4. S. F. Mason, J. Chem. Soc., No. 12, 5010 (1957).
5. J. M. Sanchez-Ruiz, J. Llor, and M. Cortigo, J. Chem. Soc., Perkin Trans. 2, No. 12, 2047 (1984).
6. D. Heinert and A. E. Martell, J. Am. Chem. Soc., 81, 3933 (1959).
7. D. J. Brown, The Pyrimidines, Interscience, New York–London (1962).
8. V. P. Lezina, A. U. Stepanyants, N. I. Golovkina, and L. D. Smirnov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 1, 98 (1980).
9. V. P. Lezina, M. M. Kozlova, S. B. Gashev, A. U. Stepanyants, and L. D. Smirnov, Khim. Geterotsikl. Soedin., No. 8, 1111 (1986).
10. N. Ya. Bernstein and Yu. L. Kaminskii, Spectrometric Analysis in Organic Chemistry [in Russian], Khimiya, Moscow (1975).
11. T. N. Rodionova, R. E. Lokhov, and K. M. Dyumaev, Khim. Geterotsikl. Soedin., No. 7, 962 (1972).
12. W. Gruber, Can. J. Chem., 31, 364 (1953).
13. J. H. Chesterfield, J. F. McOmie, and M. S. Tute, J. Chem. Soc., No. 11, 4590 (1960).
14. A. Dornow and H. Hell, Chem. Ber., 93, 1998 (1960).
15. S. B. Gashev, V. F. Sedova, L. D. Smirnov, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 9, 1257 (1983).
16. H. Brederek, R. Gompper, and H. Herlinger, Chem. Ber., 91, 2832 (1958).
17. S. B. Gashev, B. A. Korolev, L. A. Osmolovskaya, and L. D. Smirnov, Khim. Geterotsikl. Soedin., No. 9, 1262 (1983).

OXIDATION OF HYDROXYAMINO- AND NITROSOPYRIMIDINES. SYNTHESIS OF 2- AND 4-NITROPYRIMIDINES

G. G. Moskalenko, V. F. Sedova, and V. P. Mamaev*

UDC 547.853.7:542.943

Oxidation of phenyl- and methyl-substituted 2- and 4-hydroxyamino- and -nitrosopyrimidines has given the azoxy- and nitropyrimidines, respectively. The behavior of the nitropyrimidines obtained towards reduction and nucleophilic substitution is considered.

Electrophilic substitution in pyrimidines is difficult. Nitration of pyrimidines is facilitated by the presence in the ring of strongly electron-donating substituents, to give 5-nitropyrimidines only [1]. Pyrimidines with a nitro-group in even-numbered positions in the ring have until recently been difficult to obtain, being synthesized by oxidation of S,S-dimethyl-N-(2-pyrymidinyl)sulfilimine [2] or 5-dimethylamino-7-hydroxy[1,2,5]oxadiazolo[3,4-d]pyrimidine 1-oxide [3], or by oxidative photolysis of aryl-2-azidopyrimidines [4].

α-Nitroazines have been obtained from nitroso- and aminoazines by treatment with strong oxidizing agents such as ozone [2, 5], sodium hypochlorite [2], permaleic acid [6], trifluoroperacetic acid [7], H_2O_2 in concentrated sulfuric acid [8, 9], and oxygen in sodium hydroxide solution [10].

In the course of earlier investigations, it was shown that oxidation of hydroxyaminopyrimidines with activated MnO_2, Ag_2CO_3, or $BaMnO_4$ affords the 2- and 4-nitrosopyrimidines [11]. The object of the present investigation was to study further the behavior of phenyl-

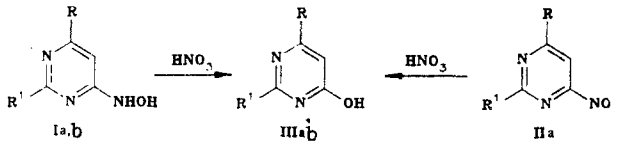
*Deceased.

Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1100-1105, August, 1989. Original article submitted January 8, 1988; revision submitted May 3, 1988.

0009-3122/89/2508-0919$12.50

and methyl-substituted 2- and 4-hydroxyamino- (I) and nitrosopyrimidines (II) on treatment with strong oxidizing agents, namely concentrated HNO_3, permaleic acid, $KMnO_4$, and alkali metal hypochlorites.

Treatment of the 4-hydroxyaminopyrimidines (Ia) and (Ib) with concentrated nitric acid (d 1.39) results in a vigorous reaction with evolution of oxides of nitrogen, but the reaction products were the corresponding 4-hydroxypyrimidines (IIIa) and (IIIb) only. The hydroxypyrimidine (IIIa) was formed similarly when the nitrosopyrimidine (IIa) was treated with concentrated nitric acid, apparently as a result of the facile hydrolytic cleavage of nitrosopyrimidines in aqueous media. Subsequent oxidation of the hydroxyamino- and nitrosopyrimidines was therefore carried out in nonaqueous or basic media



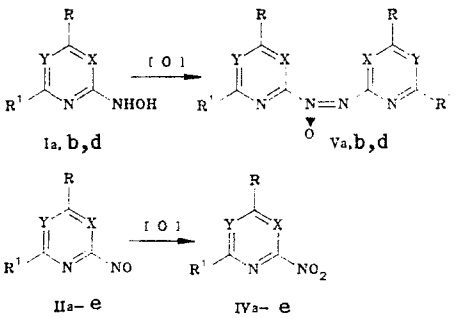
Ia,b IIIa,b IIa

I–III a R=CH_3, R^1=C_6H_5; b R=R^1=C_6H_5

As exemplified by (Ib) and (IIa), it was shown that the hydroxyaminopyrimidines (I) and nitrosopyrimidines (II) were stable to m-chloroperbenzoic acid, in accordance with a literature report of the behavior of 2-nitrosopyrimidine in the presence of this oxidant [2]. The use of a more powerful oxidant, permaleic acid, resulted in oxidation of the nitrosopyrimidine (IIa) to give 14% of 4-methyl-6-nitro-2-phenylpyrimidine (IVa). However, oxidation of the hydroxyaminopyrimidine (Ib) with permaleic acid gave 2,2',4,4'-tetraphenyl-6,6'-azoxypyrimidine (Vb), perhaps as a result of the condensation of the nitrosopyrimidine formed initially on oxidation with the starting hydroxyaminopyrimidine (Ib).

Similar reactions of the hydroxyaminopyrimidines (Ia, b, d) to give the azoxy-compounds (Va, b, d) were observed on treatment with sodium hypochlorite solution. It has been shown previously that MnO_2, Ag_2CO_3, and $KMnO_4$ also give azoxypyrimidines [11, 12].

Unlike the hydroxyaminopyrimidines, the nitroso-compounds (IIa-e) on treatment with $KMnO_4$ or sodium or potassium hypochlorites are oxidized to the nitropyrimidines (IVa-e).



Ia, b,d Va,b,d

IIa–e IVa–e

I, II, IV, V a X=CH, Y=N, R=CH_3, R^1=C_6H_5; b X=CH, Y=N, R=R^1=C_6H_5; c X=CH, Y=N, R=H, R^1=C_6H_5; d X=N, Y=CH, R=R^1=C_6H_5; e X=N, Y=C—C_6H_5, R=R^1=H

Potassium permanganate in chloroform, using tetrabutylammonium bromide as phase-transfer catalyst, oxidizes the 4-nitroso-compounds (IIa, c) to the 4-nitropyrimidines (IVa, c). The oxidation is, however, slow, and the yields of nitropyrimidines low. 2-Nitrosopyrimidines (IId, e) were not oxidized under these conditions.

Oxidation of the nitrosopyrimidines with sodium hypochlorite was examined in the cases of (IIa, b, d, e). In a two-phase system with tetrabutylammonium bromide, treatment of the nitrosopyrimidine (IIa) with sodium hypochlorite solution (3%, pH 11.2) afforded the nitro-compound (IVa). The reaction was extremely rapid, the yield of (IVa) after two minutes' oxidation being 49%. The nitropyrimidine (IVa) thus formed was unstable under these conditions, undergoing further reactions. For example, when the reaction was carried out for five minutes, the yield of (IVa) fell to 23%, and after one hour (IVa) was absent from the reaction mixture, according to TLC. Similarly, it was not possible to obtain the nitropyrimidine (IVb) by oxidation of (IIb) for one hour, but when the reaction was carried

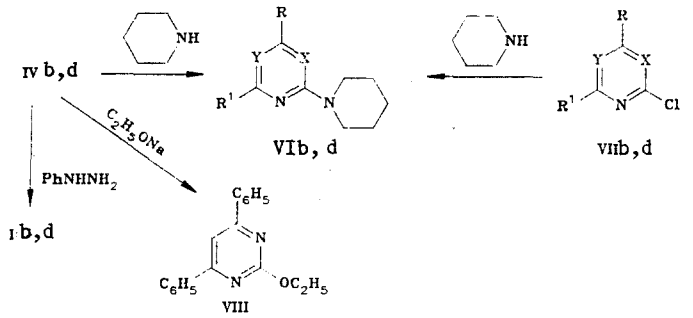
TABLE 1. Properties of Products (IVa-e) and (VIb).

Compound	Empirical formula	M	mp,* °C (alcohol)	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm			Yield, % (method)
					5-H	4-H	CH_{arom}, m	
IVa	$C_{11}H_9N_3O_2$	215	125...128	265 (4,35), 310 pl (3,38)	7,73 s**	—	7,34...7,63 (3H); 8,40...8,67 (2H)	14 (A), 37 (B), 49 (C)
IVb	$C_{16}H_{11}N_3O_2$	277	135...137	267 (4,45), 322 pl (3,74)	8,30 s	—	7,27...7,73 (6H); 8,13...8,32 (2H); 8,32...8,70 (2H)	54 (C)
IVc	$C_{10}H_7N_3O_2$	201	168...170	267 (4,36), 313 pl (3,30)	7,93 d***	9,20 d ***	7,47...7,70 (3H); 8,47...8,73 (2H)	20 (B)
IVd	$C_{16}H_{11}N_3O_2$	277	172...174	276 (4,40), 310 pl (4,28)	8,33 s	—	7,40...7,77 (6H); 7,97...8,40 (4H)	71 (D), 56 (E)
IVe	$C_{10}H_7N_3O_2$	201	205...207	288 (4,00)	—	9,53 (2H, s)	7,53...7,83 (3H); 7,90...8,20 (2H)	67 (D)
VIb	$C_{21}H_{21}N_3$	—	186...188		—	—	—	98

*(VIb) was recrystallized from petroleum ether (70-100°C).
**For the CH_3 group, δ 2.70 s.
***$J_{4,5}$ = 6 Hz.

out for four minutes the nitropyrimidine (IVb) was isolated in 54% yield. Oxidation of the 2-nitrosopyrimidines (IId, e) under these conditions afforded complex reaction mixtures from which it was not possible to isolate the nitropyrimidines. If, however, potassium hypochlorite (7%, pH 9.5) was used as the oxidant, in the presence of either tetrabutylammonium bromide or 18-crown-6, the 2-nitrosopyrimidines (IId, e) afforded high yields of the nitro-compounds (IVd, e).

The nitro-compounds (IVa-e) were obtained as colorless or yellow crystalline solids which were stable in the solid state at room temperature. The mass spectra of all the nitropyrimidines showed, in addition to the molecular ion peak, a peak with m/z $(M - 46)^+$, indicating loss of the nitro group. The IR spectra of the nitropyrimidines showed strong absorption for stretching vibrations of the nitro-group at 1520-1555 and 1355-1385 cm^{-1} (cf [13] for aromatic nitro-compounds).



VI, VIIb X=CH, Y=N, R=R¹=C_6H_5; d X=N, Y=CH, R=R¹=C_6H_5

It was shown in the cases of the 2- and 4-nitropyrimidines (IVb) and (IVd) that on treatment with phenylhydrazine the nitro-group in the 2- or 4-position of the pyrimidine ring is readily reduced to the hydroxyamino group, and with piperidine or sodium ethoxide it is readily replaced to give the piperidino-derivative (VIb, d) or the ethoxy-derivative (VIII). When the nitropyrimidines (IVb, d) or the chloropyrimidines (VIIb, d) were reacted with piperidine under the same conditions, it was found that the lability of the nitro-group in even-numbered positions in the pyrimidine ring was much greater than that of chlorine. The stability of (IVa) in acid media was examined. On keeping the nitro-compound (IVa) for 1.5 h in concentrated nitric acid (d 1.39), 40% of the starting material was recovered, showing that these nitropyrimidines are fairly stable in acidic media.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in KBr disks (c = 0.25%), and the UV spectra on a Specord UV-vis in alcohol. PMR spectra were obtained on a Varian A 56/60 instrument in $CDCl_3$, internal standard HMDS. Mass spectra were recorded on MS-902 and Finnigan MAT MS-8200 spectrometers. The compounds were identified by TLC on Silufol UV-254 plates (eluent, chloroform), their melting points, and the IR spectra. The yields, melting points, and spectral data of the compounds obtained are given in Table 1. The elemental analyses of (IV) and (VI) for C, H, and N were in agreement with the calculated values.

The syntheses of (Ia, b, d) and (IIa-e) have been described [11, 14].

Reaction of Hydroxyaminopyrimidines (Ia, b) and Nitrosopyrimidine (IIa) with Nitric Acid. To 5 ml of concentrated nitric acid (d 1.39) was added in small portions with stirring 0.20 g of the hydroxyaminopyrimidine (Ia). Stirring was continued until evolution of oxides of nitrogen ceased. The mixture was neutralized with saturated sodium bicarbonate solution, and the precipitate filtered off, washed with water, and dried to give 0.12 g (63%) of the hydroxypyrimidine (IIIa), mp 220-222°C (lit. mp 223°C [15]).

Compound (IIIa) was obtained similarly in 86% yield from the nitrosopyrimidine (IIa). The hydroxyaminopyrimidine (Ib) gave 92% of the hydroxypyrimidine (IIb), mp > 260°C (lit. mp 291°C [15]).

Reaction of Hydroxyaminopyrimidine (Ib) and Nitrosopyrimidine (IIa) with m-Chloroperbenzoic Acid. To a solution of 0.26 g (1.5 mmole) of m-chloroperbenzoic acid in 100 ml of chloroform was added at 0°C 0.26 g (1 mmole) of the hydroxyaminopyrimidine (Ib), and the mixture kept for three days in the refrigerator. It was then washed with 10% potassium

carbonate, dried over magnesium sulfate, evaporated, and the residue washed with petroleum ether to give 0.21 g of the starting material (Ib).

Treatment of the nitrosopyrimidine (IIa) with m-chloroperbenzoic acid under similar conditions gave the starting material (IIa).

Nitropyrimidines (IVa-e). A. To a solution of 2.94 g (30 mmole) of maleic anhydride in 20 ml of chloroform was added at 0°C 1.00 g (27 mmole) of 90% H_2O_2, and the mixture stirred for 10 min. To a solution of 1.00 g (5 mmole) of the nitrosopyrimidine (IIa) in 280 ml of chloroform was added at 0°C the prepared solution of permaleic acid, and the mixture kept for seven days in the refrigerator. It was then washed with 10% potassium carbonate solution and water, dried over magnesium sulfate, and evaporated. The residue was separated on a column of silica gel (140-315 μm), eluent chloroform, to give 0.15 g of the nitropyrimidine (IVa).

B. To a solution of 0.40 g (2 mmole) of the nitrosopyrimidine (IIa) in 25 ml of chloroform was added 1.00 g of $KMnO_4$ and 0.96 g (3 mmole) of tetrabutylammonium bromide, and the mixture stirred until the color of the $KMnO_4$ had disappeared. The solid was filtered off, the filtrate evaporated, and the residue extracted with ether and the ether removed to give 0.16 g of the nitropyrimidine (IVa).

Similarly, from the nitrosopyrimidine (IIc) there was obtained the nitropyrimidine (IVc).

C. To 40 ml of 3% sodium hypochlorite solution (pH 11.2) was added with stirring 0.96 g (3 mmole) of tetrabutylammonium bromide and a solution of 0.40 g (2 mmole) of the nitrosopyrimidine (IIa) in 50 ml of chloroform. The mixture was stirred rapidly for 2 min, then the organic layer was separated, evaporated, and the residue extracted with ether. The ether was evaporated, and the residue separated on a column of silica gel (140-315 μm), eluent chloroform, to give 0.21 g of the nitropyrimidine (IVa).

Similarly, from the nitrosopyrimidine (IIb) there was obtained the nitropyrimidine (IVb).

D. To a suspension of 0.26 g (1 mmole) of the nitrosopyrimidine (IId) in 25 ml of chloroform was added 0.48 g (1.5 mmole) of tetrabutylammonium bromide and 10 ml of 7% potassium hypochlorite solution (pH 9.5), and the mixture stirred rapidly for 10 min. The product was isolated and purified as in method C, to give 0.20 g of the nitropyrimidine (IVd).

Similarly, from the nitrosopyrimidine (IIe) there was obtained the nitropyrimidine (IVe).

E. To a solution of 0.52 g (2 mmole) of the nitrosopyrimidine (IId) was added 0.26 g (1 mmole) of 18-crown-6 and 25 ml of 7% potassium hypochlorite solution (pH 9.5). The mixture was stirred rapidly for 10 h. The product was isolated and purified as in method C, to give 0.31 g of the nitropyrimidine (IVd).

Azoxypyrimidines (Va, b, d). A. To a solution of 4.90 g (50 mmole) of maleic anhydride in 22 ml of chloroform was added at 0°C 0.68 ml of 30% hydrogen peroxide, and the mixture stirred for 2 h. This solution was added to a solution of 0.53 g (2 mmole) of the hydroxyaminopyrimidine (Ib) in 50 ml of chloroform at 0°C, and the mixture kept for seven days in the refrigerator. The solid was filtered off, and the filtrate washed with 10% potassium carbonate solution, dried over magnesium sulfate, evaporated, and the residue separated on a column of silica gel (140-315 μm), eluent chloroform, to give 0.15 g (29%) of the azoxypyrimidine (Vb), mp 191-194°C (decomp.) (reprecipitated from chloroform with ether). According to [11], mp 191-194°C (decomp.).

B. To a solution of 0.50 g (1.9 mmole) of the hydroxyaminopyrimidine (Ib) in 20 ml of DMF was added dropwise with stirring 10 ml of 5% sodium hypochlorite solution. The mixture was stirred for 15 min, 50 ml of water added, and the solid filtered off and dried to give 0.40 g (83%) of the azoxypyrimidine (Vb), mp 191-194°C (decomp.).

Obtained similarly were the azoxypyrimidines (Va) and (Vd). (Va), yield 63%, mp 161-162°C (decomp.) [lit. mp, 161-162°C (decomp.)]. (Vd), yield 71%, mp 185-187°C (decomp.) (lit. mp 184-187°C [12]).

Reduction of Nitropyrimidines (IVb, d). To a suspension of 0.28 g (1 mmole) of the nitropyrimidine (IVa) in 10 ml of alcohol was added 1 ml (10 mmole) of phenylhydrazine.

The mixture was boiled for 1 h, then evaporated, and the residue washed with 25 ml of hot water, dried, and recrystallized from a mixture of benzene and petroleum ether (70-100°C) to give 0.12 g (46%) of the hydroxyaminopyrimidine (Ib), mp 150-152°C (decomp.).

Similarly, the nitropyrimidine (IVd) gave 40% of the hydroxyaminopyrimidine (Id).

Reaction of Nitropyrimidines (IVb, d) with Piperidine. To a suspension of 0.20 g (1 mmole) of the nitropyrimidine (IVa) in 10 ml of alcohol was added 0.2 ml (2 mmole) of piperidine, and the mixture kept at 20°C for 2.5 h. The mixture was then evaporated, and the residue washed with water and dried to give 0.22 g of (VIb) (Table 1).

Similarly, the nitropyrimidine (IVd) gave, after 36 h, 88% of (VId), mp 161-162°C (lit. mp 161.5-162°C [15]).

Reaction of Chloropyrimidines (VIIb, d) with Piperidine. This was carried out as described above for the nitropyrimidines, to give (VIb) and (VId). Compound (VIb) was obtained after 13 days in 98% yield, and (VId) after 13 days in 61% yield [the starting pyrimidine (VIId) was present].

2-Ethoxy-4,6-diphenylpyrimidine (VIII). To a suspension of 0.10 g (0.36 mmole) of the nitropyrimidine (IVd) in 10 ml of alcohol was added at 20°C 5 ml of 50% aqueous KOH, and the mixture kept for 18 h. The solid was filtered off, washed with water, and dried to give 0.07 g (70%) of (VIII), mp 87-88°C (from hexane) (lit. mp 87-88°C [16]).

LITERATURE CITED

1. V. L. Rusinov, A. Yu. Petrov, and O. N. Chupakhin, Khim. Geterotsikl. Soedin., No. 2, 147 (1985).
2. E. C. Taylor, C.-P. Tseng, and J. B. Rampal, J. Org. Chem., 47, 552 (1982).
3. C. Tennant and C. W. Yacomeni, J. Chem. Soc. Chem. Commun., No. 1, 60 (1982).
4. V. P. Mamaev, T. A. Andreeva, V. P. Krivopalov, and V. I. Eroshkin, Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 955 (1986).
5. V. P. Mamaev, V. F. Sedova, G. G. Moskalenko, V. N. Odinokov, V. R. Akhmetova, and G. A. Tolstikov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 4, 954 (1986).
6. R. A. Abramovitch and E. M. Smith, J. Heterocycl. Chem., 12, 969 (1975).
7. M. D. Coburn, J. Heterocycl. Chem., 7, 455 (1970).
8. R. H. Wiley and J. L. Hartman, J. Am. Chem. Soc., 73, 494 (1951).
9. E. V. Brown, J. Am. Chem. Soc., 76, 3167 (1954).
10. T. Kosuge, J. Zenda, H. Sawanishi, and Y. Suzuki, Chem. Pharm. Bull., 17, 2181 (1969).
11. G. G. Moskalenko, V. F. Sedova, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 7, 962 (1989).
12. G. G. Moskalenko, V. F. Sedova, and V. P. Mamaev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 3, 701 (1987).
13. A. Cross, Introduction to Practical Infrared Spectroscopy [Russian translation], IL, Moscow (1961), p. 112.
14. G. G. Moskalenko, V. F. Sedova, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 11, 1523 (1986).
15. V. P. Mamaev (ed.), Pyrimidines. Tables of Pyrimidine Compounds. 1966-1972 [in Russian], Novosibirsk (1976), p. 1122.
16. V. A. Koptyuga (ed.), Atlas of Spectra of Aromatic and Heterocyclic Compounds [in Russian], Nauka, Novosibirsk (1976), No. 4, p. 49.