ACYLATION AND OXIDATION OF 4-CHLORO-6-HYDROXYAMINOPYRIMIDINES.
SYNTHESIS OF 4-CHLORO-6-NITRO(NITROSO)PYRIMIDINES

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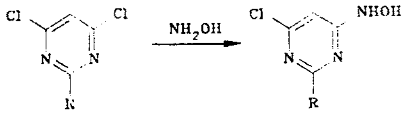
Treatment of 2-R-4,6-dichloropyrimidines with hydroxylamine gives 2-R-4-chloro-6-hydroxyaminopyrimidines, which are converted to mono- and diacyl derivatives upon acylation. Oxidation of 4-chloro-6-hydroxyaminopyrimidines with manganese dioxide or ozone gives the first reported synthesis of 4-chlorine-containing 6-nitroso- or 6-nitropyrimidines, respectively.

It has previously been demonstrated that oxidation of alkyl(aryl)-substituted 2- and 4-hydroxyaminopyrimidines provides a route for the formation of relatively inaccessible alkyl(aryl)-substituted 2- and 4-nitro(nitroso)- pyrimidine derivatives [1, 2]. In the present paper we have examined the reaction of 2-alkyl(aryl)-4,6-dichloropyrimidines (Ib, c) with hydroxylamine, and have studied the behavior of the resulting chlorine-containing hydroxyamines IIa-c in reactions with hydroxylamine, and under acylation and oxidation conditions.

Reaction of 4,6-dichloropyrimidine (Ia) with hydroxylamine results in the formation of 4-chloro-6-hydroxyaminopyrimidine (IIa) [3, 4]. We have found that compounds Ib and c also react readily with hydroxylamine to give the corresponding 2-substituted 4-chloro-6-hydroxyaminopyrimidines (IIb, c). An alcohol solution of hydroxylamine, prepared by neutralization of hydroxylamine hydrochloride with either potassium hydroxide [3] or triethylamine [5], can be used in these reactions.

Prolonged refluxing of compound IIa with an excess of either the free base or hydroxylamine hydrochloride did not give 4,6-dihydroxyaminopyrimidine. The starting material was recovered unchanged. This is apparently due to the deactivating effect of the hydroxyamino group. It is known that the nucleophilic susceptibility of a halogen in the 4(6)-position of a pyrimidine ring is deactivated by substituents of the type C_6H_5, OCH_3, and NR_2, which are capable of indirect deactivation of a reaction site in the m-position of the heterocycle [4, 6, 7].



Ia-c IIa-c

I, IIa R=H, b R=CH_3, c R=C_6H_5

Compounds IIa-c react readily to form mono- and diacyl derivatives, depending on the reagent ratio. For example, treatment of compounds IIa-c with benzoyl chloride at a reagent ratio of 1:1 gave the monobenzoyl derivatives, 2R-4-chloro-6-(N'-benzoylhydroxyamino)-pyrimidines (IIIa-c), which could be easily acylated further. Thus, reaction of compounds IIIa, b with benzoyl chloride gave the corresponding 2-R-4-chloro-6-(N'-benzoyl-N'-benzoyloxy)aminopyrimidines (IVa, b). Acetylation of compounds (IIa-c) with excess acetyl chloride led to the formation of the corresponding 2-R-4-chloro-6-(N'-acetyl-N-acetoxy)aminopyrimidines (Va-c). The structures of compounds III-V were confirmed by their IR spectra (Table 1).

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TABLE 1. Properties of Compounds II-XI

Compound	Molecular formula	mp, °C*	Yield, %	Compound	Molecular formula	mp, °C*	Yield, %
IIb	$C_5H_5ClN_3O$	170...173 (dec.)	60	VIIc	$C_{10}H_6ClN_3O$	153...157 (dec.)	80
IIc	$C_{10}H_8ClN_3O$	153...157 (dec.)	70	VIIIa	$C_{10}H_7ClN_4$	73...75 (72...73 [9])	20
IIIa	$C_{11}H_8ClN_3O_2$	207...209	94				
IIIb	$C_{12}H_{10}ClN_3O_2$	193...196	42	VIIIb	$C_{11}H_9ClN_4$	94...95	34
IIIc	$C_{17}H_{12}ClN_3O_2$	140...142	57	VIIIc	$C_{16}H_{11}ClN_4$	140...142	74
IVa	$C_{18}H_{12}ClN_3O_3$	145...147	25	IX	$C_{17}H_{15}N_5$	201...204	60 (A)
IVb	$C_{19}H_{14}ClN_3O_3$	104...107	32	X	$C_{20}H_{12}Cl_2N_6O$	176...178 (dec.)	40
Va	$C_8H_8ClN_3O_3$	77...79	64				
Vb	$C_9H_{10}ClN_3O_3$	102...105	71	XIa	$C_4H_2ClN_3O_2$	73...76	50 (A); 36 (B)
Vc	$C_{14}H_{12}ClN_3O_3$	126...128	65				
VIa	$C_{14}H_{22}ClN_5O_3$	80...83	42	XIb	$C_5H_4ClN_3O_2$	108...109	95 (A); 90 (B)
VIb	$C_{15}H_{24}ClN_5O_3$	84...86	63				
VIc	$C_{18}H_{14}ClN_5O_3$	139...145	83	XIc	$C_{10}H_6ClN_3O_2$	100...101	75 (A); 80 (B)
VId	$C_{19}H_{16}ClN_5O_3 \times 1{,}5C_4H_8O_2$	144...146	83				

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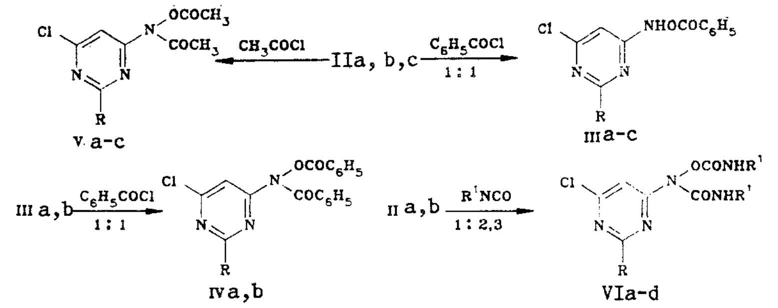
*Compounds IIb, IIIb, c, Vc, IX, and XIb, c were recrystallized from alcohol, IIc from dioxane—water, IIIa from alcohol—dioxane, IVf from methanol, IVb, Va, b, VIa, b, Xc, and XIa from petroleum ether, VIc from dioxane—pentane, VId from dioxane, VIIc from ethyl acetate, and VIIIa-c from hexane.

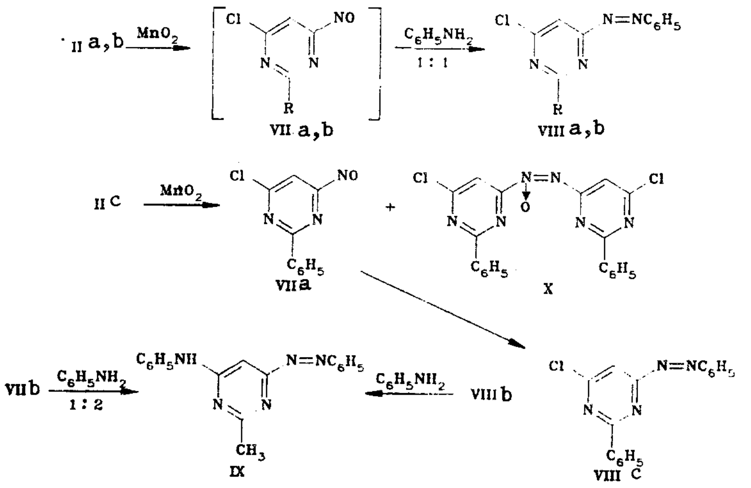


III—V a $R=H$, b $R=CH_3$, c $R=C_6H_5$; VI a $R=H$, $R^1=C_4H_9$; b $R=CH_3$, $R^1=C_4H_9$; c $R=H$, $R^1=C_6H_5$; d $R=CH_3$, $R^1=C_6H_5$

The reaction mixture arising from treatment of compound IIa with phenyl isocyanate (at a 1:1 reagent ratio) contained three compounds, the starting material, diureide VIc, and the monoureide derivative, apparently. The latter compound could not be isolated due to its low stability. Reaction of 2 moles phenyl isocyanate or butyl isocyanate with compounds IIa, b gave the corresponding 2-R-4-chloro-6-(N'-R^1-carbamoyl-N'-R^1-carbamoyloxy)-aminopyrimidines (VIa-d), which decomposed upon attempted storage.

The oxidation of compounds IIa-c was studied in order to provide a route for the synthesis of chlorine-containing 4-nitro- and 4-nitrosopyrimidines. Treatment of compounds IIa-c with activated MnO_2 in chloroform solution resulted in the rapid disappearance of starting materials and the formation of new compounds, while the solutions acquired a light green hue characteristic of nitroso derivatives [1, 8]. We were not able, however, to isolate compounds VIIa, b; these compounds decomposed to give complex mixtures of substances upon evaporation of their solutions. 2-Phenyl-4-chloro-6-nitrosopyrimidine (VIIc) was isolated and characterized both analytically and spectroscopically.

In order to confirm the formation of the 4-nitrosopyrimidines VIIa, b, and also to further characterize compound VIIc, the light green chloroform solutions obtained upon oxidation were worked up with aniline, resulting in the formation of the corresponding 2-R-4-chloro-6-phenylazopyrimidines (VIIIa-c) (see scheme on following page).

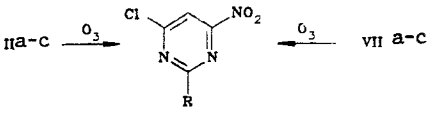


VII, VIII a R=H; b R=CH_3

Using compound VIIb as an example, we also found that addition of a twofold excess of aniline to a solution of the nitroso derivative resulted in the formation of 2-methyl-4-anilino-6-phenylazopyrimidine (IX). The same compound was obtained upon treatment of compound VIIIb with aniline. The presence of an electron acceptor azo group in the 6-position of the pyrimidine ring apparently facilitates nucleophilic substitution of the chlorine atom. This observation is confirmed by literature data concerning the reactions of substituted 4-chloro-6-phenylazopyrimidines with nucleophilic reagents [9].

Upon oxidation of compound IIc with MnO_2 a small amount of 6,6'-dichloro-2,2'-diphenyl-4,4'-azoxypyrimidine (X) was observed, in addition to the nitroso compound VIIc. As the catalyst activity was decreased, for instance, if the catalyst was used a second time in the oxidation of hydroxyaminopyrimidines, the yield of the nitrosopyrimidine derivative VIIc decreased, and the yield of the corresponding azoxy derivative X increased.

Ozonolysis of chloroform solutions of compounds IIa-c in a manner analogous to [2] gave excellent yields of the corresponding 2-R-4-chloro-6-nitropyrimidines (XIa-c), which are stable crystalline materials.



XIa R=H; b R=CH_3; c R=C_6H_5

Ozonolysis of freshly prepared solutions of the 6-nitrosopyrimidines VIIa-c also led to the formation of the 6-nitropyrimidines XIa-c. The structures of these newly synthesized compounds were established based on their analytical and spectral data (Tables 1 and 2).

The mass spectra of the nitropyrimidines XIa-c contained, in addition to molecular ion peaks (M^+ 159, 173, and 235 for compounds XIa-c, respectively), intense peaks for the corresponding $(M-NO_2)^+$ fragment ions (at 113, 127, and 189 for compounds XIa-c); these fragment ions are characteristic of compounds containing nitro groups (cf. [2]).

The IR spectra of these nitro compounds also contained new intense absorption bands, which are absent in the spectra of the starting materials Ia-c, in the regions 1580-1550, 1400-1360, and 880-840 cm^{-1}; these bands are characteristic NO_2 vibrational frequencies [10].

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer using KBr pellets at a concentration of 0.25%. UV spectra were obtained on a Specord UV-Vis spectrophotometer in ethyl alcohol, mass spectra on a Finnigan MAT 8200 spectrometer, and PMR spectra on a Varian A 56/60 spectrometer; chemical shifts are reported on the δ scale vs. HMDS as internal standard. Product purity and homogeneity were monitored by TLC on Silufol UV-254 plates. Activated manganese dioxide was synthesized from manganese sulfate according to [11].

TABLE 2. UV and PMR Spectral Data for Newly Synthesized Compounds

Compound	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm (in $CDCl_3$)*			
		$C_{(5)}$—H	R	C—H arom (m)	remaining signals
IIc	—	6,67s	7,40 ... 7,60; 8,17 ... 8,40 (m, 3 : 2)	—	9,40 (NH); 10,43 (OH)
IIIa	208 (4,24), 240 (4,34), 270 sh	6,80s	8,33 (s, $C_{(2)}$—H)	7,50 ... 7,70; 7,93 ... 8,17 (3 : 2)	—
IIIb	208 (4,23), 238 (4,30), 270 (3,98)	6,50s	2,32 (s CH_3)	7,37 ... 7,60; 7,87 ... 8,10 (3 : 2)	—
IIIc	208 (4,45), 246 (4,47), 264 sh (4,35)	6,83s	7,37 ... 7,77; 8,07 ... 8,37 (6 : 4)		—
Vb	—	7,82s	2,33 (s, CH_3)	—	2,33 (s, CH_3); 2,53 (s CH_3)**
VIIIa	206 (3,82), 225 sh (3,58), 324 (3,85)	7,64d (J = 1,1 Hz)	9,11 (d, $C_{(2)}$—H) (J = 1,1 Hz)	7,52 ... 7,62; 8,00 ... 8,06 (3 : 2)	—
VIIIb	207 (4,23), 225 sh (4,04), 326 (4,27)	—***	2,80 (s CH_3)	7,33 ... 7,67; 7,90 ... 8,13 (4 : 2)***	—
VIIIc	210 (4,37), 235 sh (4,19), 270 (3,37), 314 (4,34), 460 (2,58)	—***	7,37 ... 7,67; 7,90 ... 8,17; 8,47 ... 8,67 (7 : 2 : 2)***		—
IX	208 (4,46), 282 ... 300 (4,39), 390 (3,70)	6,87s	2,83 (s CH_3)	7,00 ... 7,67; 7,83 ... 8,10 (6 : 4)	9,30 (NH)
X	204 (4,21), 274 (4,24)	8,03s 7,80s	7,33 ... 7,62; 8,33 ... 8,63 (6 : 4)		
XIa	210 (4,25), 270 (3,89)	8,17s	9,20 (s $C_{(2)}$—H)	—	—
XIb	210 (4,20), 278 (3,86)	7,97s	2,87 (s CH_3)	—	—
XIc	204 (4,23), 272 (4,34)	7,80s	7,37 ... 7,60; 8,23 ... 8,50 (3 : 2)		—

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*The solvent used was $DMSO-D_6$ for compounds IIc, IIIb, c, and IX, and CF_3COOH for compound IIIa.

**In $DMSO-D_6$.

***The signal due to $C_{(5)}$—H overlaps the aromatic proton signals.

The physical properties and spectral characteristics of the newly synthesized compounds are given in Tables 1 and 2. The results of elemental C, H, N, and Cl analysis of these compounds agreed with their calculated values.

2-R-4-Chloro-6-hydroxyaminopyrimidines (IIa-c). To a suspension of 1.7 g (24.5 mmole) $NH_2OH \cdot HCl$ in 25 ml alcohol was added 2.5 g (24.5 mmole) triethylamine and a solution of 6.1 mmoles compound Ia-c in 5 ml alcohol. The mixture was refluxed 1 h, evaporated, and worked up with 30 ml water; the resulting precipitate was removed by filtration and dried to give compound IIa, b. The yield of compound IIa was 70%, mp 162-165°C. The literature mp is 165°C [3]. Yield of IIb, 60%.

In order to isolate compound IIc the alcohol solution was evaporated and the residue was extracted with 3 × 40 ml ether; the ether solution was then dried and evaporated.

Reaction of 4-Chloro-6-hydroxyaminopyrimidine (IIa) with Hydroxylamine. A. A mixture of 0.2 g (1.4 mmole) compound IIa and 0.4 g (5.3 mmole) $NH_2OH \cdot HCl$ in 12 ml alcohol was refluxed 4 h, evaporated, and the residue was treated with $NaHCO_3$ solution and filtered to give pyrimidine IIa.

B. A mixture of 0.2 g (1.4 mmole) compound IIa, 0.4 g (5.3 mmole) $NH_2OH \cdot HCl$, and 0.7 g (5.3 mmole) triethylamine in 10 ml alcohol was refluxed 5 h, evaporated, and then worked up with 15 ml water and filtered to give compound IIa.

2-R-4-Chloro-6-(N'-benzoyloxyamino)pyrimidines (IIIa-c). To a suspension of 4.5 mmole compound IIa-c and 4.5 mmole triethylamine in 25 ml ether was added with stirring a solution of 0.6 g (4.5 mmole) benzoyl chloride in 10 ml ether. The reaction mixture was stirred for

2 h, the precipitate was filtered and washed with 50 ml ether, and the filtrate was evaporated to give compounds IIIa-c. IR spectra, ν_{CO}: 1750 (IIIa), 1725 cm^{-1} (IIIb).

2-R-4-Chloro-6-(N'-benzoyl-N'-benzoyloxy)aminopyrimidines (IVa, b). These were prepared in a manner analogous to that described above for compounds III, at a 1:2 ratio of compound IIa, b to benzoyl chloride. IR spectra, ν_{CO}: 1700, 1785 (IVa), 1700, 1775 cm^{-1} (IVb).

2-R-4-Chloro-6-(N'-acetyl-N'-acetoxy)aminopyrimidines (Va-c). Prepared by analogy with compounds III, from compounds IIa-c and acetyl chloride at a 1:3 reagent ratio. IR spectra, ν_{CO}: 1720, 1815 (Va); 1715, 1810 (Vb); 1720, 1805 cm^{-1} (Vc).

2-R-4-Chloro-6-(N'-butylcarbamoyl-N'-butylcarbamoyloxy)aminopyrimidines (VIa, b). To a suspension of 6.2 mmoles compound IIa or b in 80 ml dioxane was added 1.4 g (14.0 mmoles) BuNCO; the mixture was stirred 2 h, the dioxane evaporated, and the residue was triturated with petroleum ether (3 × 20 ml) and filtered to give compounds VIa, b. IR spectra, ν_{CO}: 1690, 1755 (VIa); 1705, 1790 cm^{-1} (VIb).

2-R-4-Chloro-6-(N'-phenylcarbamoyl-N'-phenylcarbamoyloxy)aminopyrimidines (VIc, d). To a suspension of 6.2 mmoles compound IIa, b in 35 ml dioxane was added 14.4 mmoles phenyl isocyanate, and the mixture was stirred for 1 h. The reaction mixture was treated with 30 ml petroleum ether, and the resulting precipitate was filtered to give the diureide derivatives VIc, d. IR spectra, ν_{CO}: 1730, 1785 (VIc); 1725, 1780 cm^{-1} (VId).

2-R-4-Chloro-6-nitrosopyrimidines (VIIa-c). To a suspension of 10 g MnO_2 (activity corresponding to the data in [12]) in 250 ml chloroform, which was cooled to 5°C, was added 4.5 mmoles compound IIa-c. The mixture was stirred for 1 h at 5°C, filtered, and the MnO_2 precipitate was washed with 50 ml cold chloroform. This gave solutions of compounds VIIa-c in 300 ml chloroform. These solutions of the nitroso derivatives VIIa, b were used for subsequent reactions of these compounds. Compound VIIc was isolated by evaporation of the solution and recrystallization of the residue from ethyl acetate.

When the filtered MnO_2 precipitate was used again in a subsequent oxidation of compound IIc following the same procedure, a precipitate of azoxypyrimidine X was obtained after evaporation of the chloroform solution.

If the activity of MnO_2 was lower than that reported in [12] the reaction mixture resulting from oxidation of compound IIc contained two substances (based on TLC with chloroform eluent). Compounds VIIc and X were isolated from this mixture by chromatography on an Al_2O_3 column with chloroform eluent.

2-R-4-Chloro-6-phenylazopyrimidines (VIIa-c). To a solution of nitrosopyrimidine VIIa-c in 300 ml chloroform, prepared as described above, was added 2 ml acetic acid and 0.45 g (4.5 mmoles) aniline; the mixture was stirred for 30 min, evaporated, and the residue was passed through a layer of aluminum oxide (d = 20 mm, h = 40 mm) with ether eluent to give the azo derivatives VIIIa-c.

2-Methyl-4-Phenylamino-6-phenylazopyrimidine (IX). A. To a solution of nitrosopyrimidine VIIb in 300 ml chloroform, prepared as described above, was added 4 ml acetic acid and 0.9 g (9.0 mmoles) aniline; the mixture was stirred for 1 h, the chloroform evaporated, and the residue, a viscous oil, was allowed to stand overnight. The reaction mixture was then washed with 50 ml saturated $NaHCO_3$ solution, extracted with ether (3 × 30 ml), and evaporated to give a solid residue which was passed through a layer of aluminum oxide (d = 20 mm, h = 40 mm) with ether eluent to give the azo derivative IX.

B. A solution of 0.1 g (0.4 mmole) compound VIIIb, 40 mg (0.4 mmole) aniline, and 2 drops of acetic acid in 2 ml chloroform was allowed to stand at 20°C for 48 h. The chloroform solution was evaporated and the residue washed with 15 ml of $NaHCO_3$ solution. Further workup as in procedure A above gave the azo compound IX.

2-R-4-Chloro-6-nitropyrimidines (XIa-c). A. A stream of ozone (flow rate 2-3 mmole/h) was bubbled through a suspension of 1 mmole pyrimidine IIa-c in 50 ml chloroform, which was cooled in ice, until the starting material had disappeared (based on TLC analysis with chloroform eluent). The reaction mixture was purged with argon, the chloroform solution was evaporated, and the residue was subjected to column chromatography (250 × 10 mm) on silica gel with chloroform eluent, to give nitropyrimidines XIa-c.

B. A solution of nitrosopyrimidine VIIa-c in 300 ml chloroform prepared as described above was also sparged with ozone (flow rate 2-3 mmole/h) until the nitrosopyrimidine had disappeared (based on TLC analysis with chloroform eluent). The reaction mixture was worked up as described above in Part A, to give compounds XIa-c.

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UV SPECTROSCOPIC STUDY OF THE ACID-BASE REACTIONS OF 3-HYDROXYPYRIDINES AND 5-HYDROXYPYRIMIDINES

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The acid-base equilibrium behavior of alkyl(phenyl)-substituted 3-hydroxypyridines and 5-hydroxypyrimidines, and their dependence on pH values in aqueous solution, on the solvent, and on the phase composition, have been studied using UV spectroscopy. It has been found that in neutral aqueous solution all of the substituted 3-hydroxypyridines examined contain, in addition to the neutral form, a bipolar form, whose concentration depends on the nature and position of the substituent. In contrast, methyl substituted 5-hydroxypyrimidines form significant amounts of the bipolar form only in more acidic media.

It is known that substituted 3-hydroxypyridines I and 5-hydroxypyrimidines II act as inhibitors of radical reaction processes, and that they are also useful starting materials for the synthesis of biologically active compounds [1, 2]. It is possible that the biological activity of 3-hydroxypyridines depends on the equilibrium conversions or reactions of these compounds [3].

The acid-base reactions of 3-hydroxypyridine Ia and a variety of substituted 3-hydroxypyridines, such as pyridoxine, pyridoxal, and pyridoxamine, have been studied previously

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