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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TABLE 1. Properties of Compounds Obtained

Compound	mp, °C*	Found, %				M	Empirical formula	Calculated, %				Yield, % (method of prep.)
		C	H	Cl(S)	N			C	H	Cl(S)	N	
IIa	245—247	65,9	5,4	—	21,2	201	$C_{11}H_{11}N_3O$	65,6	5,5	—	20,9	40 (A), 23 (B), 21 (C), 40 (D)
IIb	222—223	64,2	4,5	—	22,5	187	$C_{10}H_9N_3O$	64,2	4,8	—	22,4	43 (C), 30 (D)
IIb·$HClO_4$	177—180	—	—	—	14,2	—	$C_{10}H_9N_3O \cdot HClO_4$	—	—	—	14,6	—
IIb·HCl	167—170	—	—	16,4	18,7	—	$C_{10}H_9N_3O \cdot HCl$	—	—	15,9	18,8	—
IIc**	195—197	61,2	5,5	—	19,6	217	$C_{11}H_{11}N_3O_2$	60,8	5,1	—	19,3	31 (A), 39 (D)
IIc·HCl	210—214	—	—	15,1	16,0	—	$C_{11}H_{11}N_3O_2 \cdot HCl$	—	—	14,1	16,6	—
IIc·$HClO_4$	125—127	—	—	11,3	12,5	—	$C_{11}H_{11}N_3O_2 \cdot HClO_4$	—	—	11,2	13,2	—
IId	229—233	64,3	4,7	—	22,0	—	$C_{10}H_9N_3O$	64,2	4,8	—	22,4	30 (B)
IIIa	209—211	64,0	5,4	—	17,0	243	$C_{13}H_{13}N_3O_2$	64,2	5,4	—	17,3	65
IIIb	147—149	62,7	4,6	—	18,3	229	$C_{12}H_{11}N_3O_2$	62,9	4,8	—	18,4	70
IIIc	178—180	60,2	4,9	—	16,3	259	$C_{13}H_{13}N_3O_3$	60,2	5,0	—	16,2	45
IIId	178—180	70,6	4,9	—	14,3	305	$C_{18}H_{15}N_3O_2$	70,8	4,9	—	13,8	40
IIIf	169—171	65,4	4,9	—	12,2	351	$C_{19}H_{17}N_3O_4$	64,9	4,9	—	12,0	80
IIIe·HCl	178—182	—	—	9,9	10,7	—	$C_{19}H_{17}N_3O_4 \cdot HCl$	—	—	9,1	10,8	—
IVa	188—193	55,3	4,9	13,2	15,7	—	$C_{13}H_{14}ClN_3O_2$	55,8	5,0	12,7	15,1	83
IVb	166—170	54,4	4,6	—	15,9	—	$C_{12}H_{12}ClN_3O_2$	54,2	4,5	—	15,8	50
IVc	166—168	51,3	5,0	11,8	14,4	—	$C_{13}H_{14}ClN_3O_3 \cdot 0{,}5H_2O$	51,2	4,9	11,6	13,8	74
IVd	180—190	—	—	10,0	12,9	—	$C_{18}H_{16}ClN_3O_2$	—	—	10,4	12,3	87
IVe	160	—	—	10,2	11,5	—	$C_{18}H_{16}ClN_3O_3$	—	—	9,9	11,7	92
IVf	160—170	—	—	9,5	10,5	—	$C_{19}H_{18}ClN_3O_4$	—	—	9,1	10,8	90
VIII	208—212	67,3	5,3	—	17,7	—	$C_{18}H_{16}N_4O_2$	67,5	5,0	—	17,5	25 (A), 45 (B)
IX	234—236	71,4	5,1	—	18,9	—	$C_{18}H_{16}N_4O$	71,0	5,3	—	18,4	89
Xb	152—156	—	—	(9,9)	12,7	—	$C_{13}H_{17}N_3O_5S$	—	—	(9,8)	12,8	67
Xc	183—185	42,6	4,4	10,4	12,0	—	$C_{12}H_{14}ClN_3O_5 \cdot H_2O$	43,1	4,8	10,6	12,6	54

*Solvents for recrystallization: (IIa,d) and (IIIb-d,f), alcohol; (IIb) and (IIIa), aqueous alcohol; (VIII) and (IX), alcohol—acetic acid; (IIc) acetonitrile. Compounds (IIc·HCl), (IVb,d,f) melted with decomposition, and (IVe) melted at 115-120°C, resolidified, and melted again at 160°C.
†Described in [17].

TABLE 2. IR and PMR Spectra of Compounds Obtained

Compound	IR spectrum, cm^{-1} (KBr)			PMR spectrum, δ*, ppm				
	δ_{NH_2}	$\nu_{N\to O}$	$\nu_{C=O}$	5-H**	CH_3, pyr	CH_3CO	H_{arom}	other groups
IIa	1645	1205		7,07	2,72	—	7,27	7,85 (NH_2)
IIb	1630	1180		—	—	—	7,45	8,73 (2-H), 7,80 (4-H)
IIc	1665	1225		5,68	2,43	—	7,47—6,47	7,58 (NH_2)
IId	1650	1200		7,42	—	—	8,17—7,80; 7,65—7,42 (2 : 3)	8,81 (2-H)
IIIa		1255	1715	8,67	2,70	2,18	7,80—7,55; 7,38—7,10 (2 : 3)	—
IIIb		1265	1720	—	—	1,85	7,48	8,95 (2-H), 8,11 (4-H)
IIIc		1200	1710	7,57	2,42	2,07	7,33—6,50	—
IIId		1270	1700	8,83	2,27	—	7,87—7,57; 7,48—7,13 (4 : 6)	—
IIIf		1200	1700	7,77	2,53	—	7,90—7,67; 7,47—6,63 (1 : 8)	3,80 (CH_3O)
IVa	1670		1825	7,17	2,83	1,82	7,57—7,27	—
IVb	1665		1830	—	—	1,82	7,20	9,17 (2-H), 7,98 (4-H)
IVc	1675		1825	5,87	2,47	1,78	7,33—6,63	—
IVd	1680		1785	7,23	2,83	—	8,20—7,67; 7,50—7,10 (2 : 8)	—
IVe	1675		1785	5,90	2,28	—	8,00—7,67; 7,50—6,60 (2 : 8)	—
IVf	1680		1805	5,73	2,48	—	7,83—6,63 (9H)	3,73 (CH_3O)
VIII		1240	1720	—	2,70	—	8,71—8,33; 7,77—7,43; 7,32—7,00 (2 : 4 : 5)	
IX			1710	—	2,55	—	7,50—7,10; 7,03—6,80 (6 : 5)	—
Xa	1660			7,40	2,76	—	8,13—7,73; 7,66—7,43 (2 : 3)	4,13 (CH_3O)
Xb	1670			—	2,75	—	8,16—7,73; 7,63—7,26 (2 : 4)	9,50—9,13 (NH_2), 4,13 (CH_3O) 3,43 ($CH_3OSO_3^-$)
Xc	1670			7,23	2,72	—	8,20—7,73; 7,68—7,30 (2 : 3)	9,50—9,13 (NH_2), 4,13 (CH_3O)

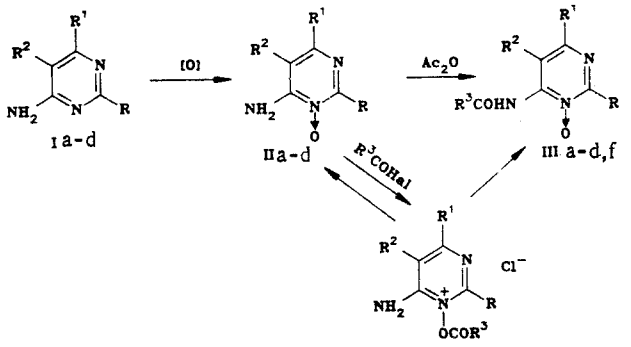
*Solvents: for (IIa,c), (IIIa,c,d,f), (IVa-f), (VIII), and (IX) CF_3COOH; for (IIb,d), (IIIb), (Xa-c), and (IIa,c) (NH_2 group signal), DMSO-D_6.

**The 5-H signal in (VIII), (IX), and (Xb) coincides with the signal for the aromatic protons.

Two reactive centers are present in aminopyrimidine N-oxides, namely the NH_2 and N → O groups, so that two modes of acylation and alkylation are possible (the nitrogen atom in the heterocycle becomes of low basicity as a result of the influence of the acceptor N-oxide group).

Acylation of N-oxides (IIa-c) by treatment with acetic anhydride or acid chlorides takes place much more rapidly than the acylation of aminopyrimidines (for example, when (IIa) is treated with acetic anhydride the reaction is complete in 40 min at 20°C, whereas in the case of (Ia) no reaction is seen after 24 h). Treatment of (IIa-c) with an equimolar amount of acetic anhydride in acetone at 20°C gives the monoacetyl derivatives, which from their IR and PMR spectra (Table 2) are the 6-acetylaminopyrimidine 1-oxides (IIIa-c). Treatment of (IIa-c) with acid chlorides in anhydrous solvents also gives monoacyl derivatives, but according to their IR spectra (ν_{CO} ~ 1880 cm^{-1}, Table 2) these are N-acyloxypyridinium salts (IVa-f) [5].

The initial attack of the acyl cation on 6-aminopyrimidine 1-oxides, as in other N-oxides [5], takes place at the oxygen of the N-oxide group with the formation of the salts (IV), the stability of which depends on the substituent in the pyrimidine ring and the type of anion. The formation of N-acyloxy derivatives (IV) on treatment with acetic anhydride has been demonstrated by the formation of the salt (IVc) on treatment of hydrochloride (IIc) with acetic anhydride. It appears that the salts (IV), in which the anion is acetate, are of low stability, and rearrange rapidly to (III). Salts (IVa,c-f) are stable in the solid state (for several months at 20°C), but as suspensions in acetone they are partially

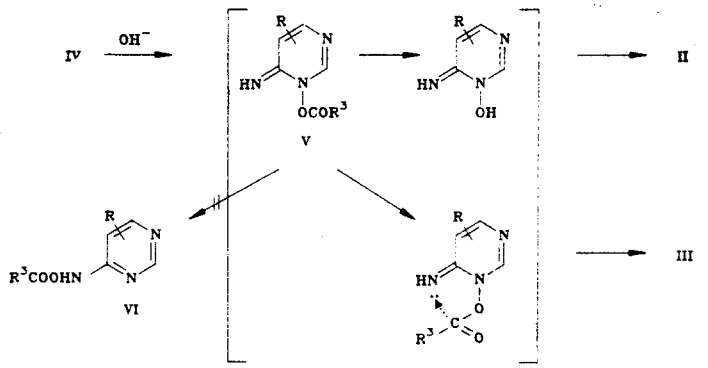


I, IIa,c R=CH3; b,d R=H; a,d R1=C6H5; b R1=H; c R1=OC6H5; a,c,d R2=H; b R2=C6H5;
III, IVa,c–f R=CH3; b R=H; a,d R1=C6H5; b R1=H; c,e,f R1=OC6H5; a,c–f R2=H;
b R2=C6H5; a-c R3=CH3; d,e R3=C6H5; f R3=o-CH3OC6H4

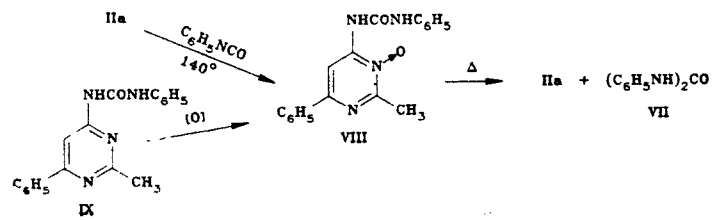
converted in the course of a few days into the starting N-oxides (II), and partially into the acetylamino-compounds (III).

The effects of substituents on the stability of the salts (IV) is shown by a comparison of the acylation of oxides (IIa,c) and (IIb) with different acid chlorides. The N-oxides (IIa,c) gave the (IVa,c-f), but the oxide (IIb) gave the chloride (IVb) only, whereas treatment with other acid chlorides gave the original oxide (IIb).

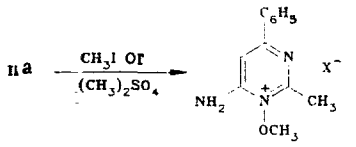
Treatment of the salts (IV) with triethylamine did not affect these compounds. Neutralization of (IV) with inorganic bases might be expected to give 1-acyloxy-6-amino-1,6-dihydropyrimidines (V) or 4-acyloxyaminopyrimidines (VI) (the latter by analogy with quinazoline derivatives [12]). However, these compounds were not found in the reaction mixture, only the N-oxides (II) (IVb → IIb) or (III) (IVd,f → IIId,f) being present, the formation of which is apparently due to the instability of dihydropyrimidines (V) [13, 14].



In contrast to the reaction with acid chlorides, the oxides (II) are less reactive towards aryl isocyanates than the corresponding pyrimidines without the N-oxide group, reaction being observed only at 140°C. Condensation of (IIa) with phenyl isocyanate gave sym-diphenylurea (VII) and 2-methyl-4-phenyl-6-(N'-phenylureido)pyrimidine 1-oxide (VIII). The latter compound was also obtained by oxidizing 2-methyl-6-phenyl-4-(N'-phenylureido)-pyrimidine (IX) with a mixture of acetic acid and hydrogen peroxide.



Compound (VIII) is unstable at elevated temperatures, and on heating in xylene gives a mixture containing, in addition to unchanged starting material, diphenylurea and the oxide (IIa). It appears that the thermal instability of (VIII) is the reason for the low yield obtained when the amine (IIa) reacts with isocyanates at elevated temperatures.



XIa X⁻=I⁻; b X⁻=$CH_3OSO_3^-$; c X⁻=ClO_4^-

Methylation of 6-aminopyrimidine 1-oxide (IIa) takes place with the formation of a single monomethyl compound, which according to its spectral data (Table 2) corresponds to the product of methylation at the oxygen of the N-oxide group. Thus, treatment of (IIa) with iodomethane or dimethyl sulfate gives 1-methoxy-2-methyl-4-phenyl-6-pyridinium iodide or methylsulfate (Xa or Xb), which on treatment with perchloric acid were converted into the perchlorate (Xc).

EXPERIMENTAL*

IR spectra were recorded on a UR-20 instrument in KBr disks (c 0.25%), or in solution in CCl_4, PMR spectra on an A 56/60 instrument, internal standard HMDS, and mass spectra on an MS-902 at 70 eV. Chromatography was carried out on Silufol UV-254 plates (TLC), or on columns of silica gel (40-100 μ) (preparative chromatography). The compounds were identified by their TLC data, melting points, and IR spectra.

Oxidation of Substituted 4-Aminopyrimidines (Ia-d). A. To a solution of 5 mmole of (Ia-c) in 40 ml of acetone was added 2.6 g (13 mmole) of 85% m-chloroperbenzoic acid. The mixture was kept at 4°C for five days, and the solid which separated was filtered off, washed with sodium carbonate solution and water, and recrystallized to give the oxides (IIa,c) (Table 1).

B. A suspension of 5 mmole of the aminopyrimidine (Ia,b, or d) and 0.2 g of sodium tugstate in 20 ml of 30% H_2O_2 was stirred at 55-60°C for 3-15 h (until all the aminopyrimidine had been consumed, followed by TLC, eluent chloroform–acetone, 9:1). The reaction mixture was diluted with an equal volume of water, concentrated under reduced pressure to one half its volume, water again added to restore the original volume, and again concentrated to half its volume. The operation was repeated until all peroxides had been decomposed (checked with starch-iodide paper). The aqueous solution was extracted with chloroform (3 × 100 ml), washed with sodium bicarbonate solution and water, dried, and evaporated to give the oxides (IIa,b, or d).

C. A mixture of 5 mmole of (Ia), 20 ml of acetic acid, and 2 ml of 30% H_2O_2 was heated at 60°C for 12 h, 2 ml of 30% H_2O_2 being added every three hours. Decomposition was carried out as in method B, and the mixture extracted with chloroform, dried, evaporated, and the residue separated on a column of silica gel, eluent ethyl acetate or acetone (the N-oxide (IIa) was eluted with acetone).

D. To a solution of 20 mmole of (Ia-c) in 20 ml of chloroform was added at 0°C 10 g of 60% p-methylcarboxyperbenzoic acid,† and the mixture was kept at 4°C for seven days. The mixture was then treated with an equal volume of chloroform, washed with 10% potassium carbonate solution and water, dried, and evaporated. The residue was recrystallized.

6-Acetylaminopyrimidine 1-Oxides (IIIa-c). A mixture of 8 mmole of the N-oxide (IIa-c) and 0.15 ml (1.6 mmole) of acetic anhydride in 2 ml of acetone was stirred at 20°C for 1-2 h. The solid which separated was filtered off and recrystallized.

2,4- or 5-Substituted-1-acyloxy-6-aminopyrimidinium Chlorides (IVa-f). A mixture of 2.5 mmole of the N-oxide (IIa-c) and 0.5 ml of the acid chloride in 10 ml of dry acetone or acetonitrile was stirred at 20°C for 30 min to 1 h, and the solid filtered off and washed with dry acetone and ether to give the salt (IVa-f).

Decomposition of (IV). A suspension of 2.5 mmole of the salt (IVb,d, or f) in a saturated solution of sodium bicarbonate was stirred at 20°C for 1 h, and the solid filtered off to give the N-oxide (IIb) from salt (IVb), and acetylaminopyrimidines (IIId,f) from salts

*With the assistance of T. A. Akhremenkova.

†We thank workers at the Institute of Chemistry, Bashkir Branch, Academy of Sciences of the USSR, for the kind gift of this peracid [15, 16].

(IVd,f). A 2.5 mmole suspension of the salt (IVa-c) in 10 ml of acetone was stirred for several hours, and the solid filtered off to give the N-oxide (IIb) from salt (IVb), and mixtures of (IIa) + (IIIa) and (IIc) + (IIIc) from salts (IVa) and (IVc), respectively (according to TLC). These mixtures were separated on a column of silica gel, eluent chloroform (IIIa,c) followed by acetone (IIa,c).

2-Methyl-4-phenyl-6-(N'-phenylureido)pyrimidine (IX). A mixture of 1.0 g (5 mmole) of (Ia) and 0.6 ml (5 mmole) of phenyl isocyanate in 20 ml of dry xylene was kept at 140°C for 6 h. The solid which separated was filtered off, and recrystallized to give (IX).

2-Methyl-4-phenyl-6-(N'-phenylureido)pyrimidine 1-Oxide (VIII). A. A mixture of 1.0 g (5 mmole) of the N-oxide (IIa) and 0.6 ml (5 mmole) of phenyl isocyanate in 20 ml of dry xylene was kept at 140°C for 6 h. The solid which separated was filtered off, and separated on a column of silica gel (eluent, chloroform). There were successively obtained 0.6 g (50%) of diphenylurea (VII), mp 246-247°C (alcohol), 0.3 g (25%) of the ureido-compound (VIII), mp 208-212°C (from alcohol–acetic acid), and 0.2 g (17%) of the N-oxide starting material (IIa).

B. Compound (IX) (5 mmole) was oxidized as described above, method B. The solid which separated from the reaction mixture was filtered off, washed with water, and recrystallized to give (VIII), yield 45%.

1-Methoxy-6-amino-2-methyl-4-phenylpyrimidinium Iodide (Xa). A solution of 0.5 g (2.5 mmole) of the N-oxide (IIa) and 0.5 ml (8 mmole) of iodomethane in 5 ml of methanol was kept at 20°C for 3 days. Addition of 50 ml of dry ether to the reaction mixture precipitated 0.15 g of (Xa) (18%), mp 228-231°C (decomposed on purification). The structure of (Xa) was confirmed by its PMR spectrum (Table 2), and by conversion to the perchlorate (Xc) (see below).

1-Methoxy-6-amino-2-methyl-4-phenylpyrimidinium Methylsulfate (Xb). A solution of 0.5 g (2.5 mmole) of the N-oxide (IIa) and 0.3 ml (3 mmole) of dimethyl sulfate was heated in 12 ml of toluene at 90°C for 6 h. The solid was filtered off to give (Xb).

1-Methoxy-6-amino-2-methyl-4-phenylpyrimidinium Perchlorate (Xc). To a solution of the salt (Xa) or (Xb) in methanol was added an equimolar amount of perchloric acid. The solid which separated was filtered off, and washed with ether to give (Xc) (30% from (Xa), 54% from (Xb)).

LITERATURE CITED

1. G. Rey-Bellet, R. Reiner, and D. E. Schwartz, Ger. Offen 2,026,997; Chem. Abstr., 74, 76443 (1971).
2. J. C. Muller and R. Ramuz, Ger. Offen 2,804,518; Chem. Abstr., 89, 197,595 (1978).
3. T. J. Delia and D. L. Venton, J. Heterocycl. Chem., 9, 73 (1972).
4. J. M. McCall, R. E. Ten Brink, M. E. Royer, and H. Ko, J. Heterocycl. Chem., 15, 1529 (1978).
5. V. F. Sedova, T. Yu. Mustafina, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 1, 1515 (1981).
6. R. A. Jones and A. R. Katritzky, J. Chem. Soc., No. 1, 2937 (1960).
7. L. W. Deady, Synth. Commun., No. 7, 509 (1977).
8. E. A. Oostveen and H. C. van der Plas, Recl. Trav. Chim., 96, 64 (1977).
9. S. Takahashi and T. Jatsunami, Chem. Pharm. Bull., 26, 2286 (1978).
10. R. Peereboom, H. C. van der Plas, and A. Koudius, Recl. Trav. Chim., 93, 58 (1974).
11. E. Ochiai, Aromatic Amine Oxides, Elsevier, Amsterdam (1967), p. 44.
12. H. Goncalves, F. Mathis, and C. Foulcher, Bull. Soc. Chim. Fr., No. 7, 2615 (1970).
13. D. J. Brown and K. Jenega, J. Chem. Soc., Perkin Trans. 1, No. 3, 375 (1974).
14. D. J. Brown and M. N. Paddon-Row, J. Chem. Soc., C, No. 9, 903 (1967).
15. N. S. Vostrikov, U. M. Dzhemilev, G. S. Bylina, A. M. Moiseenkov, A. V. Semenovskii, and G. A. Tolstikov, Izv. Akad, Nauk SSSR, Ser. Khim., No. 10, 2337 (1978).
16. G. S. Bylina, U. M. Dzhemilev, N. S. Vostrikov, G. A. Tolstikov, A. M. Moiseenkov, A. V. Semenovskii, and S. S. Shavanov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 447 (1978).
17. US Patent No. 3,464,987; Chem. Abstr., 81, 164,337 (1969).