PYRIMIDINES.

LXII.* SOME TRANSFORMATIONS OF CYANO DERIVATIVES OF PYRIMIDINE

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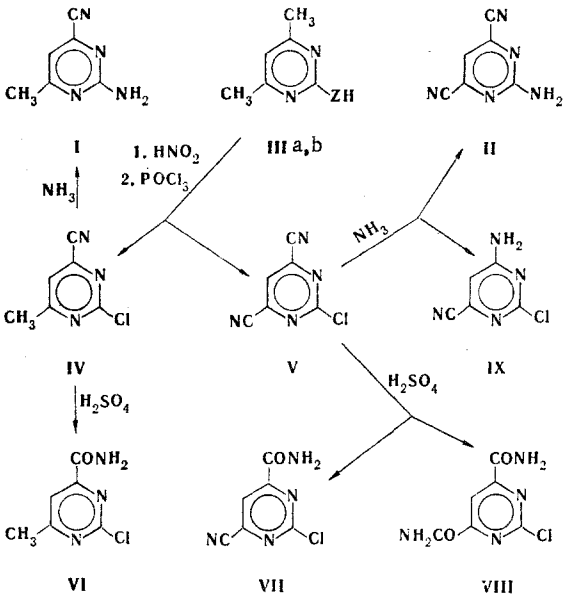
The synthesis of 2-amino-6-cyano-4-methylpyrimidine and 2-amino-4,6-dicyanopyrimidine from the corresponding chloro derivatives is described. It is shown that the reaction of ammonia with chlorodicyanopyrimidine proceeds in two directions — one observes substitution of either the chlorine atom or the cyano group.

During a study of the PMR spectra of a number of 2-aminopyrimidines we found it necessary to synthesize the previously undescribed 2-amino-6-cyano-4-methylpyrimidine (I) and 2-amino-4,6-dicyanopyrimidine (II). The selected synthetic scheme includes nitrosation of 2-hydroxy(amino) derivatives of 4,6-dimethylpyrimidine (IIIa, b), conversion of the resulting mono- and dioximino derivatives to 2-chloro-6-cyano-4-methylpyrimidine (IV) and 2-chloro-4,6-dicyanopyrimidine (V), and subsequent replacement of the chlorine atom by an amino group:



III a Z = O; b Z = NH

The nitrosation of IIIa was carried out by the method in [2] to obtain the monooximino derivative. In this case it was found that even the use of an equimolar ratio of IIIa and sodium nitrite leads to the formation of a small amount of dioximino derivative along with the expected monooximino derivatives. This was established by conversion of the crude nitrosation product by the action of $POCl_3$ to a mixture of 2-chloro-6-cyano-4-methylpyrimidine (IV) and 2-chloro-4,6-dicyanopyrimidine (V).† Dicyano derivative V was obtained as the principal reaction product in the nitrosation of 2-amino-4,6-dimethylpyrimidine (IIIb) in

*See [1] for communication LXI.

†The preparation of V was reported in [3], but the synthetic method and the physical constants of this compound were not presented.

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TABLE 1. Composition of the Mixtures Obtained from IIIa and IIIb

Starting compound	Yields of the identified products, %			
	IV	V	VI	VII
IIIa	24	4	<1	<1
IIIb	1	28	Traces	3

actic acid solution with the aid of a threefold amount of sodium nitrite [4] and subsequent refluxing of the nitrosation product in $POCl_3$. In addition to these products, we isolated very small amounts of carbamoylpyrimidines VI and VII (Table 1). They are probably formed through partial hydrolysis of the cyano derivatives when the reaction mixtures are treated with water. The structure of IV-VIII follow from the transformations presented in the scheme above and are confirmed by the spectral data.

The stretching vibrations of the C≡N bond in the vibrational spectra of cyano derivatives IV, V, and VII are characteristic and show up at 2250-2260 cm^{-} . However, these vibrations show up differently in the IR and Raman spectra. Whereas the corresponding band is quite strong in the IR spectrum of dicyano derivative V, it is of low intensity in the IR spectrum of IV, and it is difficult to identify at all in the spectrum of VII (compare with the data in [2, 5]). However, the presence of distinct bands in the Raman spectra of IV and VII over the above-indicated range confirms the presence of cyano groups in these compounds. The stretching vibrations of the carbamoyl C=O groups show up in the IR spectra of VI-VIII as very intense absorption bands at ∿1700 cm^{-1}. The signal of the protons of the carbomyl groups is found in the PMR spectra of these compounds at 7.8-8.4 ppm in conformity with the data in [6]. It is characteristic that these resonance signals are markedly diffuse and have a symmetrical double-peaked structure, indicating a difference in the shielding of the protons of the carbomoyl group.

We established that replacement of the chlorine atom in IV by an amino group takes place smoothly in tetrahydrofuran (THF) saturated with ammonia to give the expected 2-amino-6-cyano-4-methylpyrimidine (I). Dioxane was found to be less suitable as a solvent, since VI was established chromatographically as an impurity in the reaction products, indicating partial addition of ammonia to the C≡N bond to give the easily hydrolyzed amidine. This side process begins to play a significant role when the amination is carried out in more polar solvents (in acetone, for example).

We found that the amination of dicyano derivative V may take place in two directions — with replacement of the chlorine atom or the cyano group. 2-Amino-4,6-dicyanopyrimidine (II) and 2-chloro-6-amino-4-cyanopyrimidine (IX), respectively, are formed in this case. The ratio of the amination products depends on the nature of the solvent. Thus, whereas the ratio of II-IX is 1:1 in benzene, the principal product in dioxane and PHF is II, and only traces of IX are detected. The structures of I, II, and IX were established on the basis of the results of elementary analysis and the spectral data. The band of stretching vibrations of the C≡N bond at ∿2260 cm^{-1} in the IR spectra indicates the presence of a cyano group in these compounds. In the case of dicyano derivative II the indicated band is of low intensity but shows up distinctly in the Raman spectrum. The amino group in I, II, and IX were identified by means of the IR and PMR spectra, and the chemical shifts of the protons of the amino groups calculated via an additive scheme from the data for 2- and 4-aminopyrimidines [7] are in agreement with the experimentally found values.

Replacement of a cyano group in the even-numbered positions of the pyrimidine ring is a known fact. However, reactions of this type usually take place under the influence of strong nucleophilic agents (for example, sodium methoxide [8-11], sodium mercaptide [10], and sodium hydroxide [12]). In the case of additional activation, substitution of the cyano group may also occur under the influence of weaker nucleophilic agents. This has been demonstrated [13] in the case of the reaction of 4,5-dicyano-2-methylpyrimidine with water, methanol, and ammonia. In the case of V the replacement of the cyano group by an amino group may also be explained by mutual activation of the two cyano groups. Despite the fact that they are formally in the meta position relative to one another, this sort of activation is due to the high conductivity of electronic effects of substituents from the 6 position of the pyrimidine ring to the 4 position [14].

EXPERIMENTAL

The IR spectra of 5% solutions of the compounds in $CHCl_3$ or KBr pellets were recorded with a UR-20 spectrometer. The Raman spectra of crystalline samples were recorded with a Coderg PH-1 spectrometer with a helium-neon laser. The PMR spectra of 5% solutions of the compounds in $CDCl_3$ or dimethyl surfoxide (DMSO) were recorded with a Varian A 56/60 spectrometer with hexamethyldisiloxane as the internal standard. The molecular weights were determined mass spectrometrically with an MS-902 spectrometer.

2-Chloro-6-cyano-4-methylpyrimidine (IV). A 15.3-g (0.1 mole) sample of the hydrochloride of IIIa was nitrosated by the method in [2] with 7.5 g (0.11 mole) of sodium nitrite. The isolated product (8.1 g) was added to 75 ml of $POCl_3$, and the temperature of the mixture was raised carefully until a vigorous reaction commenced (at 80-90°); at the end of this reaction 41 ml of diethylaniline was added, and the mixture was refluxed for 1 h. The excess $POCl_3$ was removed by vacuum distillation, and the residue was poured over ice. The aqueous mixture was extracted with ether, and the extract was washed with sodium bicarbonate solution and water and dried. The solvent was then evaporated, and the residue was dissolved and chromatographed on silica gel in a $CHCl_3$–ethyl acetate system (1:1). The fraction with R_f 0.85 on Silufol was collected. The eluate was evaporated, and the residue was crystallized from light petroleum ether and vacuum sublimed to give 3.7 g (24%) of a product with mp 45-46°. IR spectrum ($CHCl_3$): 2260 cm^{-1} (C≡N). Raman spectrum: 2255 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$): 2.63 (4-CH_3) and 7.45 ppm (5-H). According to the data in [2], this compound has mp 45-47°.

Workup of the fraction with R_f 0.95 yielded 0.6 g (4%) of V.

2-Chloro-4,6-dicyanopyrimidine (V). A solution of 21 g (0.3 mole) of sodium nitrite in 35 ml of water was added dropwise at 18-20° in the course of 4 h to a solution of 12.3 g (0.1 mole) of IIIb in a mixture of 60 ml of acetic acid and 10 ml of water, and the mixture was stirred for 2 h. The resulting precipitate was removed by filtration, washed with water, and dried. The product (12.4 g) was triturated finely and added gradually with stirring to 50 ml of $POCl_3$. The temperature of the mixture was raised slowly until the reaction commenced (at 90°). After 15 min, 4.5 ml of diethylaniline was added, and the mixture was heated at 120-130° for 45 min. It was then cooled and poured over ice. The aqueous mixture was extracted with $CHCl_3$, and the extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel in a $CHCl_3$–ethyl acetate system (1:1). The fraction with R_f 0.95 on Silufol was collected. The eluate was evaporated, and the residue was vacuum sublimed to give 4.6 g (28%) of V with mp 115-115.5 (from CCl_4). IR spectrum ($CHCl_3$): 2260 cm^{-1} (C≡N). PRM spectrum ($CDCl_3$): 7.89 ppm (5-H). Found: C 44.0; H 0.90; Cl 21.5; N 34.2%. C_6HClN_4. Calculated: C 43.8; H 0.61; Cl 21.6; N 34.0%.

Workup of the fraction with R_f 0.65 yielded 0.5 g (3%) of VII, identical to the product obtained by hydrolysis of V.

2-Chloro-4-methyl-6-carbamoylpyrimidine (VI). A 0.31-g (2 mmole) sample of IV was added to 1 ml of concentrated H_2SO_4 at 10°, and the mixture was stirred at room temperature for 4 h. It was then poured over ice, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.22 g (65%) of a product with mp 181-182° (from alcohol). IR spectrum: 1700, 1715, 3200, and 3420 cm^{-1} ($CONH_2$). PMR spectrum (DMSO): 7.80-8.30 ($CONH_2$) and 7.92 ppm (5-H). According to the data in [15], this compound has mp 181-182°.

2-Chloro-4-cyano-6-carbamoylpyrimidine (VII) and 2-Chloro-4,6-dicarbamolypyrimidine (VIII). A 0.84-g (5 mmole) sample of V was dissolved in 2.5 ml of concentrated H_2SO_4 at 10°, and the mixture was maintained at room temperature for 4 h, after which it was poured over ice. The resulting precipitate was removed by filtration, washed with water, and dried. The produce (0.81 g) was refluxed in 400 ml of ethyl acetate, and the ethyl acetate extract was evaported to dryness. The residue was crystallized from alcohol to give 0.29 g (32%) of VII with mp 185.5-186.5°. IR spectrum (KBr): 1710 (amide C=O); 3200, 3290, and 3460 cm^{-1} (NH_2). Raman spectrum: 2255 cm^{-1} (C≡N). PMR spectrum (DMSO): 8.16, 8.38 ($CONH_2$); 8.54 ppm (5-H). Found: C 38.9; H 1.77; Cl 19.4; N 30.3%; M 182 and 184 (intensity 3:1). $C_6H_3ClN_4O$. Calculated: C 39.4; H 1.64; Cl 19.5; N 30.7%; M 182 and 184.

The ethyl acetate-insoluble residue was crystallized from alcohol to give 0.40 g (40%) of VIII with mp 288-289.5°. IR spectrum (KBr): 1695 (amide C=O); 3160, 3250-3310, and 3445 cm^{-1} (NH_2). PMR spectrum (DMSO): 8.07, 8.33 ($CONH_2$); 8.39 ppm (5-H). Found: C 35.8; H 2.46; Cl 18.0; N 27.6%. $C_6H_3ClN_4O_2$. Calculated: C 35.9; H 2.49; Cl 17.7; N 27.9%.

2-Amino-6-cyano-4-methylpyrimidine (I). A solution of 0.77 g (5 mmole) of IV in 10 ml of dry THF was saturated with ammonia and allowed to stand for 3 days. It was then evaporated, and the residue was treated with water and extracted with ethyl acetate. The extract was dried and evaporated to dryness, and the residue was crystallized from $CHCl_3$ to give 0.36 g (53%) of product with mp 199-200°. IR spectrum (KBr): 1660, 3190, 3330, and 3460 (NH_2); 2245 cm^{-1} (C≡N). PMR spectrum (DMSO): 6.93 (5-H) and 7.07 ppm (2-NH_2). Found: C 53.6; H 4.41; N 41.4%. $C_6H_6N_4$. Calculated: C 53.7; H 4.47; N 41.8%.

2-Amino-4,6-dicyanopyrimidine (II). Ammonia was bubbled through a solution of 0.49 g (3 mmole) of V in 10 ml of dry THF for 30 min, after which it was allowed to stand for 24 h. It was then evaporated to dryness, and the residue was treated with water. The solid material was removed by filtration and dried to give 0.35 g (80%) of a product with mp 195.5-196.5° (from benzene). IR spectrum (KBr): 1630, 1650, 3235, 3365, 3425, and 3475 (NH_2); 2260 cm^{-1} (C≡N). Raman spectrum: 2255 cm^{-1} (C≡N). PMR spectrum (DMSO): 7.67 (5-H) and 7.87 ppm (2-NH_2). Found: C 49.4; H 2.21; N 47.8%; M 145. $C_6H_3N_5$. Calculated: C 49.7; H 2.97; N 48.3%; M 145.

2-Chloro-4-amino-6-cyanopyrimidine (IX). Ammonia was bubbled through a solution of 0.33 g (2 mmole) of V in 15 ml of dry benzene, after which it was allowed to stand for 3 days. It was then evaporated, and the residue was washed with water, dried, and chromatographed in a thin layer of silica gel [$CHCl_3$—ethyl acetate (1:1)]. The lower zone (R_f 0.61 on Silufol) was collected (elution with ethyl acetate). The eluate was evaporated to give 0.11 g (36%) of IX with mp 232-234° [alcohol—benzene (1:4)]. IR spectrum (KBr): 1660, 3200, 3330, 3380, and 3430 (NH_2); 2250-2260 cm^{-1} (C≡N). PMR spectrum (DMS): 6.90 (5-H) and 8.03 ppm (4-NH_2). Found: C 38.8; H 2.05; Cl 23.3; N 36.0%. $C_5H_3ClN_4$. Calculated: C 38.8; H 1.94; Cl 23.0; N 36.3%.

Workup of the upper zone (R_f 0.89 on Silufol) in the same way yielded 0.11 g (38%) of II.

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