SYNTHESIS OF 2- AND 4-NITROPYRIMIDINES AND 2-NITRO-sym-TRIAZINES BY OZONIZATION OF HYDROXYAMINO AND NITROSO DERIVATIVES*

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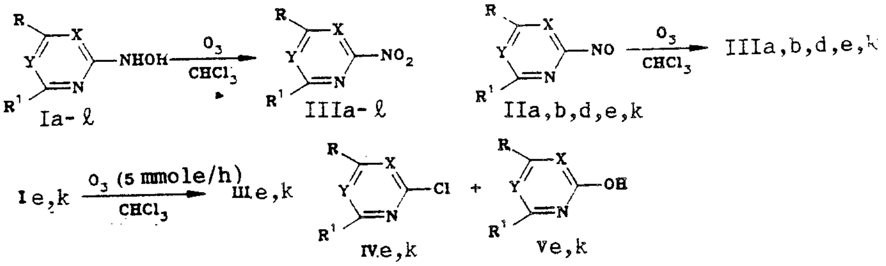
The action of ozone on aryl(methyl)-substituted 2- and 4-hydroxyamino- or -nitrosopyrimidines in chloroform gave 2- and 4-nitropyrimidines. The unambiguous character of the process depends on the molar ratio of the substrate and ozone; the side formation of azoxy-, chloro-, and hydroxypyrimidines is possible. 2-Nitro-sym-triazines were obtained by ozonization of substituted 2-hydroxyamino-sym-triazines.

Pyrimidine derivatives with a nitro group in the even-numbered positions of the ring have heretofore been difficult to obtain [3, 4]. We have previously shown that phenyl(methyl)-substituted 2- and 4-nitropyrimidines can be obtained by oxidation of nitrosopyrimidines with permaleic acid, potassium permanganate, or alkali metal hypochlorites; however, the yields are low, and instability of the nitropyrimidines has been noted in the alkaline media of hypochlorites [4]. Hydroxyaminopyrimidines are converted to azoxy derivatives by the action of these oxidizing agents [4].

It is known that nitro derivatives in both the aliphatic series [5] and in the aromatic series [6, 7] are formed by the action of ozone on substituted hydroxylamines. The method makes it possible to also obtain polynitrobenzenes [7]. Ozone has been successfully used for the oxidation of the nitroso group to a nitro group in azines [8].

In the present paper we report the action of ozone on aryl(methyl)-substituted 2- and 4-hydroxyamino- (Ia–j) and 2- and 4-nitrosopyrimidines IIa, b, d, e, as well as on 2-hydroxyamino-sym-triazines Ik–n and 2-nitroso-sym-triazine IIk.



a. R=R¹=Ph, b R=Me, R¹=Ph, c R=Ph, R¹=Me, d R=H, R¹=Ph, e R=R¹=Ph, f R=R¹=H, g R=Ph, R¹=H, h R=R¹=Me, i R=Ph, R¹=4-FC$_6$H$_4$, j R=R¹=Ph, k R=R¹=NMe$_2$, ℓ R=R¹=piperidino a-d X=CH, e-ℓ X=N; a-d, k, ℓ Y=N, e,g-i Y=CH, f Y=C—Ph, j Y=C—NO$_2$

The passage of ozone through a solution of 4-nitroso-2,6-diphenylpyrimidine (IIa) in chloroform or methylene chloride at 0–5°C led to 4-nitro-2,6-diphenylpyrimidine (IIIa) in high yield. Substituted 2- and 4-nitropyrimidines IIIb, d, e, which were identical to the previously described compounds [4], were similarly synthesized from IIb, d, e.

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*See [1, 2] for our preliminary communications.

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Hydroxyaminopyrimidines Ia–j are also converted to nitro derivatives IIIa–j by the action of ozone; the yields are comparable to those obtained for the nitropyrimidines obtained by oxidation of the nitroso derivatives. However, the oxidation of hydroxyaminopyrimidines Ia–j proceeds more slowly, and the formation of a green coloration, which constitutes evidence for the formation of nitroso compounds (also confirmed by TLC data), is initially observed in some cases. The direct oxidation of the hydroxyamino group to a nitro group in pyrimidine derivatives makes it possible to avoid the prior production of nitrosopyrimidines, which is particularly important in the case of unstable compounds (see [9]).

In the case of the oxidation of Ii, j it has been shown that aryl-containing hydroxyaminopyrimidines and pyrimidine derivatives with functional groups that are resistant to the action of ozone can be successfully used for the synthesis of nitropyrimidines; in the case of the oxidation of Ib, c, h it is possible to obtain methyl-substituted nitropyrimidines.

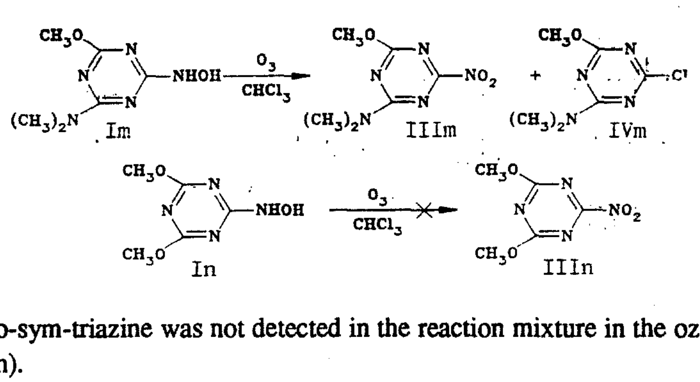
In a study of the action of ozone on hydroxyaminopyrimidines it was noted that the unambiguous character of the oxidation and the yields of nitropyrimidines depend on the concentration and the amount of the solution of the starting substance in chloroform used and the ozone stream. The highest yields of III were obtained when ozone was passed at a rate of 2–3 moles/h into 50 ml of a 0.02 M solution of hydroxyaminopyrimidine I in chloroform. The formation of azoxypyrimidines was observed in the case of retention of the indicated concentration but with an increase in the volume of the solution, or when the concentration of the solution was increased. Complex mixtures of products were obtained in many cases when the rate of passage of the ozone stream was accelerated. Thus, after ozonization of Ie with a stream of ozone passed at a rate of 5 mmoles/h, we isolated nitropyrimidine IIIe, 2-chloro-4,6-diphenylpyrimidine (IVe), and 2-hydroxy-4,6-diphenylpyrimidine (Ve) from the reaction medium. In other cases, according to the mass-spectral data, the reaction mixtures contained, in addition to III–V, substances containing either two chlorine atoms or a chlorine atom and a hydroxy group and substances with unestablished structures. The formation of white polymeric products was observed in some experiments.

It is known that complex mixtures of products are often formed in the ozonization of amines, including hydroxylamines, in chlorine-containing solvents. Thus the presence of substituted mono- and dichlorobenzenes was noted in the oxidation of N-aryl-hydroxylamines with ozone [7], while RCl, ROH, R_2O, RNHOH·HCl, and other compounds were detected in the oxidation of aliphatic hydroxylamines [5]. The formation of these substances and polymeric products was explained by decomposition of the amine–ozone adduct not only through the loss of a molecule of oxygen and the formation of an amine oxide, but also through dissociation of the adduct to give ion-radical particles [5, 10, 11].

It is possible that the formation of complex mixtures from hydroxyaminopyrimidines under the influence of a strong stream of ozone is associated with similar decomposition of the hydroxyaminopyrimidine–ozone adduct, although the increased nucleophilic lability of the nitroso and nitro groups should also be taken into account for the compounds under investigation [4, 9].

We investigated the oxidation of the hydroxyamino group in series of derivatives of sym-triazines, in which the first 2-nitro derivatives were obtained only in 1987 by oxidative photolysis of 2-azido-sym-triazines [12]. Upon ozonization sym-triazines Ik, *l* and IIk also form 2-nitro-sym-triazines IIIk, *l*, their yields amount to only 30–50%. Chloro-sym-triazines, hydroxy-sym-triazines, and other compounds were also detected in the reaction mixtures in the case of a stronger ozone stream.

Under the influence of ozone Im forms a mixture of nitro and chloro derivatives IIIm and IVm (in a ratio ranging from 4:1 to 1:4). A change in the ozonization conditions (a temperature from –5°C to +5°C, an ozone flow rate from 2 to 5 mmoles/h, and a solution concentration from 0.01 to 0.02 mole/liter) did not make it possible to obtain nitro-sym-triazine IIIm without admixed chloro derivative IVm.



The corresponding 2-nitro-sym-triazine was not detected in the reaction mixture in the ozonization of 2-hydroxyamino-4,6-dimethoxy-sym-triazine (In).

TABLE 1. Oxidation of Hydroxyamino Azines I and Nitroso Azines II with Ozone

Nitro-azine obtained	Yield of III,* %		mp,** °C (ethanol)	Literature
	from I	from II		
IIIa	70	75	136...137	[1, 4]
IIIb	80	80	125...128	[4]
IIIc	64	—	109...111	—
IIId	80	95	168...170	[4]
IIIe	90	94	172...174	[1, 4]
IIIf	97	—	205...207	[4]
IIIg	62	—	122...123	—
IIIh	98	—	118...120	—
IIIi	95	—	186...188	—
IIIj	56	—	161...163	—
IIIk	28	50	124...126	[2, 12]
IIIℓ	50	—	114...116	—
IIIm	30***	—	155...157	[12]

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*The yield of the isolated substance.

**Compounds IIIk–m were recrystallized from petroleum ether.

***The yield of the mixture of IIIm and IVm (4:1) according to PMR data.

TABLE 2. Characteristics of the Synthesized Ii, j and IIIc, g–j, *l*

Compound	Empirical formula	PMR spectrum, δ, ppm	M^+ (M^+-46)*
Ii	$C_{16}H_{12}FN_3O$	—	—
Ij	$C_{16}H_{12}N_4O$	—	308,0949
IIIc	$C_{11}H_9N_3O_2$	2,90 (s, CH_3); 7,33...7,73 (m, 3H arom); 7,97...8,33 (m, 2H arom); 8,30 (s, 5-H)	215 (169)
IIIg	$C_{10}H_7N_3O_2$	7,36...7,71 (m, 3H arom); 7,97...8,37 (m 2H arom + 5-H); 8,97 (d, 6-H)	201 (155)
IIIh	$C_6H_7N_3O_2$	2,67 (s, $2CH_3$); 7,50 (s 5-H)	153 (107)
IIIi	$C_{16}H_{10}FN_3O_2$	—	—
IIIj	$C_{16}H_{10}N_4O_4$	—	322,0636 (276)
IIIℓ	$C_{13}H_{20}N_6O_2$	—	292,1641 (246)

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*Found by mass spectrometry. Calculated M^+: 308.0936 for Ij, 322.0702 for IIIj, and 292.1648 for III*l*.

EXPERIMENTAL

The PMR spectra of solutions in $CDCl_3$ were recorded with a Varian A 56/60 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with a Finnigan MAT-8200 spectrometer. The compounds were identified by means of TLC (on Silufol UV-254 plates, elution with chloroform) and by their melting points and IR spectra. The synthesis of hydroxyaminopyrimidines Ia–h was described in [9, 13], the synthesis of nitrosopyrimidines IIa, b, d, e was described in [9], and the synthesis of hydroxyamino- and nitroso-sym-triazines Ik–m and IIk was described in [2, 14]. The results of elementary analysis for C, H, and N for Ii, j and IIIc, g–j were in agreement with the calculated values.

Hydroxyaminopyrimidines Ii, j. These compounds were obtained as in [13] from the corresponding chloropyrimidines. Compound Ii had mp 162–164°C (decomp., from benzene), while Ij had mp 170–172°C (decomp., from benzene).

Ozonization of Hydroxyamino and Nitro Azines. A. A stream of ozone (2–3 mmoles/h) was passed at 0–5°C into a solution of 0.26 g (1 mmole) of hydroxyaminopyrimidine Ia in 50 ml of $CHCl_3$ until the starting substance disappeared (monitoring by TLC). The reaction mixture was purged with argon, the solution was evaporated, and the residue was chromatographed with a column packed with silica gel (140–315 μm) by elution with $CHCl_3$ to give 0.19 g of nitro derivative IIIa.

Nitro azines IIIa–*l* (Tables 1 and 2) were similarly obtained from hydroxyaminopyrimidines Ib–*l* and nitrosopyrimidines IIa, b, d, and e.

In the case of Im we obtained a mixture of IIIm and IVm (4:1) with mp 155–157°C. Found: M^+ 199.0704 (for IIIm, $C_6H_9N_5O_3$, calculated M^+ 199.0705) and 188 (for IVm, $C_6H_9ClN_4O$, calculated value in the case of ^{35}Cl 188). PMR spectrum: 4.13 (OCH_3 for IIIm), 4.05 (OCH_3 for IVm), 3.33 [$N(CH_3)_2$ for IIIm], and 3.23 ppm [$N(CH_3)_2$ for IVm]. According to the data in [12], sym-triazine had mp 158–160°C.

B. The ozonization of Ie was carried out as in method A, but the ozone flow rate was 5 mmoles/h. The residue was chromatographed with a column packed with silica gel (140–315 μm) by elution with $CHCl_3$ to give the following fractions: a) 0.13 g of a mixture of IIIe and IVe [M^+ 277 and 266 (for ^{35}Cl)]; b) 0.05 g of a mixture of compounds with unestablished structures; c) 0.03 g of Ve [M^+ 248, mp 290°C (mp 291°C [15])].

sym-Triazines IIIk, IVk, and Vk were obtained from Ik under similar conditions and were isolated.

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