 13,4 | 17,0 | 5,3 | 8,72 | ~7,88[c] | 7,72 | β- and γ-H 2,45[b] δ-H 2,05 | 96 |

[a]The symbol (1')-NH pertains to the protons of the amino group of pyrimidine, and (3')-NH pertains to the protons of the NHR' group.

[b]The assignment of the proton signals of the adamantyl group was made with allowance for the results in [2].

[c]This line is overlapped by the $C_6H_5$ multiplet.

The IR spectra of V-XII are characterized by an intense and frequently structured carbonyl band at 1700 $cm^{-1}$ and absorption bands at 3100-3300 $cm^{-1}$, which are characteristic for associated $>NH$ groups.

The possibility of self-association of the $>NH\cdots O=C<$ type for both tautomeric forms and the complexity of the separation of the overlapped bands of the associates make it impossible to thoroughly analyze the A $\rightleftharpoons$ B system from the IR spectra. Additional information was obtained from the PMR spectra of V-XII and the $^{35}Cl$ NQR data. The different degree of delocalization of the $\pi$-electron density of the pyrimidine ring in tautomers A and B should lead to greater shielding of the proton in the 5 position (V, VI, IX, and X) in the case of tautomer B and to the appearance of two singlet signals corresponding to the two tautomers. It is apparent from Table 1 that the PMR spectra of V, VI, IX, and X at 7-8 ppm are characterized by one singlet line. This constitutes evidence for practically complete shifting of the A $\rightleftharpoons$ B equilibrium to favor one of the tautomeric forms. A comparison of the spectra of the indicated compounds with the spectrum of 4,6-dichloropyrimidine [3], which has a structure similar to that of tautomer A, provides a basis for the assumption that the equilibrium is shifted to favor tautomer A. In view of the similarity in the compounds, the conclusion is valid for the entire V-XII series, and the signals at 8.30-8.70 ppm can be assigned to the (1')-NH protons of the amino group of pyrimidine in tautomer A. When the solution is diluted, these signals, as well as the signals of the (3')-NH protons of IX-XII, are shifted to strong field; this indicates the formation of intermolecular hydrogen bonds (IHB) in both cases.

The anomalous chemical shifts in the 11-ppm region in the spectra of IX and XI are probably associated with deshielding of the (3')-NH protons by the phenyl ring and its smaller steric volume, which promotes the formation of IHB, as compared with adamantyl derivatives X and XII.

The problem of the predominance of tautomeric structure A is solved quite unambiguously for the crystalline state of the investigated compounds. The $^{35}Cl$ NQR spectra of VI and VIII are characterized, respectively, by doublet (35.456 and 35.416 MHz) and singlet (35.890 MHz) signals. This makes it possible, despite the influence of crystal effects that lead to structural nonequivalence of the chlorine atoms (on the order of several tens of megahertz in the spectra of 4,6-dichloropyrimidines [4]), to note in our case that the extremely low splitting of the signals (0.040 MHz) of VI and the absence of splitting in the spectrum of VIII attest to chemical equivalence of the chlorine atoms and are in agreement with symmetrical structure A.

## EXPERIMENTAL

The IR spectra of benzene solutions and KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of $CDCl_3$ solutions were recorded at room temperature with a Tesla BS 487B spectrometer (80 MHz) with hexamethyldisiloxane as the external standard. The $^{35}Cl$ NQR spectra at 77°K were obtained with an ISSh-1-13 pulse spectrometer. The basicity constants of I and II were determined spectrophotometrically in sulfuric acid solutions of various concentrations at 25°C with Specord UV-Vis and SF-16 spectrophotometers. The $H_0$ function, the values of which for solutions of various concentrations were taken from [5], was used to characterize the acidities of the solutions.

The individuality of the synthesized compounds was monitored by thin-layer chromatography (TLC) on a fixed silica gel–gypsum layer in a chloroform–methanol system (50:1); the chromatograms were developed in a gaseous chlorine atmosphere with subsequent spraying with an iodine–starch solution.

The starting 2-aminopyrimidines (I and II) were obtained by the methods in [6, 7].

4,6-Dichloro-2-isocyanatopyrimidine (III). A solution of 9.53 g (0.075 mole) of oxalyl chloride in 40 ml of absolute benzene was added dropwise with stirring to a solution of 2.46 g (0.015 mole) of I in 150 ml of absolute benzene, and the mixture was refluxed for 2 h until hydrogen chloride and carbon monoxide evolution ceased. The mixture was then cooled to 20°C and filtered without access to moisture. The benzene mother liquor was evaporated, after which the syrupy residual III began to crystallize. Workup gave 2.7 g (95%) of colorless crystals with mp 37-38°C [bp 48-50°C (0.03 mm)]. Found: C 31.1; H 0.76; Cl 37.6; N 22.5%. $C_5HCl_2N_3O$. Calculated: C 31.6; H 0.53; Cl 37.3; N 22.1%.

4,6-Dichloro-2-isocyanato-5-phenylpyrimidine (IV). This compound [2.6 g (98%)], with mp 144-147°C, was obtained from 2.4 g (0.01 mole) of II and 6.35 g (0.05 mole) of oxalyl chloride in 170 ml of absolute benzene, as in the preparation of III. Found: C 49.5; H 2.1; Cl 26.7. N 15.7%. $C_{11}H_5Cl_2N_3O$. Calculated: C 49.6; H 1.9; Cl 26.6; N 15.8%.

Hydrolysis of Isocyanate III. A 0.98-g (5.2 mmole) sample of III was dissolved in 30 ml of acetone, and 1 ml of water was added. The solution was allowed to stand at 20°C for 18 h, after which the solvent was removed by vacuum distillation to give 0.84 g (99%) of I with mp 218-221°C (from ethanol); no melting-point depression was observed for a mixture of this product with a genuine sample.

Hydrolysis of Isocyanate IV. Hydrolysis was carried out with 1.33 g (5 mmole) of IV in 50 ml of acetone, as in the hydrolysis of III. Workup gave 1.2 g (100%) of II with mp 217-219°C (from ethanol); no melting-point depression was observed for a mixture of this product with a genuine sample.

5-Substituted 4,6-Dichloro-2-pyrimidinylcarbamic Acid Esters (V-VIII). A solution of 0.01 mole of methanol (or 2-naphthol) in 30 ml of absolute benzene was added to a solution of 0.01 mole of III or IV in 50 ml of absolute benzene, and the mixture was allowed to stand overnight. The solvent was removed by vacuum distillation, and the residue was purified by recrystallization. Workup gave acicular crystals of V, VI, and VIII and prisms of VII.

N'-Substituted N-(4,6-Dichloro-5-Substituted 2-Pyrimidinyl)urea (IX-XII). A 0.01-mole sample of the corresponding amine in 30 ml of absolute benzene was added to 0.01 mole of III or IV in 50 ml of absolute benzene, and the mixture was allowed to stand at 20°C for 18 h. The precipitate was removed by filtration, and the benzene filtrate was evaporated to dryness. The residue was combined with the precipitate and recrystallized to give IX and XII as lamellar crystals, X as needles, and XI as long prisms.

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# 4-(o-CARBOXYPHENYLAMINO)PYRIMIDINES


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2-Chloro-4-(o-carboxyphenylamino)pyrimidines were synthesized by reaction of 2,4-dichloropyrimidines with anthranilic acid in aqueous media in the presence of hydrochloric acid. A number of their derivatives – 2-hydroxy-, 2-methoxy-, and 2-amino-4-(o-carboxyphenylamino)pyrimidines – were obtained.


Pyrimidine derivatives that contain an o-carboxyphenylamino group are of interest as potential physiologically active substances [1, 2]. In this connection the preparation of new compounds of this series and the study of their properties are of importance.

In the present paper we describe 4-(o-carboxyphenylamino)pyrimidines (IIa-g) obtained by the reaction of 2,4-dichloropyrimidines (Ia-g) with anthranilic acid:


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