SYNTHESIS OF SUBSTITUTED 2- AND 4-HYDROXYAMINOPYRIMIDINES

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The reaction of 2- and 4-chlorine-containing alkyl(aryl)pyrimidines with hydroxylamine was studied. It was shown that, depending on the amount of hydroxylamine, N,O-dipyrimidinylhydroxyamines or the corresponding 2- and 4-hydroxyaminopyrimidines are formed together with 2- and 4-oxodihydropyrimidines.

The reaction of halopyrimidines with hydroxylamine has been until now little investigated [1]. It is known that with pyrimidine derivatives, not only a nucleophilic substitution of the chlorine atom [2, 3], but also a more complex reaction course with formation of 2-aminopyrimidine-N-oxide, is possible [2], while in the case of 4-chloro-2,6-dimethoxypyrimidine, the reaction with hydroxylamine does not occur [4].

We were interested in the derivatives of hydroxyaminopyrimidines as compounds with potential pesticidal activity [5]. It was therefore important to have suitable methods of synthesis of hydroxyaminopyrimidines and to know the factors promoting or hindering the nucleophilic substitution of halogen by a hydroxyamino group in pyrimidine derivatives. In the present work, we studied the behavior of halogen-containing alkyl(aryl)pyrimidines in reaction with hydroxylamine.

The reaction of 4-chloropyrimidines (Ia,c) with a twofold excess of hydroxylamine did not lead to the formation of the expected 4-hydroxyaminopyrimidines. When the reaction was carried out in alcohol or ethylcellosolve at 80°C, the main reaction products were 4-oxodihydropyrimidines (IIa,c), while at room temperature, a compound was obtained from chloropyrimidine (Ia) with an empirical formula $C_{20}H_{15}N_5O$, corresponding to hetarylation of hydroxylamine by two molecules of halopyrimidine. In a similar way, isomeric dipyrimidinylhydroxylamines were obtained from chloropyrimidines Ib,c, with an empirical formula $C_{22}H_{19}N_5O$. In all cases, small amounts of 4-oxopyrimidines II were also isolated.

It is known that alkylation and arylation of N-monosubstituted hydroxylamines usually proceed at the more nucleophilic nitrogen atom, and lead to the formation of N,N-disubstituted hydroxylamines [6]. However, in the case of the presence of an acceptor substituent at the N atom of monosubstituted hydroxylamines (the azinyl or dinitrophenyl groups), the oxygen atom becomes more nucleophilic, so that N,O-disubstituted hydroxylamines are formed preferentially [7, 8]. The PMR spectra of the first representatives of dipyrimidinylhydroxylamines that we obtained (Table 2) indicate a nonequivalency of the pyrimidinyl substituents (two different signals of the CH_3 groups or protons at the 2- and 5- positions of the pyrimidine ring), which corresponds to the structure of N,O-dipyrimidinylhydroxylamine III, and rejects the structure of N,N-dipyrimidinylhydroxylamine IV, in which the signals of these substituents should be equivalent.

In the mass spectrum of compound IIIa, as well as the low-intensity peak of the molecular ion (M^+ 341), there are strong peaks at m/z 172 and 171 which, analogously with mass spectrometric data for N,O-diarylhydroxylamines [8], can be assigned to ions of 4-hydroxy- and 4-amino-6-phenylpyrimidines, respectively. Similar fragments were observed in the mass spectrum of compounds IIIb, and IIc.

After treatment of compound IIIb with acetyl chloride, a monoacetyl derivative is obtained, in the IR spectrum of which, in comparison with the starting compound, the absorption bands at 3500-3200 cm^{-1} (ν_{NH}) disappear, an absorption band appears at 1720 cm^{-1} (ν_{CO}),

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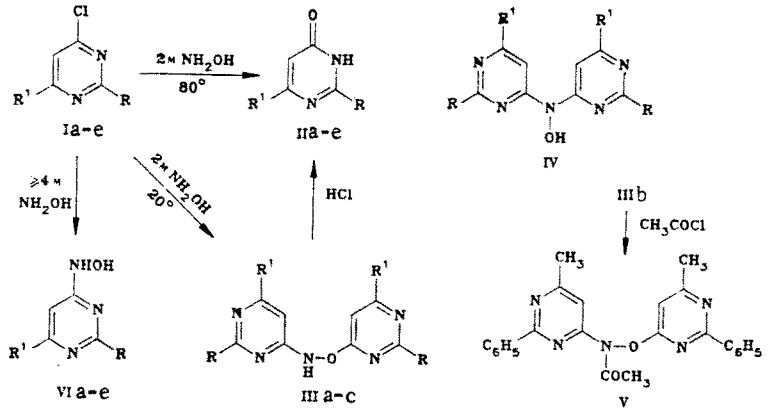


I—IV, VI a R=H, b,d R=C_6H_5, c,e R=CH_3; a,c,d R^1=C_6H_5, b,e R^1=CH_3

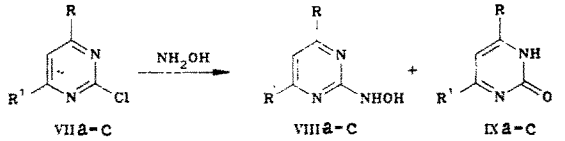
while in the 1300-1200 cm^{-1} region there are no new absorption bands corresponding to the stretching vibrations of the C—O bond. These data correspond to the structure of N-acetyl-N,O-di(2-phenyl-6-methyl-4-pyrimidinyl)hydroxylamine (V) for the O-acetyl derivative, $\nu_{CO} \geq$ 1740 cm^{-1} should be expected [8-10]).

Compounds IIIa-c are stable in the solid state at room temperature and do not change on heating in alcohol. Using compound IIIa as an example, it was shown that dipyrimidinylhydroxylamines do not change on boiling in alcohol in the presence of hydroxylamine, but in an acid—alcoholic solution are hydrolyzed to oxopyrimidines II. Along with other arylhydroxylamines, they are only slightly stable in alkaline media.

When the amount of free hydroxylamine is increased in the reaction mixture, the formation of a mixture of 4-oxypyrimidines IIa,b and 4-hydroxyaminopyrimidines VIa,b from compounds Ia,b was observed. A good yield of compounds VIa,b,d was obtained when 4-8-fold molar excess of hydroxylamine was used. Compound VIc was obtained from Ic in a yield of 34% (30% of oxopyrimidine IIc is formed). The formation of compound VIe could be observed from the mass spectrum (M^+ 139) and a qualitative reaction with ferric chloride in mixture with oxopyrimidine IIe, the main reaction product.

In the reaction of chloropyrimidines Ia-e with hydroxylamine, the ratio of compounds VIa-e and IIa-e formed depends to a certain extent on the nature of the base [KOH, Na_2CO_3, $N(C_2H_5)_3$], used for obtaining the free hydroxylamine from its hydrochloride. The most suitable base was found to be triethylamine. When it was used, high yields of hydroxyaminopyrimidines VIa-d were obtained, and an increase in the rate of the reaction of chloropyrimidines Ia-d with hydroxylamine was noted (see methods of preparation C and D for compounds VIa-c). It is possible that triethylamine forms a quaternary salt with chloropyrimidine, which as known [11] readily enters nucleophilic substitution reactions.

When hydroxylamine hydrochloride and triethylamine are used, substituted 2-chloropyrimidines VIIa-c also react with hydroxylamine to form the corresponding substituted 2-hydroaminopyrimidines VIIIa-c in good yield.* 2-Oxodihydropyrimidines IXa-c were isolated in small amounts.



VII—IX a R=R^1=CH_3, b R=H; R^1=C_6H_5, c R=R^1=C_6H_5

In contrast with compounds Ia-d and VIIa-c, in the reaction of chloropyrimidine Ie with free hydroxylamine under all the above discussed conditions, hydroxyaminopyrimidine VIe was obtained in appreciable yields, and the main reaction product was oxopyrimidine IIe. It was also found that under the above conditions, oxopyrimidines IIa-e and IXa-c are not the

*After the experimental part of this investigation was completed and prepared for printing, a report appeared on the synthesis of compounds VIe and VIIIa by the reaction of chloropyrimidines with hydroxylamine at a 1:10 ratio of the reagents [3].

TABLE 1. Characteristics of Compounds Obtained

Compound	Method of preparation (time, h)	mp, °C	M (mass-spectrometrically)	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
IIIa	A (480)	194—197	341	70,2	4,6	20,2	$C_{20}H_{15}N_5O$	70,4	4,4	20,5	47
IIIb	A (648)	182—195*	369	—	—	—	—	—	—	—	59
IIIc	A (480)	169—171	369	71,6	5,2	18,9	$C_{22}H_{19}N_5O$	71,5	5,1	18,9	58
V	—	174—177	—	69,9	5,1	17,0	$C_{24}H_{21}N_5O$	70,0	5,1	17,0	27
VIa	C (6)	195—196	187	64,3	5,0	23,1	$C_{10}H_9N_3O$	64,2	4,9	22,4	70
	D (1)										96
VIb	C (8)	139—140	201	65,4	5,5	20,8	$C_{11}H_{11}N_3O$	65,7	5,5	20,9	67
	D (2)										75
	E (1)										34
VIc	C (720)	153—155	201	65,9	5,6	20,4	$C_{11}H_{11}N_3O$	65,7	5,5	20,9	34
	D (2)										75
VId	D (8)	143—145	263	73,0	5,1	16,1	$C_{16}H_{13}N_3O$	73,0	5,0	15,9	91
VIe	D (1)										≈10
	E (1)	198—202 (198—200 [3])	139	51,3	6,5	30,3	$C_6H_9N_3O$	51,8	6,5	30,2	43
VIIIa	D (3,5)	211—216 (207—210 [3])	—	—	—	—	—	—	—	—	68
VIIIb	D (3)	155—157	187	64,3	4,6	22,7	$C_{10}H_9N_3O$	64,2	4,9	22,4	57
VIIIc	D (5)	177—179	263	72,5	5,1	16,0	$C_{16}H_{13}N_3O$	73,0	5,0	15,9	50

*Analytically pure sample could not be obtained because of insufficient stability.

TABLE 2. Spectral Data of Synthesized Compounds

Compound	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum,* δ, ppm		
		5-H** (2-H)	CH_3	CH_{arom}
IIIa	266 (4,58), 340 sh (3,81)	6,99; 7,82 (8,82; 9,02)	—	7,22—7,79 (10H)
IIIb	—	6,66; 7,16	2,36; 2,56	7,23—7,56; 7,56—8,13 (6 : 4)
IIIc	268 (4,58), 340 sh (3,87)	6,69; 7,66	2,42; 2,72	7,79—7,63; 7,84—8,26 (6 : 4)
V	—	6,83; 7,70	2,40; 2,53; 2,57	7,29—7,63; 7,84—8,26 (6 : 4)
VIa	248 (4,54), 300 (3,66)	7,22 (8,59)	—	7,36—7,69; 7,89—8,29 (3 : 2)
VIb	246 (4,44), 275 (3,87)	6,59	2,47	7,31—7,61; 8,19—8,51 (3 : 2)
VIc	246 (4,39), 294 sh (3,68)	7,22	2,49	7,39—7,69; 8,08—8,29 (3 : 2)
VId	255 (4,66), 305 sh (3,69)		—	—
VIe	242 (4,12), 270 sh (3,79)	6,49	2,16; 2,32	—
VIIIa	—	6,45	2,22***	—
VIIIb	—		—	6,93—7,50; 7,50—8,10 (4 : 2)
VIIIc	—		—	6,90—7,43; 7,43—7,93 (4 : 2)

*Solvent for compounds IIIa,b, VId,e, VIIIa-c) CF_3COOH, for IIIc, V) $CDCl_3$, for VIa,b) DMSO-D_6, and for VIc) $(CD_3)_2CO$.
**The 5-H signal of compounds VIIIb,c coincides with the aromatic protons region.
***Intensity of 6-H signal.

products of a hydrolytic splitting of chloropyrimidines Ia-e and VIIa-c and hydroxyaminopyrimidines VIa-e and VIIIa-c.

In nucleophilic substitution reactions, free hydroxylamine is usually used [1, 2, 6]. It is known that in the case of 2-dialkylamino-4-chloropyrimidine, the reaction was successfully accomplished by reacting the latter compound with hydroxylamine hydrochloride [12]. Compounds Ib,e also react with hydroxylamine hydrochloride to form the corresponding hydroxyamino derivatives VIb,e. The yield of compound VIb was thus somewhat lower than in

the case when free hydroxylamine was used, while the yield of compound VI considerably increased.

Hydroxyaminopyrimidines VIa-e and VIIIa-c in the solid state are stable compounds, give an intense color with ferric chloride and have absorption bands in the IR spectrum in the 3600-3200 cm^{-1} region, characteristic of compounds with strong intermolecular hydrogen bonds.

Similarly to the arylation of N-substituted hydroxylamines [6-8], hydroxyaminopyrimidines react with chloropyrimidines. Compound VIb reacts at room temperature with chloropyrimidine Ib with the formation of N,O-dipyrimidinylhydroxylamine IIIb, which indicates a higher nucleophilicity of the oxygen atom in hydroxyaminopyrimidines, compared with phenylhydroxylamine [8].

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets (c 0.25%) or in solutions, the PRM spectra on a Varian A 56/60 spectrometer, using HMDS as an internal standard, and the mass spectra on a MS-902 spectrometer at 14 and 70 eV. The compounds were identified by comparison according to TLC on Silufol UV-254 plates (eluent chloroform), melting points and IR spectra.

Reaction of Halopyrimidines with Hydroxylamine. A. A 10 ml portion of an alcoholic solution of hydroxylamine, obtained by neutralization of an alcoholic solution of 0.7 g (100 mmoles) of $NH_2OH \cdot HCl$ by an alcoholic solution of 0.6 g (10 mmoles) of KOH or 1.0 g of Na_2CO_3, is added to a solution of 5 mmoles of substituted 4-chloropyrimidine Ia-c in 20 ml of alcohol, and the reaction mixture is left to stand at 20°C for 20-27 days. The precipitate that separates is filtered to yield compound IIIa-c. The compound is reprecipitated from an alcoholic solution of NaOH by addition of acetic acid (Table 1).

B. An alcoholic solution of 5 mmoles of compounds Ia,c and 10 mmoles of NH_2OH, obtained as described above, is boiled for 5 h. The solution is cooled and the crystals that precipitate are filtered to yield compounds IIa,c.

C. A 25 mmole portion of chloropyrimidine Ia-c is added to 150 ml of a NH_2OH solution, obtained as described above from 13.9 (200 mmoles) of $NH_2OH \cdot HCl$, and the solution is boiled (for Ia,b) or allowed to stand at 20°C (for Ic). The solvent is distilled in vacuo, the solid residue is extracted by ether (4•60 ml), ether is evaporated, and the residue is recrystallized from benzene to yield compound VIa-c (Table 1).

D. A solution of 20 mmoles of chloropyrimidine Ia-e or VIIa-c, 80 mmoles hydroxylamine hydrochloride, and 80 mmoles of triethylamine in 20 ml of alcohol is boiled up to the disappearance of the initial chloropyrimidine in the reaction mixture (according to TLC). The solution is evaporated, 30 ml of a saturated sodium bicarbonate solution are added to the residue, and the mixture is extracted by ether (4•60 ml). The ether extract is dried and evaporated to yield hydroxyaminopyrimidines VIa-d or VIIIa-c. The crystals insoluble in ether are filtered and dried to yield oxodihydropyrimidines IIa-e or IXa-c (yield, %: IIa — traces, IIb — 11, IIc — 30, IId — 8, IIe — 40).

E. A solution of 20 mmoles of chloropyrimidine Ib,e and 80 mmoles of $NH_2OH \cdot CHl$ in 20 ml of alcohol is boiled. The solution is evaporated; for the starting Ie, the precipitate is washed with 30 ml of a saturated sodium bicarbonate solution to yield compound VIe; for the starting Ib, the reaction mixture is treated as in method D.

N-Acetyl-N,O-di(2-phenyl-6-methyl-4-pyrimidinyl)hydroxylamine (V). A 0.13 g portion (1.3 mmole) of triethylamine is added to a suspension of 0.37 g (1.0 mmole) of compound IIIb in 10 ml of dry dioxane, and then a solution of 0.1 g (1.3 mmole) of acetyl chloride in 10 ml of dry dioxane is added dropwise. The reaction mixture is stirred at 20°C for 5 h, the precipitate filtered, the filtrate is evaporated, and the residue is washed with 20 ml of water and 20 ml of ether to yield 0.1 g (27%) of N-acetyl derivative V.

LITERATURE CITED

1. A. Tomazic, M. Tisler, and B. Stanovnik, J. Heterocycl. Chem., 16, 861 (1979).
2. A. Tomazic, M. Tisler, and B. Stanovnik, Tetrahedron, 37, 1787 (1981).
3. D. T. Hurst, Heterocycles, 22, 79 (1984).
4. P. K. Chang, J. Med. Chem., 8, 884 (1965).

5. N. N. Mel'nikov, Chemistry and Technology of Pesticides [in Russian], Khimiya, Moscow (1974), p. 269.
6. Houben-Weyl, Methoden der Organischen Chemie, Vol. 10/1, G. Thieme Verlag, Stuttgart (1971), p. 1099.
7. H. Sawanishi and Y. Kamiya, Chem. Pharm. Bull., 23, 2949 (1975).
8. A. S. Bailey, M. Maung, G. W. F. Orpwood, and J. K. White, Tetrahedron, 22, 995 (1966).
9. L. J. Bellamy, The Infrared Spectra of Complex Molecules, 2nd edn., Vol. 2, Chapman and Hell, London (1980), p. 185.
10. S. Prabhaker, A. M. Labo, and M. M. Margues, Tetrahedron Lett., 23, 1391 (1982).
11. V. P. Mamaev, O. V. Zagulyaeva, and S. M. Shein, Khimiya Geterotsikl. Soedin., No. 6, 723 (1973).
12. P. F. H. Freeman, M. C. Shephard, and B. K. Snell, GB Patent No. 1229413; Ref. Zh. Khim. 1H450 (1972).

6-AMINOPYRIMIDINE 1-OXIDES. ACYLATION AND METHYLATION

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Acylation of 6-aminopyrimidine 1-oxides gives both O- and N-acylation products, but with methylating agents only O-alkyl derivatives are obtained.

Aminopyrimidine N-oxides, which display interesting biological activity [1, 2], remain a little-known group of compounds. Reports of methods of synthesis and the chemical properties of these compounds are few in number, the most accessible compounds being the oxides of di- and triaminopyrimidines [1-4]. Continuing a study of the effects of the N-oxide group on the reactivity of the amino-group in pyrimidines [5], we have examined the behavior of 6-aminopyrimidine 1-oxides on acylation and methylation.

The starting materials used were the 6-aminopyrimidine 1-oxides (IIa-d), obtained by oxidizing the 4-amino-compounds (Ia-d) in various ways. Oxidation of the amino-N-oxides (IIa-c) with perbenzoic acids gave yields of up to 40% without the formation of by-products. The use of mixtures of acetic acid and hydrogen peroxide or hydrogen perioxide and sodium tungstate [5] was of little use in the synthesis of (II), low yields being obtained and the reaction mixtures being complex as a result of extensive destructive oxidative degradation of the aminopyrimidine starting materials. In the IR spectra of (IIa-d), as reported in the literature [6], $\nu_{N\to O}$ absorption was present at 1225-1180 cm^{-1}, together with δ_{NH_2} at 1665-1630 cm^{-1} using different methods of oxidation. Only one of the two possible isomeric pyrimidine N-oxides was obtained.

On the basis of literature information, it was assumed that the ring nitrogen atom in the α-position to the amino-group was oxidized [7], this being the more basic. In the case of (IIb), this was confirmed by the fact that in the PMR spectrum the signals for the 2-H and 4-H protons were singlets, whereas in the isomeric 4-amino-5-phenylpyrimidine 1-oxide doublets would be expected with $J \approx 2$ Hz [8, 9]. Compound (IId) differed from 4-amino-6-phenylpyrimidine, the preparation of which by a different method has been described in the literature [10]. The structure of (IIa) is evidently analogous to that of (IId), since the introduction of the CH_3 group has no effect on the course of the oxidation [11]. When a phenoxy-group is present in diazines, oxidation of the nitrogen remote from this substituent takes place [11], and consequently in the case of (Ic), the N-oxide (IIc) is evidently formed.

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