REACTION OF SUBSTITUTED 4-PHENYLPYRIMIDINE 1,3-DIOXIDES WITH PHOSPHORUS OXYCHLORIDE

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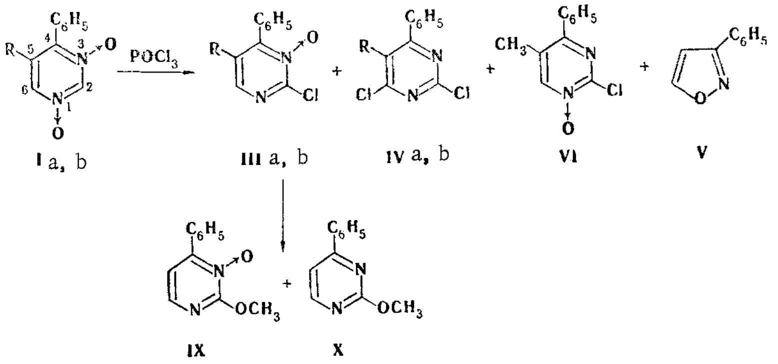
2-Chloropyrimidine 1-oxides are formed in the reaction of substituted 4-phenylpyrimidine 1,3-dioxides with phosphorus oxychloride; in addition, 2,4-dichloropyrimidines and 3-phenylisoxazoles were isolated.

Chloropyrimidine N-oxides are difficult-to-obtain compounds and are formed only in certain cases by oxidation of the corresponding chloropyrimidines [1]. Continuing our study of pyrimidine 1,3-dioxides [2], we examined the reaction of phosphorus oxychloride with 4-phenyl-, 5-methyl-4-phenyl-, and 6-methyl-4-phenylpyrimidine 1,3-dioxides (Ia, b, II) under the assumption that by means of this method we would be able to obtain chloropyrimidine N-oxides and that the presence of a phenyl group in the 4 position of these compounds would make it possible to use the UV spectra to establish the structures of the isomeric pyrimidine N-monoxides.

When we carried out the reaction of Ia with phosphorus oxychloride both without a solvent and in chloroform we isolated 2-chloro-6-phenylpyrimidine 1-oxide (IIIa) and the previously described 2,4-dichloro-6-phenylpyrimidine (IVa) and 3-phenylisoxazole (V). The ratio of IIIa, IVa, and V and their overall yield vary as a function of the reaction conditions: one obtains 50% IIIa, 10% IVa, and 3% V in phosphorus oxychloride at room temperature; the yield of dichloropyrimidine IVa increases to 25%, and the yield of IIIa decreases when the temperature is raised to 70°C; one obtains 28% IIIa, 3% IVa, and 8% V with phosphorus oxychloride in chloroform. The position of chlorine in IIIa follows from data from the PMR spectrum (Table 1) and in both IIIa and IVa corresponds to known data on the formation of α- and γ-chloro derivatives in the reaction of azine N-oxides with phosphorus oxychloride [4]. The position of the N-oxide group in IIIa was determined from a comparison of its UV spectrum (Table 2) with the UV spectra of 4-phenyl- and 6-phenylpyrimidine 1-oxides [3].



I, III, IV a R=H; b R=CH$_3$

Compound Ib reacts with phosphorus oxychloride in the same way. However, in this case workup of the reaction mixture yielded, in addition to 2-chloro-5-methyl-6-phenylpyrimidine 1-oxide (IIIb) and 2,4-dichloro-5-methyl-6-phenylpyrimidine (IVb), yet another monochloro derivative, which, according to the spectral and analytical data, is 2-chloro-5-methyl-4-phenylpyrimidine 1-oxide (VI) (Tables 1 and 2). The yield of VI is one third the yield of

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TABLE 1. PMR Spectra of Pyrimidine II-IV, VI, VII, IX, and X (in $CDCl_3$)

Compound	δ, ppm (J, Hz)			
	R_2	R_5	R_6	C_6H_5
II	9,12 s	H[a]	2,49 s	7,3—7,5, 7,8—8,0 m
IIIa	—	7,38 d (4,5)	8,02 d (4,5)	7,4—7,5, 7,7—7,9 m
IIIb	—	2,13 d (0,5)	8,04 q (0,5)	7,4—7,7 m
IVa	—	7,65 s	—	7,4—7,6, 7,8—8,2 m
IVb	—	2,38 s	—	7,51 s
VI	—	2,39 s	8,48 s	7,4—7,7 m
VII	—	H[a]	2,65 s	7,4—7,7, 7,9—8,2 m
IX	4,18 s	7,13 d (5,0)	7,90 d (5,0)	7,4—7,7, 7,9—8,1 m
X	4,00 s	7,23 d (5,0)	8,45 d (5,0)	7,2—7,4, 7,9—8,1 m

[a] The signal coincided with the region of absorption of the protons of the benzene ring.

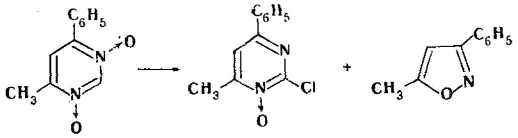
TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp,[a] °C	UV spectrum, λ_{max}, nm (log ε)[b]	Found, %				Empirical formula	Calc., %			
			C	H	Cl	N		C	H	Cl	N
II	164 (dec.)	271 (4,48), 313 (4,19), 371 sh (3,09)	65,3	5,0	—	14,0	$C_{11}H_{10}N_2O_2$	65,3	5,0	—	13,9
IIIa	125—128	220 (4,04), 254 (4,35), 286 (3,83), 333 (3,45)	58,2	3,4	16,9	13,4	$C_{10}H_7ClN_2O$	58,1	3,4	17,2	13,6
IIIb	133—134	226 (4,30), 254 (4,18), 267 sh (3,96), 323 (3,53)	60,3	4,1	16,4	12,6	$C_{11}H_9ClN_2O$	59,9	4,1	16,1	12,7
IVa	85—86[c]	261 (4,26), 288 (4,13)	—	—	31,0	12,4	$C_{10}H_6Cl_2N_2$	—	—	31,5	12,4
IVb	92—93[d]	253 (3,88), 282 (4,02)	55,3	3,3	29,3	11,5	$C_{11}H_8Cl_2N_2$	55,2	3,4	29,7	11,7
V	Oil[e]	240 (4,22)	—	—	—	9,2	C_9H_7NO	—	—	—	9,7
VI	153—155	227 (4,18), 286 (4,14), 335 (3,98)	59,6	4,4	16,2	12,3	$C_{11}H_9ClN_2O$	59,9	4,1	16,1	12,7
VII	175—177	220 (4,39), 306 (4,27), 328 (4,28)	59,9	4,1	16,5	12,4	$C_{11}H_9ClN_2O$	59,9	4,1	16,1	12,7
VIII	37—38[f]	241 (4,16)	75,1	5,9	—	8,4	$C_{10}H_9NO$	75,4	5,7	—	8,8
IX	161—163	250 (4,38), 286 (3,90), 322 (3,71)	65,4	5,0	—	13,7	$C_{11}H_{10}N_2O_2$	65,3	5,0	—	13,9
X	Oil	252 (4,16), 290 (4,30)	—	—	—	14,8	$C_{11}H_{10}N_2O$	—	—	—	15,0

[a] The compounds were recrystallized: II from dioxane, IIIa from isooctane, VII from hexane, and IX from methanol; IIIb, IV-VI, and VIII-X were purified by chromatography. [b] Shoulder is denoted by sh. [c] According to [11], this compound has mp 88°C. [d] According to the data in [11], this compound has mp 89-90°C. [e] According to the data in [12], this compound has mp 1-2°C. [f] According to the data in [13], this compound has mp 42°C and a UV spectrum with λ_{max} 240 nm (log ε 4.15).

IIIb. The position of the chlorine atom in IIIb and VI follows from the data from the PMR spectra (Table 1), while the position of the N-oxide group follows from a comparison of the UV spectra of IIIb and VI (Table 2) and the known 4-phenyl- and 6-phenyl-5-methylpyrimidine 1-oxides [3].

The reaction of 1,3-dioxide II with phosphorus oxychloride in chloroform proceeds with pronounced resinification. 2-Chloro-6-methyl-4-phenylpyrimidine 1-oxide (VII) and the previously described 5-methyl-3-phenylisoxazole (VIII) were isolated in low yields from the reaction mixture. The position of the N-oxide group in VII was established by comparison of the UV spectra of VII (Table 2) and the isomeric 4- and 6-phenylpyrimidine 1-oxides [3]. The formation of products of the reaction of 1,3-dioxide II with phosphorus oxychloride with participation of the methyl group was not observed.



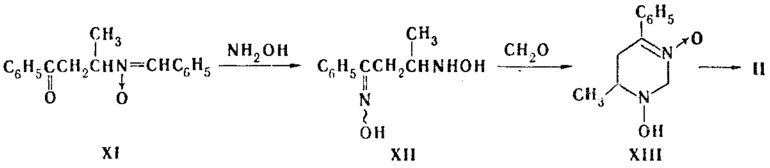
II VII VIII

In conformity with the literature data [5] it may be assumed that isoxazoles V and VIII are products of the conversion of 1,3-dioxides Ia and II or substituted 6-phenylpyrimidine 1-oxides, which under the reaction conditions undergo ring opening with subsequent recyclization.

Thus in the reaction of pyrimidine 1,3-dioxides I and II with phosphorus oxychloride the principal reaction pathway is attack by the chloride anion on the 2 position of the heteroring to give 2-chloropyrimidine N-monoxides.

The chlorine atom in IIIa is more labile than that in 2-chloro-4-phenylpyrimidine (see [6]). Thus in the reaction with sodium methoxide chlorine in the first compound is replaced by a methoxy group in 30 min, whereas the second compound requires several hours of heating. In the reaction of IIIa with sodium methoxide, in addition to the product of replacement of a chlorine atom, viz., 2-methoxy-6-phenylpyrimidine 1-oxide (IX), we isolated the product of its deoxygenation, viz., 2-methoxy-4-phenylpyrimidine (X).

Let us note that 6-methyl-4-phenylpyrimidine 1,3-dioxide (II) was obtained via the scheme



EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A-56-60A spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with an MS-902 spectrometer. The course of the reaction was monitored on Silufol UV-254 plates; the spots were developed with UV light.

N-(1-Oxo-1-phenyl-3-butyl)-α-phenylnitrone (XI), with mp 147-148°C (from alcohol), was obtained in 85% yield by the method in [7]. UV spectrum, λ_{max} (log ε): 243 (4.23), 294 (4.34), and 305 (sh) nm (4.19). Found: C 76.5; H 6.4; N 5.0%. $C_{17}H_{17}NO_2$. Calculated: C 76.4; H 6.4; N 5.2%. N-(1-Hydroxyimino-1-phenyl-3-butyl)hydroxylamine (XII), with mp 157-158°C (from alcohol) (mp 151-152°C [9]), was obtained in 87% yield by the method in [8]. UV spectrum, λ_{max} 244 nm (log ε 4.04). Found:C 61.5; H 7.1; N 14.5%. $C_{10}H_{14}N_2O_2$. Calculated: C 61.9; H 7.3; N 14.4%. 1-Hydroxy-6-methyl-4-phenyl-1,2,5,6-tetrahydropyrimidine 3-oxide (XIII), with mp 143-145°C (from dioxane), was obtained in 95% yield by the method in [10]. UV spectrum, λ_{max} 282 nm (log ε 4.00). Found: C 63.7; H 6.8; N 13.4%. $C_{11}H_{14}N_2O_2$. Calculated: C 64.0; H 6.8; N 13.6%. 6-Methyl-4-phenylpyrimidine 1,3-dioxide (II) was obtained in 53% yield by the method in [3]. The spectral and analytical data for 1,3-dioxide II and III-X are presented in Tables 1 and 2.

Reaction of 1,3-Dioxide Ia with Phosphorus Oxychloride. A) A 1.2-g (6.4 mmole) sample of 1,3-dioxide Ia was dissolved in 30 ml of phosphorus oxychloride, and the solution was maintained at 20°C for 5 h. It was then evaporated, and the residue was poured over ice and extracted with chloroform. The chloroform layer was washed with 5% sodium bicarbonate and water, dried with magnesium sulfate, and evaporated. The residual mixture was chromatographed with a column filled with silica gel [elution with ether—petroleum ether (1:1) and ether] to give 0.14 g (10%) of 2,4-dichloro-6-phenylpyrimidine (IVa), 0.03 g (3%) of 3-phenylisoxazole (V), and 0.66 g (50%) of 2-chloro-6-phenylpyrimidine 1-oxide (IIIa). Found for V: M 145.0511. C_9H_7NO. Calculated: M 145.0527. The choice between the 3- and 5-phenylisoxazole structures was made on the basis of a comparison of the mass spectra at 70 eV [14]. When the reaction was carried out at 70°C, 25% IVa and 5% IIIa were obtained.

B) A suspension of 0.40 g (2.1 mmole) of 1,3-dioxide Ia in 10 ml of chloroform and 0.70 g (4.6 mmole) of phosphorus oxychloride was stirred at 20°C for 6 h, after which it was diluted with chloroform and treated with stirring with 30 ml of a 5% solution of sodium bicarbonate. The chloroform solution was separated, washed with water, dried with magnesium sulfate, and evaporated. Workup as in method A gave 14 mg (3%) of IVa, 25 mg (8%) of V, and 123 mg (28%) of IIIa.

The reaction of 1,3-dioxides Ib and II with phosphorus oxychloride was carried out by method B with reaction times of 4 and 3 h, respectively. Compound Ib yielded 1% IVb, 48% IIIb, and 14% VI, while II yielded 3% VIII and 8% VII. Found for VIII: M 159.0678. $C_{10}H_9NO$. Calculated: M 159.0684. PMR spectrum of VIII (in CCl_4): 2.41 (3H, s, CH_3), 6.18 (1H, s, 4CH); 7.3-7.5, 7.6-7.9 ppm (5H, m, C_6H_5).

2-Methoxy-6-phenylpyrimidine 1-Oxide (IX) and 2-Methoxy-4-phenylpyrimidine (X). A 70-mg (0.34 mmole) sample of IIIa was added to a solution of 0.5 mmole of sodium methoxide in 2.5 ml of methanol. After 30 min, the solution was neutralized with acetic acid and evaporated. The residue was treated with chloroform, washed with water, dried with magnesium sulfate, and evaporated. The residue was chromatographed with a column filled with silica gel (elution with ether and ethyl acetate) to give 30 mg (48%) of oily X and 20 ml (29%) of IX.

Compound X was obtained in 80% yield by alternative synthesis from 2-chloro-4-phenylpyrimidine by heating with sodium methoxide for 4 h.

LITERATURE CITED

1. R. Peereboom, H. C. van der Plas, and A. Koudijs, Rec. Trav. Chim., 93, 58 (1974).
2. A. Ya. Tikhonov, L. B. Volodarskii, O. A. Vakolova, and M. I. Podgornaya, Khim. Geterotsikl. Soedin., No. 1, 110 (1981).
3. A. Ya. Tikhonov and L. B. Volodarskii, Khim. Geterotsikl. Soedin., No. 2, 259 (1977).
4. A. R. Katritzky and J. M. Lagowski, Chemistry of the Heterocyclic N-Oxides, Academic Press, London—New York (1971), p. 259.
5. T. Sakamoto, S. Niitsuma, M. Mizugaki, and H. Yamanaka, Chem. Pharm. Bull., 27, 2653 (1979).
6. V. F. Sedova, A. S. Lisitsyn, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 10, 1392 (1978).
7. A. Ya. Tikhonov and L. B. Volodarskii, Zh. Org. Khim., 9, 770 (1973).
8. A. Ya. Tikhonov, L. B. Volodarskii, and O. M. Sokhatskaya, Khim. Geterotsikl. Soedin., No. 9, 1265 (1979).
9. K. Auwers and H. Müller, J. Prakt. Chem., 137, 81 (1933).
10. A. Ya. Tikhonov and L. B. Volodarskii, Khim. Geterotsikl. Soedin., No. 2, 252 (1977).
11. V. P. Mamaev (editor), Pyrimidines. Tables of Compounds of the Pyrimidine Series (1966-1972) [in Russian], Novosibirsk (1976), p. 230.
12. Beilstein, Band 27, II, p. 27.
13. G. Bianchi and P. Grünanger, Tetrahedron, 21, 817 (1965).
14. E. Stenhagen, S. Abrahamsson, and F. W. McLafferty (editors), Registry of Mass-Spectral Data, Vol. 1, Wiley-Interscience (1974), p. 351.