A New Ring Closure Reaction of 2-Phenoxyphenols and 3-(Phenoxy)pyridines. Synthesis of Halogenated 10-Methylphenoxazines and 10-Methyl[1,4]benzoxazino[3,2-*b*]pyridines

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The cyclization of 2-(2-chloro(bromo)phenoxy)anilines and 3-(phenoxy)pyridines to 10-methylphenoxazines and 10-methyl[1,4]benzoxazino[3,2-*b*]pyridines, respectively, by means of dimethyl methylphosphonate is reported. The cyclization reaction proceeded with expulsion of methyl ether. Demethylation of some 10-methylphenoxazines was achieved with pyridine hydrobromide. Nitration was carried out with sodium nitrite, and by reduction of the nitro groups the corresponding amines were prepared.

J. Heterocyclic Chem., 16, 1121 (1979).

Introduction.

Considerable attention has been paid in the past to the synthesis of phenoxazines as a result of the antitubercular activity of some of their derivatives (1a-c).

The clinical effectiveness of the chloropromazine (2a,b) has prompted further the synthesis of a number of structural analogues such as the 10-alkylated phenoxazines. A large number of their derivatives with halogen substituents attached to the benzo-rings have been reported in the search for new agents having pharmacodynamic activity (2a,b). The available methods for their syntheses have been critically surveyed (1a,b), and experimentally tested for their general applicability.

They are further summarized in a comprehensive treatise dealing with the general aspects of different synthetic approaches to the preparations of phenoxazines (3).

More recently there has been renewed interest in dialkylamino substituted phenoxazines which serve as precursers for a group of brilliant dyestuffs (4a-d).

The principal methods for the technical preparation of phenoxazines that have been considered thus far can be classified as follows: (a) the condensation of activated (*e.g.*, by *o*-nitro substituents) halogenated benzenes with *o*-halogenated phenols (1a); (b) condensation of *o*-aminophenols with catechols (1a); (c) the method used by Turpin (1a,16); (d) the condensation of *o*-nitrosophenol ethers with substituted phenols (4a-d).

We have been interested in finding new conditions for the cyclizations of substituted 2-(2-chlorophenoxy)anilines and 2-amino-3-(2-chlorophenoxy)pyridines, respectively, whereby the ring closure should occur with the elimination of hydrogen chloride, leading to the formation of variously substituted phenoxazines and benzoxazino pyridines, respectively.

It had become obvious from previous experiments (2a,b) that the normal ring closure between an amino group and a halogen atom, occupying the 2- and the 2′-positions, respectively, of the phenyl ether moiety, with loss of hydrogen halide, did not represent a practicable synthetic procedure (2a,b). Even the 2-(2-bromophenoxy)-5-chloroaniline afforded the corresponding phenoxazine only in low yield on treatment with potassium carbonate in dimethylformamide (2a), although *N*-monoalkylated derivatives gave excellent yields of *N*-substituted phenoxazines (1a,b). Further work, however, seemed to indicate that the ring closure reaction was strongly promoted, and proceeded in acceptable yield, by substitution of the nitrogen atom with groups other than alkyl. Prominent examples were the ring closure of the *N*-phenylsulfone of phenyl ether (5), of (pentafluorophenoxy)-*N*-formylaniline (6) and of several halogenated 2-(phenoxy)-*N*-formylanilines (7).

Most methods for preparing benzoxazinopyridines utilized the ring closure of *N*-(2-hydroxyphenyl)-3-(2-chloropyridyl)amines, but only in a few examples the intermediates were isolated and characterized as such (8).

Therefore, a new method to achieve this synthetic goal which was simple and efficient, while also amenable to large scale preparation was sought.

Results and Discussion.

Appropriately substituted 2-phenoxynitrobenzenes are largely used as precursers for the synthesis of a variety of 2-phenoxyphenols. The general synthetic route involves reduction of the nitro group to the corresponding amine, followed by diazotization and finally hydrolysis of the diazonium salt to the phenol. The condensation of a number of *o*-chloronitrobenzenes with halogenated phenols was carried out by melting an intimate mixture of the two reactants in the presence of potassium hydroxyde at temperatures ranging from 120-150° (Scheme 1). The applied technique has been amply demonstrated and requires no further comments (9). Compounds **3a-k** (Table 1) were prepared according to this procedure but no attempts were made to improve the yields of the products

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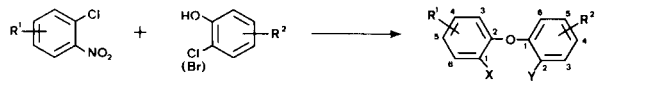
obtained.

The polychloro-substituted phenyl ethers **3g-k** were accompanied by significant amounts of trimeric products such as **11g-k** (Scheme 2, Table 2). Their formation can be explained by displacement of the two chlorine atoms situated in the *o*- and the *p*-positions of the nitrophenyl part of the molecule, by two moles of the phenolate anion.

The compositions of the crude product mixtures were first determined by gas chromatography. The phenyl ethers **3g-k** were then isolated from the 2:1 components and other high boiling fractions by high vacuum distillation. The undistillable residue could be readily crystallized yielding the pure 2:1 products (**11g-k**) (Table 2), which

Scheme 1

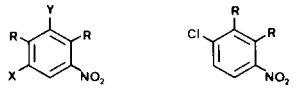


3a-k, X = NO_2
4a-k, X = NH_2
5a-k, X = $N(CH_3)_2$
6a-k, X = $(CH_3)_3N^{(+)}CH_3SO_4^{(-)}$

	Y	R^1	R^2
3-6a	Cl	H	H
b	Br	5-CH_3	H
c	Br	5-CF_3	H
d	Br	5-Br	4-Br
e	Cl	5-Cl	5-Cl
f	Cl	5-Cl	4-Cl
g	Cl	4-Cl	5-Cl
h	Cl	4,5-Cl_2	4-Cl
i	Cl	3,4-Cl_2	4-Cl
k	Cl	4,5-Cl_2	4,5-Cl_2

Scheme 2

Halogenated Bis(phenoxy)nitrobenzenes and Bis(pyridyloxy)-nitrobenzenes, 2:1 Condensation Products of *ortho*-Chloronitrobenzenes with Halogenated Phenols and with Hydroxypyridines



11g-l
12a-b

11k

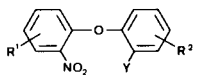
Compound No.	X	Y	R
11g	H	H	2,5-Dichlorophenoxy
11h	Cl	H	2,4,5-Trichlorophenoxy
11i	Cl	H	2,4-Dichlorophenoxy
11k	—	—	2,4-Dichlorophenoxy
12a	Cl	H	2-Chloro-6-methyl-3-pyridyloxy
12b	H	Cl	2-Chloro-6-methyl-3-pyridyloxy

were characterized by their nmr spectra (Table 3).

Although it seemed likely that conducting the condensation reactions in solvents of high dielectric constants, such as dimethyl sulfoxide or dimethylacetamide, would bring about larger amounts of trimeric products (10), the high yields of phenyl ethers obtained in hexamethylphosphorus triamide as solvent (11), seemed to contradict any generalizations along this line of reasoning. This is further confirmed by the failure of this method (11) to yield the appropriate phenyl ether when it was attempted to con-

Table 1

Substituted 2-Phenoxynitrobenzenes



Compound No.	Y	R^1	R^2	M.p. °C (Solvent) B.p. °C (Torr)	Yield	Formula		Analysis, %			
3a	Cl	H	H	48-48.5 (Ethanol) (a)	76.2	$C_{12}H_8ClNO_3$	Calcd.	C, 57.73	H, 3.23	Cl, 14.20	N, 5.61
							Found	C, 57.72	H, 3.31	Cl, 14.34	N, 5.70
3b	Br	5-CH_3	H	68-69; 150 (10^{-2}) (c)	32.6	$C_{13}H_{10}BrNO_3$	Calcd.	C ,50.68	H, 3.27	Br, 25.93	N, 4.55
							Found	C, 50.81	H, 3.34	Br, 26.04	N, 4.81
3c	Br	5-CF_3	H	52-53 (Petrol Ether) (c)	68.2	$C_{13}H_7BrF_3NO_3$	Calcd.	C, 43.12	H, 1.95	Br, 22.07	N, 3.87
							Found	C ,43.30	H, 1.90	Br, 21.91	N, 4.02
3d	Br	5-Br	4-Br	102-103.5 (Ethanol)	55.4	$C_{12}H_6Br_3NO_3$	Calcd	C, 31.89	H, 1.34	Br, 53.05	N, 3.10
							Found	C, 32.11	H, 1.42	Br, 53.40	N, 3.21
3e	Cl	5-Cl	5-Cl	68-70 (Ethanol)	79.1	$C_{12}H_6Cl_3NO_3$	Calcd.	C, 45.25	H, 1.90	Cl, 33.39	N, 4.40
							Found	C, 45.09	H, 2.03	Cl, 33.70	N, 4.38
3f	Cl	5-Cl	4-Cl	84-85 (Ethanol) (b)	84.0	$C_{12}H_6Cl_2NO_3$	Calcd.	C, 45.25	H, 1.90	Cl, 33.39	N, 4.40
							Found	C, 45.08	H, 2.01	Cl, 33.58	N, 4.37
3g	Cl	4-Cl	5-Cl	95-97 (Ethanol) (e); 150 (10^{-1})	79.7	$C_{12}H_6Cl_3NO_3$	Calcd.	C, 45.25	H, 1.90	Cl, 33.39	N, 4.40
							Found	C, 45.11	H, 2.02	Cl, 33.47	N, 4.33
3h	Cl	4,5-Cl_2	4-Cl	112-115 (Ethanol); 175-177 (6 × 10^{-2})	47.9	$C_{12}H_5Cl_4NO_3$	Calcd.	C, 40.83	H, 1.43	Cl, 40.18	N, 3.97
							Found	C, 40.81	H, 1.54	Cl, 40.08	N, 4.04
3i	Cl	3,4-Cl_2	4-Cl	171-172 (10^{-1})	67.0	$C_{12}H_5Cl_4NO_3$	Calcd.	C, 40.83	H, 1.43	Cl, 40.18	N, 3.97
							Found	C, 40.87	H, 1.48	Cl, 39.97	N, 4.11
3k	Cl	4,5-Cl_2	4,5-Cl_2	202 (6.5 × 10^{-2}) (d)	44.9	$C_{12}H_4Cl_5NO_3$	Calcd.	C, 37.20	H, 1.04	Cl, 45.76	N, 3.62
							Found	C, 37.40	H, 1.12	Cl, 46.10	N, 3.72

(a) H. McCombie, W. G. Mac Millan and H. A. Scarborough, *J. Chem. Soc.*, 529, 532 (1931) report m.p. 49°. (b) L. G. Grover, E. E. Turner and G. I. Sharp, *J. Chem. Soc.*, 512 (1929) report m.p. 86°. (c) Lit. (7) reports b.p. 140-155°/0.5 torr. (e) German Patent 506,339 (1927) reports m.p. 97-98°.

Table 2

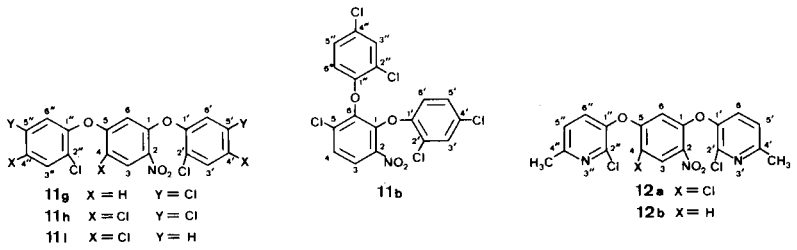
2:1 Condensation Products of *o*-Chloronitrobenzene with Halogenated Phenols and with Hydroxypyridines

Compound No.	Crude Mixtures of Phenyl Pyridyl Ethers and 2:1 Products % Composition		M.p. (Solvent) °C	Formula	Analysis, % Calculated C	H	Cl	N	Found C	H	Cl	N
11g	79.8;	16.4	122-124 (Isopropanol)	$C_{18}H_9Cl_4NO_4$	48.57	2.04	31.86	3.15	48.71	2.21	31.92	3.35
11h	58.9;	25.8	62-62.5 (a)	$C_{18}H_6Cl_7NO_4$	39.42	1.10	45.25	2.55	39.41	1.02	45.32	2.63
11i	60.6;	23.9	137-138 (Acetone)	$C_{18}H_8Cl_5NO_4$	45.08	1.68	36.97	2.92	45.35	1.80	36.92	3.04
11k	69.5;	17.5	141-145 (Acetone)	$C_{18}H_8Cl_5NO_4$	45.08	1.68	36.97	2.92	44.92	1.65	36.73	3.03
12a	66.2;	29.3	149-151 (Acetone)	$C_{18}H_{12}Cl_3N_3O_4$	49.06	2.75	24.14	9.54	49.25	2.82	24.29	9.70
12b	69.2;	28.5	173-174 (Acetone)	$C_{18}H_{12}Cl_3N_3O_4$	49.06	2.75	24.14	9.54	49.31	2.87	24.18	9.65

(a) Isolated by distillation: b.p. 235-240°/4 × 10^{-2} torr.

Table 3

Nuclear Magnetic Resonance Parameterss (Pmr and Cmr) of the Condensation Products **11g-k** and **12a-b**



11g X = H Y = Cl
11h X = Cl Y = Cl
11i X = Cl Y = H

11b

12a X = Cl
12b X = H

Compound No.	Solvent	Type	Chemical Shift in Ppm
11g	Acetone-d_6	Pmr	8.18 (d, 1H, J = 9.0, H_3); 6.95 (d, d, 1H, J = 9.0 and 2.5, H_4); 6.78 (d, 1 H, J = 2.5, H_6); 6.58 (d, 2H, J = 8.0, $H_{3'}$ and $H_{3''}$); 6.45-6.20 (m, 4H, $H_{4'}$, $H_{4''}$, $H_{6'}$ and $H_{6''}$)
11h	Acetone-d_6	Pmr	8.40 (s, 1H, H_3); 7.18 (s, 1H, H_6); 7.78 (s, 1H, $H_{3''}$); 7.74 (s, 1H, $H_{3'}$); 7.56 (s, 1H, $H_{6''}$); 7.36 (s, 1H,$H_{6'}$)
11i	Acetone-d_6	Pmr	8.36 (s, 1H, H_3); 6.70 (s, 1H, H_6); 7.60 (d, 1H, J = 2.0, $H_{3''}$); 7.56 (d, 1H, J = 2.0, $H_{3'}$); 7.50-7.10 (m, 4H, $H_{5'}$ and $H_{5''}$, $H_{6'}$ and $H_{6''}$)
11k	Acetone-d_6	Pmr	8.16 (d, 1H, J = 9.0, H_3); 7.65 (d, 1H, J = 9.0, H_4); 7.5-7.4 (m, 2H, $H_{3'}$ and $H_{3''}$); 7.65 (d, d, 1H, J = 8.0 and 2.0, $H_{5''}$); 7.26 (d, d, 1H, J = 8.0 and 2.0, $H_{5'}$); 7.06 (d, 1H, J = 8.0, $H_{6'}$); 6.83 (d, 1H, J = 8.0, $H_{6'}$)
12a	DMSO-d_6	Pmr	8.53 (s, 1H, H_3); 6.9 (s, 1H, H_6); 6.65 (d, 1H, J = 8.0, $H_{6''}$); 6.50 (d, 1H, J = 8.0, $H_{6'}$); 7.36 (d, 1H, J = 8.0, $H_{5''}$); 7.26 (d, 1H, J = 8.0, $H_{5'}$)
		Cmr	145.9 (C_1), 136.6 (C_2), 127.6 (C_3), 119.0 (C_4), 155.3 (C_5), 110.7 (C_6), 148.3 and 144.5 ($C_{1'}$ and $C_{1''}$); 140.2 and 139.2 ($C_{2'}$ and $C_{2''}$); 155.9 and 154.0 ($C_{4'}$ and $C_{4''}$); 124.1 and 123.7 ($C_{5'}$ and $C_{5''}$); 129.9 and 128.3 ($C_{6'}$ and $C_{6''}$)
12b	Deuteriochloroform	Pmr	7.98 (d, 1H, J = 9.0, H_3); 6.70 (d, 1H, J = 9.0, H_4); 7.26 (d, 1H, J = 8.0, $H_{5''}$); 7.50 (d, 1H, J = 8.0, $H_{6''}$); 6.86 (d, 1H, J = 8.0, $H_{5'}$); 7.05 (d, 1H, J = 8.0, $H_{6'}$)

dense, for example, pentachlorophenol and 2,5-dichloronitrobenzene in hexamethylphosphorus triamide.

Some of the halogenated 2-phenoxynitrobenzenes and also amines have been reported previously as intermediates in synthetic schemes, without, however, having been further characterized by their physical or spectral data (7,9). These compounds have been included in the tables together with appropriate references.

Reduction of the (2-phenoxy)nitrobenzenes (**3a-k**) to the corresponding amines (**4a-k**) was carried out by low pressure hydrogenation in the presence of Raney nickel in dioxane as solvent (Table 4). This method gave consistently excellent yields and appears preferable to the reported reduction with hydrazine and Raney nickel in ethanol as solvent (10).

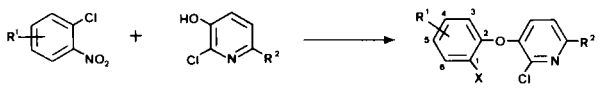
The preparation of the analogous compounds (**7a-e**) in which one of the benzo-rings was replaced by a pyridine nucleus, followed the same general synthetic pattern

(Scheme 3), namely condensation of an appropriately substituted *o*-chloronitrobenzene with a 2-chloro-3-hydroxypyridine derivative. Some phenoxypyridines have also been prepared previously (12) by condensation of 2-chloro-3-nitro-6-methylpyridine with the sodium salts of substituted phenols, which represents again a variation of method a which was mentioned in the introduction.

Two commercially available pyridines were selected as starting materials, 2-chloro-3-hydroxypyridine and 2-methyl-5-hydroxypyridine, of which the latter was chlorinated to yield 2-chloro-3-hyroxy-6-methylpyridine according to a known procedure (13). They were reacted with a number of substituted chloronitrobenzenes yielding the corresponding 2-chloro-3-(2-nitrophenoxy)pyridines (**7a-e**) (Scheme 3, Table 5). Catalytic reduction of the nitro groups as described above yielded the corresponding (aminophenoxy)pyridines (**8a-e**) (Scheme 3, Table 5).

The same type of 2:1 condensation products (**12a,b**) were also isolated from the mixtures obtained when 2-chloro-3-hydroxy-6-methylpyridine was reacted with 2,3,4- and 2,4,5-trichloronitrobenzene (Scheme 3). The composition of the product mixtures, their separation and the isolation technique which have proven fruitful in the phenyl ether series were also applied here. The results pertaining to compounds **12a,b** are also recorded in Table 2 and their nmr spectra are compiled in Table 3.

Scheme 3



7a–e, X = NO_2
8a–e, X = NH_2

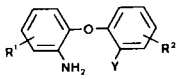
a R^1 = 5-Cl, R^2 = H
b R^1 = 5-Cl, R^2 = 6-CH_3
c R^1 = 4-Cl, R^2 = 6-CH_3
d R^1 = 4,5-Cl_2, R^2 = 6-CH_3
e R^1 = 3,4-Cl_2, R^2 = 6-CH_3

The amines (**4a-k**) were converted into their *N,N*-dimethylamino derivatives (**5a-k**) (Scheme 1, Table 6) on heating with dimethyl methylphosphonate for a period of 2-4 hours, following a method reported previously (14) for the *N,N*-dimethylation of chlorinated anilines. Further methylation to the corresponding trimethylammonium salts and their isolation as methyl sulfates (**6a-k**) (Scheme 1, Table 7) was achieved by heating the dimethylamino compounds (**5a-k**) with dimethyl sulfate. The salts were purified by crystallization from water.

Although dimethyl methylphosphonate has previously been used successfully for the preparation of trimethylammonium salts of aliphatic amines in which the anionic counterion is represented by the methylphosphonate anion (15), it proved to be unsuitable for the preparation of aromatic trimethylammonium salts.

Table 4

Substituted 2-Phenoxyanilines

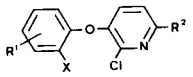


Compound No.	Y	R^1	R^2	M.p. °C (Solvent) B.p. °C (Torr)	Yield %	Formula	Analysis, %				
4a	Cl	H	H	130 (10^{-1})	95.1	$C_{12}H_{10}ClNO$	Calcd.	C, 65.61	H, 4.59	Cl, 16.14	N, 6.38
							Found	C, 65.68	H, 4.63	Cl, 16.21	N, 6.60
4b	Br	5-CH_3	H	159-163 (1)	88.4	$C_{13}H_{12}BrNO$	Calcd.	C ,56.13	H, 4.35	Br, 28.73	N, 5.04
							Found	C, 56.32	H, 4.42	Br, 29.04	N, 4.93
4c	Br	5-CF_3	H	111-113 (4 × 10^{-3})	66.6	$C_{13}H_9BrF_3NO$	Calcd.	C, 47.02	H, 2.73	Br, 24.06	N, 4.22
							Found	C, 47.26	H, 2.84	Br, 23.93	N, 4.31
4d	Br	5-Br	4-Br	82-84; 185-191 (10^{-3})	89.6	$C_{12}H_6Br_3NO_2$	Calcd	C, 34.16	H, 1.91	Br, 56.82	N, 3.32
							Found	C, 34.31	H, 2.10	Br, 57.02	N, 3.51
4e	Cl	5-Cl	5-Cl	154-156 (4 × 10^{-2})	93.0	$C_{12}H_7Cl_3NO$	Calcd.	C, 49.95	H, 2.79	Cl, 36.86	N, 4.85
							Found	C, 50.02	H, 2.81	Cl, 36.84	N, 4.92
4f	Cl	5-Cl	4-Cl	67	91	$C_{12}H_7Cl_3NO$	Calcd.	C, 49.95	H, 2.79	Cl, 36.86	N, 4.85
							Found	C, 50.03	H, 2.84	Cl, 36.89	N, 4.91
4g	Cl	4-Cl	5-Cl	150-153 (10^{-3})	76.0	$C_{12}H_7Cl_3NO$	Calcd.	C, 49.95	H, 2.79	Cl, 36.86	N, 4.85
							Found	C, 49.88	H, 2.91	Cl, 36.82	N, 4.93
4h	Cl	4,5-Cl	4-Cl	88-91; 171 (10^{-1})	86.5	$C_{12}H_7Cl_4NO$	Calcd.	C, 44.62	H, 2.19	Cl, 43.90	N, 4.34
							Found	C, 44.94	H, 2.28	Cl, 43.74	N, 4.44
4i	Cl	3,4-Cl_2	4-Cl	106-108; 165-170 (10^{-3})	92.0	$C_{12}H_7Cl_4NO$	Calcd.	C, 44,62	H, 2.19	Cl, 43.90	N, 4.34
							Found	C, 44.70	H, 2.31	Cl, 43.78	N,4.48
4k	Cl	4,5-Cl_2	4,5-Cl_2(a)	190-195 (2 × 10^{-2})	98.0	$C_{12}H_6Cl_5NO$	Calcd.	C, 40.32	H, 1.69	Cl, 49.59	N, 3.92
							Found	C, 40.41	H, 1.70	Cl, 49.63	N, 4.03

(a) Lit. (5) no physical data are reported.

Table 5

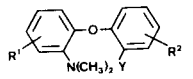
Substituted 3-(Phenoxy)pyridines



Compound No.	X	R¹	R²	M.p. °C (Solvent) B.p. °C (Torr)	Yield %	Formula	Analysis, % Calculated C	H	N	Cl	Found C	H	N	Cl
7a	NO_2	5-Cl	H	96-97 (Ethanol)	44.4	$C_{11}H_6Cl_2N_2O_3$	46.34	2.12	9.83	24.87	46.33	2.20	9.87	24.82
7b	NO_2	5-Cl	6-CH_3	85.5-86.5 (Ethanol)	66.8	$C_{12}H_8Cl_2N_2O_3$	48.19	2.70	9.37	23.71	48.21	2.83	9.42	23.53
7c	NO_2	4-Cl	6-CH_3	114-115.5 (Ethanol)	45.2	$C_{12}H_8Cl_2N_2O_3$	48.19	2.70	9.37	23.71	47.98	2.74	9.44	23.72
7d	NO_2	4,5-Cl_2	6-CH_3	116 (Ethanol)	41.4	$C_{12}H_7Cl_3N_2O_3$	43.21	2.12	8.40	31.89	43.14	2.21	8.51	31.74
7e	NO_2	3,4-Cl_2	6-CH_3	164.5-168 (Ethanol)	40.1	$C_{12}H_7Cl_3N_2O_3$	43.21	2.12	8.40	31.89	43.15	2.18	8.40	32.01
8a	NH_2	5-Cl	H	163-167 (0.5)	96.8	$C_{11}H_8Cl_2N_2O$	51.79	3.16	10.98	27.79	51.63	3.37	11.03	27.85
8b	NH_2	5-Cl	6-CH_3	87-89 (Petroleum Ether)	94.7	$C_{12}H_{10}Cl_2N_2O$	53.56	3.75	10.41	26.35	53.70	3.79	10.58	26.29
8c	NH_2	4-Cl	6-CH_3	67-70 (Ethanol)	96	$C_{12}H_{10}Cl_2N_2O$	53.56	3.75	10.41	26.35	53.62	3.73	10.51	26.19
8d	NH_2	4,5-Cl_2	6-CH_3	137-139 (Methanol)	89.6	$C_{12}H_9Cl_3N_2O$	47.48	2.99	9.23	35.04	47.33	3.15	9.30	34.98
8e	NH_2	3,4-Cl_2	6-CH_3	158.5-160 (Methanol)	97.2	$C_{12}H_9Cl_3N_2O$	47.48	2.99	9.23	35.04	47.54	3.03	9.40	35.01

Table 6

Substituted 2-Phenoxy-*N,N*-dimethylaminoanilines



Compound No.	Y	R¹	R²	M.p. °C (Solvent) B.p. °C (Torr)	Yield %	Formula	Analysis, %				
5a	Cl	H	H	—	(a)	$C_{14}H_{14}ClNO$		—	—	—	—
5b	Br	4-CH_3	H	(b)	65.5	$C_{15}H_{16}BrNO$	Calcd.	C, 58.84	H, 5.27	Cl, 26.10	N, 4.58
							Found	C, 58.72	H, 5.45	Cl, 26.24	N, 4.62
5c	Br	5-CF_3	H	(b)	62.0	$C_{15}H_{13}BrF_3NO$	Calcd.	C, 50.02	H, 3.62	Br, 22.19	N, 3.89
							Found	C, 50.30	H, 3.72	Br, 21.99	N, 3.62
5d	Br	5-Br	4-Br	(b)	83.5	$C_{14}H_{12}Br_3NO$	Calcd.	C, 37.37	H, 2.69	Br, 53.27	N, 3.11
							Found	C, 37.60	H, 2.61	Br, 53.37	N, 3.14
5e	Cl	5-Cl	5-Cl	138-142 (10^{-3})	91.6	$C_{14}H_{12}Cl_3NO$	Calcd.	C, 53.11	H, 3.82	Cl, 33.59	N, 4.42
							Found	C, 53.18	H, 3.87	Cl, 33.44	N, 4.37
5f	Cl	5-Cl	4-Cl	138-142 (5×10^{-3})	91.2	$C_{14}H_{12}Cl_3NO$	Calcd.	C, 53.11	H, 3.82	Cl, 33.59	N, 4.42
							Found	C, 53.28	H, 3.91	Cl, 33.41	N, 4.65
5g	Cl	4-Cl	5-Cl	87-88 (Methanol)	80.4	$C_{14}H_{12}Cl_3NO$	Calcd.	C, 53.11	H, 3.82	Cl, 33.59	N, 4.42
							Found	C, 52.89	H, 3.86	Cl, 33.71	N, 4.40
5h	Cl	4,5-Cl_2	4-Cl	84-85 (b)	96.5	$C_{14}H_{11}Cl_4NO$	Calcd.	C, 47.90	H, 3.16	Cl, 40.40	N, 3.99
							Found	C, 48.03	H, 3.30	Cl, 40.50	N, 4.16
5i	Cl	3,4-Cl_2	4-Cl	158 (10^{-3})	98.8	$C_{14}H_{11}Cl_4NO$	Calcd.	C, 47.90	H, 3.16	Cl, 40.40	N, 3.99
							Found	C, 48.05	H, 3.18	Cl, 40.19	N, 4.02
5k	Cl	4,5-Cl_2	4,5-Cl_2	90-91 (b)	92.0	$C_{14}H_{10}Cl_5NO$	Calcd.	C, 43.62	H, 2.61	Cl, 45.98	N, 3.63
							Found	C, 43.77	H, 2.74	Cl, 46.17	N, 3.72

(a) Not isolated. (b) Purified *via* the hydrobromic acid salt as exemplified for **5b** in the Experimental.

Presumably the variously substituted aminophenoxypyridines (**8a-e**) (Scheme 3) also yielded initially with dimethyl methylphosphonate, the *N,N*-dimethylamino derivatives (14) which, however, underwent subsequent cyclization under the reaction conditions employed, thus resulting in the formation of the benzoxazinopyridines (**13a-e**).

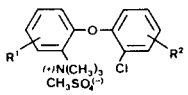
Halogenated 10-Methylphenoxazines and 10-Methylbenzoxazinopyridines.

While the formation of 2-(2-chlorophenoxy)-*N,N*-dimethylanilines (**5a-k**) and isolation of the products by distillation proceeded smoothly, the subsequent slow cyclization reaction proceeding with expulsion of methyl chloride between the *o*-halogen atom and the *o*-dimethylamino group, both attached to the two different phenyl rings of the phenyl ether moiety, took place to a small extent. However, when the dimethylamino compounds (**5a-k**) were refluxed in dimethyl methylphosphonate for an extended period of time, cyclization was brought to completion and the 10-methylphenoxazines (**9a-k**) (Scheme 4, Table 8) were obtained in good yield.

Compounds **9a-k** have also been prepared more conveniently directly from the corresponding amines (**4a-k**) and this served as a general method for their preparation, the

Table 7

Substituted 2-Phenoxy-*N,N,N*-trimethylanilinium Methylsulfates



Compound No.	Y	R^1	R^2	M.p. °C	Yield %	Formula		Analysis, %				
6a	Cl	H	H	(a)	—							
6b	Br	5-CH_3	H	149-150	62.2	$C_{17}H_{22}BrNO_5S$	Calcd.	C, 47.23	H, 5.13	Br, 18.48	N, 3.24	S, 7.42
							Found	C, 47.30	H, 5.20	Br, 18.51	N, 3.31	S, 7.41
6c	Br	5-CF_3	H	208-209	78.2	$C_{17}H_{19}BrF_3NO_5S$	Calcd.	C, 41.99	H, 3.94	Br, 16.43	N, 2.88	S, 6.59
							Found	C, 42.02	H, 3.87	Br, 16.29	N, 3.12	S, 6.69
6d	Br	5-Br	4-Br	225-226	87.6	$C_{16}H_{18}Br_3NO_5S$	Calcd.	C, 33.36	H, 3.15	Br, 41.61	N, 2.43	S, 5.56
							Found	C, 33.54	H, 3.24	Br, 41.70	N, 2.54	S, 5.63
6e	Cl	5-Cl	5-Cl	190-193	88.1	$C_{16}H_{18}Cl_3NO_5S$	Calcd.	C, 43.41	H, 4.10	Cl, 24.02	N, 3.17	S, 7.24
							Found	C, 43.60	H, 4.08	Cl, 23.94	N, 3.23	S, 7.28
6f	Cl	5-Cl	4-Cl	231-234	96.3	$C_{16}H_{18}Cl_3NO_5S$	Calcd.	C, 43.41	H, 4.10	Cl, 24.02	N, 3.17	S, 7.24
							Found	C, 43.32	H, 4.09	Cl, 23.84	N, 3.09	S, 7.30
6g	Cl	4-Cl	5-Cl	219	96.5	$C_{16}H_{18}Cl_3NO_5S$	Calcd.	C, 43.41	H, 4.10	Cl, 24.02	N, 3.17	S, 7.24
							Found	C, 43.52	H, 4.21	Cl, 24.00	N, 3.40	S, 7.39
6h	Cl	4,5-Cl_2	4-Cl	212	83.0	$C_{16}H_{17}Cl_4NO_5S$	Calcd.	C, 40.27	H, 3.59	Cl, 29.72	N, 2.94	S, 6.72
							Found	C, 40.34	H, 3.72	Cl, 29.63	N, 2.91	S, 6.83
6i	Cl	3,4-Cl_2	4-Cl	226-228	59.0	$C_{16}H_{17}Cl_4NO_5S$	Calcd.	C, 40.27	H, 3.59	Cl, 29.72	N, 2.94	S, 6.72
							Found	C, 40.35	H, 3.45	Cl, 29.75	N, 3.14	S, 7.01
6k	Cl	4,5-Cl_2	4,5-Cl_2	240.5	76.2	$C_{16}H_{16}Cl_5NO_5S$	Calcd.	C, 37.56	H, 3.15	Cl, 34.65	N, 2.74	S, 6.27
							Found	C, 37.62	H, 3.23	Cl, 34.78	N, 2.80	S, 6.28

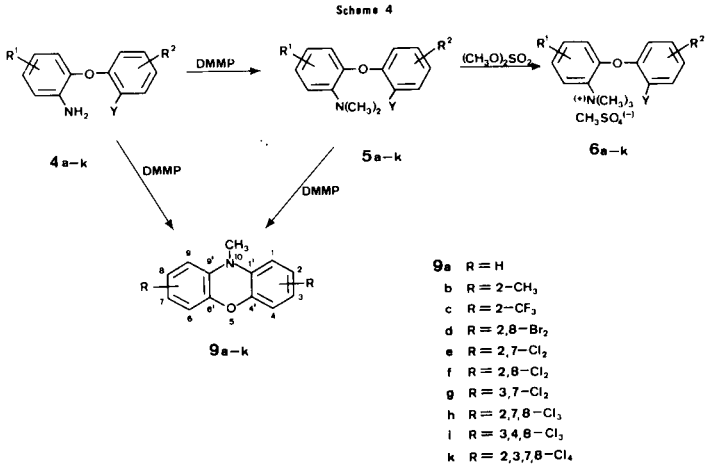
(a) Not isolated.

given yields (Table 8) referring to this process. Cyclization of the amine **4a** to the phenoxazine **9a** occurred only in very low yield, and therefore it is preferable to prepare larger quantities of **9a** by subsequent dehalogenation of **9f**, which is described below.

Although the formation of 10-methylphenoxazines proceeded at a very slow rate, crystalline products were formed in good yields and excellent purity without formation of by-products. There was little indication of an acceleration of the cyclization reaction when the aromatic chlorine atom wich was displaced during the cyclization process was replaced by a bromine atom, as for example, in the preparation of compound **4d**.

It has already briefly been mentioned above that (*N,N*-dimethylaminophenoxy)pyridines (**10**) could not be isolated because under the applied reaction conditions formation of the *N*-methyl substituted [1,4]benzoxazino[3,2-*b*]pyridines (**13a-e**) (Scheme 5, Table 10) proceeded much faster than the oxazine ring closure of the structurally analogous phenyl ethers (**9a-k**). The formation of the phenoxazines usually requird 100-150 hours, whereas the reaction time for the completion of the ring closure to benzoxazinopyridines was only 1-5 hours. Qualitative data for the approximate times required for completion of the ring closure of different 2-phenoxyanilines and (2-aminophenoxy)pyridines are compiled in Table 8 and 10, respectively. Samples were withdrawn intermittently from the reaction mixtures and disappearance of the starting material was followed by thin layer chromatography.

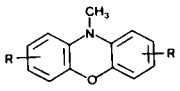
Scheme 4



The importance of the influence of solvent on the cyclization process was recognized when dimethyl methylphosphonate was replaced by other high boiling polar solvents such as sulfolane, dimethylsulfoxide or dimethylformamide. For example, when the amine **4f** was subjected to cyclization in sulfolane, a mixture of products resulted which contained only traces of the phenoxazine

Table 8

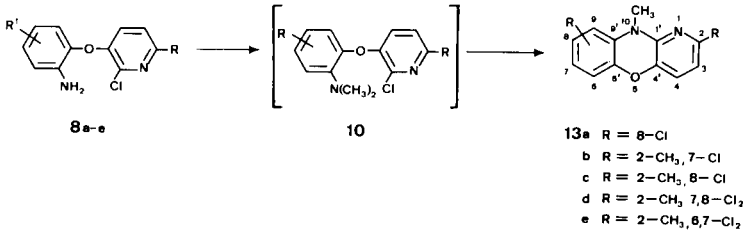
Substituted 10-Methylphenoxazines



Compound No.	R	M.p. °C B.p. °C (Torr)	Crystallization Solvent	Reflux, Hours	Yield %	Formula		Analysis, %			
9a	H	115 (7 x 10^{-2})	—	138	17.3	$C_{13}H_{11}NO$	Calcd.	C, 79.17	H, 5.62	—	N, 7.10
							Found	C, 79.13	H, 5.78	—	N, 7.03
9b	2-CH_3	142 (7 x 10^{-1})	—	40	55.7	$C_{14}H_{13}NO$	Calcd.	C, 79.60	H, 6.20	—	N, 6.63
							Found	C, 79.54	H, 6.30	—	N, 6.60
9c	2-CF_3	48.5-50	Methanol	144	50.3 (a)	$C_{14}H_{10}F_3NO$	Calcd.	C, 63.40	H, 3.80	F, 21.49	N, 5.28
							Found	C, 63.58	H,4.01	F, 21.37	N, 5.25
9d	2,8-Br_2	106-107	Isopropanol	28	83.1 (a)	$C_{13}H_9Br_2NO$	Calcd.	C, 43.98	H, 2.56	Br, 45.01	N, 3.95
							Found	C, 44.05	H, 2.59	Br, 45.00	N, 4.10
9e	2,7-Cl_2	105.5-108	Petroleum Ether	162	37.6 (a)	$C_{13}H_9Cl_2NO$	Calcd.	C, 58.67	H, 3.41	Cl, 26.64	N, 5.26
							Found	C, 58.49	H, 3.35	Cl, 26.46	N, 5.30
9f	2,8-Cl_2	96-97.5	Methanol	115	94.9	$C_{13}H_9Cl_2NO$	Calcd.	C, 58.67	H, 3.41	Cl, 26.64	N, 5.26
							Found	C, 58.58	H, 3.45	Cl, 26.55	N, 5.25
9g	3,7-Cl_2	121-122	Ethanol	96	85.3	$C_{13}H_9Cl_2NO$	Calcd.	C, 58.67	H, 3.41	Cl, 26.64	N, 5.26
							Found	C, 58.80	H, 3.35	Cl, 26.60	N, 5.12
9h	2,3,8-Cl_3	154-156	Ethanol	120	70.1	$C_{13}H_8Cl_3NO$	Calcd.	C, 51.95	H, 2.68	Cl, 35.39	N, 4.66
							Found	C, 52.10	H, 2.59	Cl ,35.21	N, 4.71
9i	2,6,7-Cl_3	166.5-167	Propanol	92	99.0	$C_{13}H_8Cl_3NO$	Calcd.	C, 51.95	H, 2.68	Cl, 35.39	N, 4.66
							Found	C, 51.97	H, 2.73	Cl, 35.33	N, 4.58
9k	2,3,7,8-Cl_4	231-232	Butanol	87.5	87.5	$C_{13}H_7Cl_4NO$	Calcd.	C, 46.61	H, 2.11	Cl, 42.33	N, 4.18
							Found	C, 46.58	H, 2.03	Cl, 42.29	N, 4.33

(a) Yield after recrystallization.

Scheme 5



8a-e **10**

13a R = 8-Cl
b R = 2-CH_3, 7-Cl
c R = 2-CH_3, 8-Cl
d R = 2-CH_3 7,8-Cl_2
e R = 2-CH_3, 6,7-Cl_2

9f. Attempted metal catalysis by alkali or by copper salts was of no avail, and the use of trimethyl phosphate gave also no improvement in yield.

No formation of 10-ethylphenoxazine occurred when **4f** was refluxed with diethyl ethylphosphonate for 72 hours. Only the *N,N*-diethylamino derivative could be isolated and was characterized as its hydrobromic acid salt.

The structures of **9a-k** and **13a-e** were supported by their nmr spectra (Tables 9 and 11, respectively.)

In particular, the ^{13}C-nmr spectra of **9f** and **9e**, respectively, confirmed that the original positions of the chlorine atoms relative to the nitrogen and the oxygen atoms had not changed, and consequently no Smiles rearrangement (16) had preceeded the ring closure to the oxazine.

The gas evolved during the cyclization reaction of **4f** to **9f** was collected in a cold trap at -70° over a reaction period of 14 hours (12% of the total reaction time) and identified by its infrared and mass spectra as dimethyl ether containing a small amount of methyl chloride.

These results suggested that one of the intermediate species might be the quaternary ammonium salt (**14**) (Scheme 6), which subsequently eliminates methyl chloride in the process of ring closure. Most of the methyl chloride reacts presumably with the dimethyl methylphosphonate to form the methyl ether and methyl methylphosphonous chloride, which in turn reacts again with excess dimethyl methylphosphonate, yielding polymeric methyl phosphonic acids (17).

A quaternary ammonium salt of similar structure is presumed to be an intermediate in the intramolecular *N*-arylation of tetrafluorophenyl cyclohexylenamine which proceeds with elimination of methyl flouride, yielding the tetrafluoro tetrahydrocarbazole derivative (18).

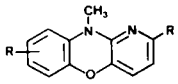
Table 9

Nuclear Magnetic Resonance Parameters (Pmr and Cmr) of Different 10-Methylphenoxazines

Compound	Solvent	Type	Chemical Shift in Ppm
9a	Acetone-d_6	Pmr	6.5-6.9 (m, 8H, ArH, H_1-H_4 and H_6-H_9); 2.96 (s, 3H, N-CH_3)
		Cmr	112.4 (C_1 and C_9); 124.6 (C_2 and C_8); 121.5 (C_3 and C_7); 115.6 (C_4 and C_6); 135.7 (C_1' and C_9'); 146.0 (C_4' and C_6'); 30.9 (N-CH_3)
9b	Acetone-d_6	Pmr	6.5-6.9 (m, 7H, ArH, H_1, H_3 and H_4, H_6-H_9); 3.02 (s, 3H, N-CH_3); 2.18 (s, 3H, CH_3 at C_2)
		Cmr	not measured
9c	Acetone-d_6	Pmr	6.6-7.05 (m, 7H, ArH, H_1, H_3 and H_4, H_6-H_9); 3.10 (s, 3H, N-CH_3)
		Cmr	109.0 (C_1); 126.5 (C_2); 118.9 (C_3); 116.0 (C_4); 115.8 (C_6); 122.3 (C_7); 125.3 (C_8); 113.0 (C_9); 134.7 (C_1'); 149.0 (C_4'); 145.5 (C_6'); 136.5 (C_9'); 31.2 (N-CH_3); 125.3 (CF_3)
9d	Acetone-d_6	Pmr	6.78 (dd, 2H, J = 8.0 and 1.8, H_3 and H_7); 6.73 (d, 2H, J = 1.8, H_1 and H_9); 6.50 (d, 2H, J = 8.0, H_4 and H_6); 3.03 (s, 3H, N-CH_3)
		Cmr	115.5 (C_1 and C_9); 116.8 (C_2 and C_8); 124.5 (C_3 and C_7); 117.2 (C_4 and C_6); 136.4 (C_1' and C_9'); 145.1 (C_4' and C_6'); 31.5 (N-CH_3)
9e	Acetone-d_6	Pmr	6.50-6.70 (m, 5H, H_1, H_3, H_4, H_6 and H_9); 6.82 (dd, 1H, J = 8.0 and 2.0, H_7); 3.00 (s, 3H, N-CH_3)
		Cmr	112.7 (C_1); 129.6 (C_2); 121.0 (C_3); 116.7 (C_4); 116.0 (C_6); 126.2 (C_7); 124.4 (C_8); 113.7 (C_9); 136.4 (C_1'); 144.3 (C_4'); 146.4 (C_6'); 133.8 (C_9'); 31.4 (N-CH_3)
9f	Acetone-d_6	Pmr	6.60 (s, br, 6H, H_1, H_3, H_4, H_6, H_7 and H_9); 3.04 (s, 3H, N-CH_3)
		Cmr	113.1 (C_1 and C_9); 129.6 (C_2 and C_8); 121.5 (C_3 and C_7); 116.8 (C_4 and C_6); 136.3 (C_1' and C_9'); 144.8 (C_4' and C_6'); 31.4 (N-CH_3)
9g	Acetone-d_6	Pmr	6.86 (dd, 2H, J = 8.0 and 1.8, H_2 and H_8); 6.64 (d, 2H, J = 1.8, H_4 and H_6); 6.60 (d, 2H, J = 8.0, H_1 and H_9); 3.04 (s, 3H, N-CH_3)
		Cmr	not measured
9h	Acetone-d_6 + DMSO-d_6	Pmr	6.82 (s, 1H, H_4); 6.80 (s, 1H, H_1); 6.76-6.64 (m, 3H, H_6, H_7 and H_9); 3.10 (s, 3H, N-CH_3)
		Cmr	not measured
9i	Acetone-d_6	Pmr	7.06 (d, 1H, J = 8.2, H_8); 6.75 (m, 3H, H_1, H_3 and H_4); 6.64 (d, 1H, J = 8.2, H_9); 3.10 (s, 3H, N-CH_3)
	DMSO-d_6	Cmr	112.3 (C_1); 129.0 (C_2); 120.6 (C_3); 116.3 (C_4); 118.3 (C_6); 123.6 (C_7); 124.3 (C_8); 111.2 (C_9); 134.9 (C_1'); 142.7 (C_4'); 141.8 (C_6'); 134.0 (C_9'); 31.4 (N-CH_3)
9k		Pmr	6.70 (s, 2H, H_4 and H_6); 6.50 (s, 2H, H_1 and H_9); 2.97 (s, 3H, N-CH_3)
		Cmr	not measured

Table 10

Substituted 10-Methyl[1,4]benzoxazino[3,2-*b*]pyridines



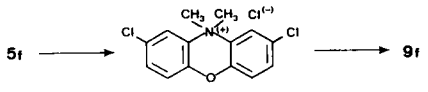
Compound No.	R	M.p.°C	Crystallization Solvent	Heating Time, Hours	Yield %	Formula		Analysis, %			
13a	8-Cl	103.5-104.5	Methanol	1	68.8	$C_{12}H_9ClN_2O$	Calcd.	C, 61.95	H, 3.90	Cl, 15.24	N, 12.04
							Found	C, 61.91	H, 4.03	Cl, 15.40	N, 12.01
13b	2-CH_3, 8-Cl	93.5-94.5	Ethanol/ Water	2	79.8	$C_{13}H_{11}ClN_2O$	Calcd.	C, 63.29	H, 4.49	Cl, 14.37	N, 11.35
							Found	C, 63.30	H, 4.61	Cl, 14.31	N, 11.51
13c	2-CH_3, 7-Cl	118-119	Ethanol/ Water	1.5	72.6	$C_{13}H_{11}ClN_2O$	Calcd	C, 63.29	H, 4.49	Cl, 14.37	N, 11.35
							Found	C, 63.59	H, 4.62	Cl, 14.10	N, 11.50
13d	2-CH_3, 7,8-Cl_2	143-144	Ethanol		59.4	$C_{13}H_{10}Cl_2N_2O$	Calcd.	C, 55.54	H, 3.59	Cl, 25.22	N, 9.97
							Found	C, 55.80	H, 3.71	Cl, 24.89	N, 10.01
13e	2-CH_3, 6,7-Cl_2	187-188	Acetone	4.5	66.5	$C_{13}H_{10}Cl_2N_2O$	Calcd.	C, 55.54	H, 3.59	Cl, 25.22	N, 9.97
							Found	C, 55.52	H, 3.65	Cl, 25.14	N, 9.89

Table 11

Nuclear Magnetic Resonance Parameters (Pmr and Cmr) of 10-Methyl[1,4]benzoxazino[3,2-*b*]pyridines

Compound No.	Solvent	Type	Chemical Shift in Ppm
13a	Deuteriochloroform	Pmr	7.63 (d, d, 1H, J = 5.2 and 1.8, H_2); 6.74 (d, d, 1H, J = 8.0 and 1.8, H_4); 6.68-6.42 (m, 4H, H_3, H_6, H_7 and H_9); 3.16 (s, 3H, N-CH_3)
13b	DMSO-d_6	Pmr	6.44 (d, 1H, J = 8.0, H_3); 6.80 (d, 1H, J = 8.0, H_4); 6.65 (s, br, 3H, H_6, H_7 and H_9); 3.10 (s, 3H, N-CH_3); 2.19 (s, 3H, CH_3 at C_2)
		Cmr	149.6 (C_2); 115.6 (C_3); 121.0 (C_4); 115.6 (C_6); 120.5 (C_7); 127.8 (C_8); 112.3 (C_9); 143.7 (C_1'); 137.5 (C_4'); 142.4 (C_6'); 134.5 (C_9'); 27.9 (N-CH_3); 23.0 (CH_3 at C_2)
13c	Acetone-d_6 and DMSO-d_6	Pmr	6.90-6.70 (m, 3H, H_3, H_4 and H_6); 6.95 (d, d, 1H, J = 8.0 and 1.8 H_8); 6.54 (d, 1H, J = 8.0, H_9); 3.22 (s, 3H, N-CH_3); 2.28 (s, 3H, CH_3 at C_2)
		Cmr	149.8 (C_2); 114.7 (C_3); 123.5 (C_4); 115.3 (C_6); 124.8 (C_7); 121.2 (C_8); 113.6 (C_9); 144.0 (C_1'); 132.3 (C_4'); 144.2 (C_6'); 137.4 (C_9'); 27.9 (N-CH_3); 23.0 (CH_3 at C_2)
13d	Deuteriochloroform	Pmr	6.40 (d, 1H, J = 8.0, H_3); 6.70 (d, 1H, J = 8.0, H_4); 6.70 (s, 1H, H_6); 6.56 (s, 1H, H_9); 3.20 (s, 3H, N-CH_3); 2.30 (s, 3H, CH_3 at C_2)
13e	Deuteriochloroform and DMSO-d_6	Pmr	6.50 (d, 1H, J = 8.0, H_3); 6.90 (d, 1H, J = 8.0, H_4); 7.06 (d, 1H, J = 8.5, H_8); 6.62 (d, 1H, J = 8.5, H_9); 3.30 (s, 3H, N-CH_3); 2.30 (s, 3H, CH_3 at C_2)

Scheme 6



14

N-alkylation of phenoxazines is reported to be difficult in general but with sodamide and the requisite halide the 10-substituted derivatives are obtained (3,19).

The halogenated 10-methylphenoxazines dissolve in concentrated sulfuric acid, the solution showing a violet-red fluorescence.

Demethylation of 10-Methylphenoxazines.

In contrast to the large number of *N*-alkylsubstituted chlorophenoxazines which have been prepared in the course of an investigation of their pharmacological properties, there exists only scarce information about chlorinated phenoxazines which are unsubstituted at the nitrogen atom. While the cyclization of 2-(2-bromophenoxy)-5-chloroaniline yielded 2-chlorophenoxazine (1a) in modest yield, the analogous 2,8-dichlorophenoxazine (20) was obtained in a yield of only 8% by heating a mixture of 2-(2-aminophenoxy)aniline with its corresponding hydrochloride, and thus the structure of a previously obtained compound (21) could be confirmed, the positions of the chlorine atoms not having been assigned previously with certainty. The *N*-benzyl-2,7-dichlorophenoxazine had been prepared earlier by a modified Turpin reaction, but further attempts to debenzylate the compound failed (20).

Some renewed interest in chlorinated phenoxazines also stems from the recognition of the extremely toxic properties of the structurally related tetrachloro-1,4-dibenzodioxine (22). Although it had been shown that a change in the basic structure of the symmetrical tetrachloro-1,4-dibenzodioxine led to a dramatic reduction in toxicity (13), the question as to what extent a change in the character of the heteroatoms could bring about a variation in the toxicological properties of the compounds remains largely unanswered.

The *dosis lethalis* (LD_{50}) of 10-methyl-2,3,7,8-tetrachlorophenoxazine (**9k**) is 2800 mg./kg. (as tested on rats), and thus it is by several orders of magnitude less toxic than the corresponding 2,3,7,8-tetrachloro-1,4-dibenzodioxine (22).

The demethylation of halogenated 10-methylphenoxazines with pyridine hydrobromide at 200° (23) proved to be successful only with compounds **9a-c** and **9f**, yielding the parent phenoxazines **15a-c** and **15f** (Scheme 7, Table 12). Attempts to demethylate other chlorinated 10-methylphenoxazines with pyridine hydrobromide resulted only in the formation of tarry products, and various other methods known to effect *N*-demethylation proved likewise to be of no avail.

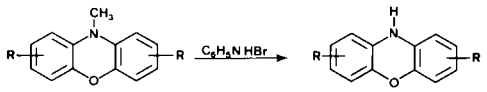
The boiling points of **15a** and **15f**, respectively, were similar to those previously reported (3b,24). The confirmation of their identity with the reported compounds and final proof of structure was obtained by the analytical results and nmr spectral data, in particular the absence of a signal for the *N*-methyl group.

Very little work has been reported on the direct halogenation of unsubstituted phenoxazines. Thus, chlorination with thionyl chloride yielded 1,3,7,9-tetrachlorophenoxazine (3), bromination gave a mixture of 3-bromo and 3,7-dibromophenoxazine (3) and other chlorinated derivatives such as carboxylic acids have been prepared by one of the above listed procedures (3).

Dehalogenation of **9f**.

The cyclization of **5a** with dimethyl methylphosphonate to yield **9a** occurred only in 17% yield. Therefore larger quantities of **9a** were prepared by dehalogenation of **9f** with palladium on carbon catalyst in the presence of sodium acetate in acetic acid solution, the compound previously having been synthesized by reaction of 10-phenoxazinyl sodium with methyl iodide (3,19).

Scheme 7

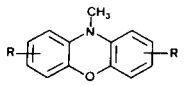


9a R=H
b R=2-CH_3
c R=2-CF_3
f R=2,8-Cl_2

15a R=H
b R=2-CH_3
c R=2-CF_3
f R=2,8-Cl_2

Table 12

Demethylation of 10-Methylphenoxazines



Compound No.	R	M.p. °C	Crystallization Solvent	Yield %	Formula	Analysis, % Calculated C	H	Cl,F	N	Found C	H	Cl,F	N
15a	H	152-154	Ethanol/ Water (2:1)	75.4	$C_{12}H_9NO$	78.67	4.95		7.65	78.55	5.10		7.60
15b	2-CH_3	142.5-143.5	Cyclohexane	33.5	$C_{13}H_{11}NO$	79.17	5.62		7.10	79.30	5.78		7.20
15c	2-CF_3	150-151	Cyclohexane	4	$C_{13}H_8F_3NO$	62.16	3.21	22.69	5.58	62.34	3.13	22.52	5.73
15f	2,8-Cl_2	199-200	Cyclohexane	47.6	$C_{12}H_7Cl_2NO$	57.17	2.80	28.13	5.56	57.01	2.94	28.18	5.57

Nitration of Chlorinated 10-Methylphenoxazines.

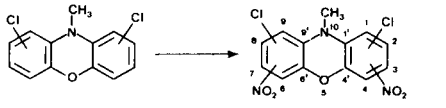
The nitration of chlorinated 10-methylphenoxazines (**9a-k**) with nitric acid in a solution of sulfuric acid, or in organic solvents such as acetic acid or chlorinated hydrocarbons failed to yield any identifiable products. Nitration, however, could be realized by adding one mole of crystalline sodium nitrite at room temperature to a solution of the chlorinated 10-methylphenoxazine in acetic acid, containing an equimolar amount of ferric chloride (Scheme 8, Table 13). This method gave consistently good yields of mononitrophenoxazines with compounds **9e-g, i**. The reactions were complete within about 20 minutes and products (**16a-d**) were isolated in high yield without any appreciable formation of dinitro derivatives on dilution of the reaction mixture with water. This method was essentially analogous to a previously reported procedure (25) concerning the substitution of the parent phenoxazine by a nitro or by a phenyl sulfone group using sodium nitrite or the sodium salt of the phenylsulfinic acid, respectively. It was found that mononitration of **9f** proceeded very smoothly without ferric chloride when solid sodium nitrite was added to a solution of **9f** in acetic acid. The extremely insoluble mononitroderivative precipitated instantaneously from the solution. Presumably, the insolubility of **16b** hampered its further nitration to a dinitroderivative.

Dinitration of **9f**, however, could be achieved by treating a solution of the compound in acetic acid with two moles of crystalline sodium nitrite in the presence of ferric chloride (Scheme 8), only at higher temperature. The reaction was followed by thin layer chromatography until disappearance of the initially formed mononitroderivative **16b** was complete. The structures of the nitro compounds were elucidated from their nmr spectral data, which are compiled in Table 14.

Previously, nitrophenoxazines have been prepared by ring closure of 2-hydroxy-2′-nitrodiphenylamines. This ring closure was facilitated by substitution of the amino hydrogen atom. Thus, for example, 2-hydroxy-*N*-alkyl-2′,4′-dinitrodiphenylamines could be cyclized to 10-alkyl-3-nitrophenoxazines with sodium hydroxide (26,27).

The 10-methylchloronitrophenoxazines form orange to dark red crystals which are sparingly soluble in organic solvents, but can be recyrstallized from nitrobenzene.

Scheme 8



9e R=2,7-Cl_2
f R=2,8-Cl_2
g R=3,7-Cl_2
i R=3,4,8-Cl_3
f R=2,8-Cl_2

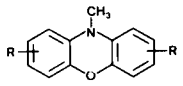
16a R=2,7-Cl_2,8-NO_2
b R=2,8-Cl_2,3-NO_2
c R=3,7-Cl_2,1-NO_2
d R=3,4,8-Cl_3,2-NO_2
e R=2,8-Cl_2,3,7-$(NO_2)_2$

10-Methylaminochlorophenoxazines.

The 10-methyl monoaminodichloro- (**17a**) and the diaminodichlorophenoxazine (**17b**) were obtained by

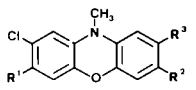
Table 13

10-Methylchloronitrophenoxazines



Compound No.	R	M.p. °C	Crystallization Solvent	Yield %	Formula	Analysis, %				
16a	2,7-Cl_2, 8-NO_2	190.5-191.5	Chlorobenzene	97	$C_{13}H_8Cl_2N_2O_3$	Calcd.	C, 50.19	H, 2.59	Cl, 22.79	N, 9.01
						Found	C, 50.23	H, 2.58	Cl, 22.58	N, 8.77
16b	2,8-Cl_2, 3-NO_2	248-250	Chlorobenzene	98.5	$C_{13}H_8Cl_2N_2O_3$	Calcd.	C, 50.19	H, 2.59	Cl, 22.79	N, 9.01
						Found	C, 50.04	H, 2.70	Cl, 22.91	N, 9.00
16c	3,7-Cl_2, 1-NO_2	163.5-164.5	Chlorobenzene	83.2	$C_{13}H_8Cl_2N_2O_3$	Calcd.	C, 50.19	H, 2.59	Cl, 22.79	N, 9.01
						Found	C, 50.24	H, 2.53	Cl, 22.94	N, 9.03
16d	2,6,7-Cl_3, 3-NO_2	254-256	Chlorobenzene	94	$C_{13}H_7Cl_3N_2O_3$	Calcd.	C, 45.18	H, 2.04	Cl, 30.78	N, 8.11
						Found	C, 45.35	H, 2.00	Cl, 30.80	N, 8.15
16e	2,8-Cl_2, 3.7-$(NO_2)_2$	302 dec.	Nitrobenzene	99	$C_{13}H_7Cl_2N_3O_5$	Calcd.	C, 43.85	H, 1.98	Cl, 19.91	N, 11.80
						Found	C, 43.72	H, 1.94	Cl, 20.12	N, 11.67

Scheme 9



18 R^1 = H, R^2 = NH_2, R^3 = Cl
18 R^1 = NH_2, R^2 = NH_2, R^3 = Cl
19 R^1 = H, R^2 = NO_2, R^3 = NH_2
20 R^1 = H, R^2 = NH_2, R^3 = NH_2

reduction of the corresponding mononitro- (**16b**) and the dinitroderivatives (**16e**) with Raney nickel in tetrahydrofuran (Scheme 9, Table 15). This was the general approach for the synthesis of aminophenoxazines which has been used previously (26,27). Replacement of the chlorine atom adjacent to the nitrogroup by an amino group in **16b** could be carried out with ammonia in ethanol in the presence of copper (I) chloride at 180° yielding **18**, but failed with the corresponding 2,8-dichloro-3,7-dinitrophenoxazine (**16e**). Reduction of the nitro group in **18** with platinum on carbon catalyst gave *N*-methyl-2,3-diamino-8-chlorophenoxazine (**19**) as off-white crystals which, on exposure to air, darkened in several minutes, presumably because of the ready oxidizability of 3-aminophenoxazines to phenazine.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The nuclear magnetic resonance spectra were obtained in the specified solvents with either a HA-100-D or an XL-100-12 spectrometer using tetramethylsilane as an internal standard. The cmr spectra were measured with a XL-100-15 instrument. Chemical shifts are given in parts per million. Coupling constants (J) are given in Hertz. The abbreviations s, d, t, q and m indicate singlet, doublet, triplet, quartet

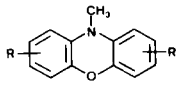
Table 14

Nuclear Magnetic Resonance Parameters (Pmr and Cmr) of 10-Methylchloronitrophenoxazines

Compound No.	Solvent	Type	Chemical Shift in Ppm
16a	Deuteriochloroform + DMSO-d_6	Pmr	7.00-6.70 (m, 3H, H_1, H_3 and H_4); 7.32 (s, 2H, H_6 and H_9); 3.10 (s, 3H, N-CH_3)
16b	DMSO-d_6	Pmr	6.80 (s, 1H, H_1); 7.25 (s, 1H, H_4); 6.60-6.80 (m, 3H, H_6, H_7 and H_9); 3.10 (s, 3H, N-CH_3)
		Cmr	113.9 (C_1); 133.2 (C_2); 146.0 (C_3); 112.1 (C_4); 116.4 (C_6); 122.4 (C_7); 129.0 (C_8); 113.5 (C_9); 139.2 ($C_{1'}$); 142.6 ($C_{4'}$ and $C_{6'}$); 133.3 ($C_{9'}$); 31.9 (N-CH_3)
16c	Deuteriochloroform	Pmr	7.38 (d, 1H, J = 2.0, H_2); 6.88 (d, d, 1H, J = 2.0, H_4); 6.78 (d, 1H, J = 1.8, H_6); 6.97 (dd, 1H, J = 8.2 and 1.8, H_8); 6.59 (d, 1H, J = 8.2, H_9); 3.0 (s, 3H, N-CH_3)
16d	DMSO-d_6	Pmr	6.90 (s, 1H, H_1); 7.40 (s, 1H, H_4); 7.12 (d, 1H, J = 8.0, H_8); 6.78 (d, 1H, J = 8.0, H_9); 3.10 (s, 3H, N-CH_3)
16e	DMSO-d_6	Pmr	7.08 (s, 2H, H_1 and H_9); 7.45 (s, 2H, H_4 and H_6); 3.20 (s, 3H, N-CH_3)
16f	DMSO-d_6	Pmr	7.00 (s, 1H, H_1); 7.40 (s, 1H, H_4); 6.95 (s, 1H, H_6); 7.05 (s, 1H, H_9); 3.17 (s, 3H, N-CH_3)

Table 15

10-Methylaminochlorophenoxazines



Compound No.	R	M.p. °C (Solvent)	Yield %	Formula		Analysis, %			
17a	3-NH_2, 2,8-Cl_2	160-161 (Chlorobenzene)	96	$C_{13}H_{10}Cl_2N_2O$	Calcd.	C, 55.54	H, 3.59	Cl, 25.22	
					Found	C, 55.80	H, 3.51	Cl, 24.93	
17b	3,7-$(NH_2)_2$, 2,8-Cl_2	>300 (Chlorobenzene)	98	$C_{13}H_{11}Cl_2N_3O$	Calcd.	C, 52.72	H, 3.74	Cl, 23.94	N, 14.19
					Found	C, 53.01	H, 3.92	Cl, 24.20	N, 14.35
18	2-NH_2, 8-Cl, 3-NO_2	>300 (Nitrobenzene)	68.5	$C_{13}H_{10}ClN_3O_3$	Calcd.	C, 53.53	H, 3.46	Cl, 12.16	N, 14.41
					Found	C, 53.45	H, 3.45	Cl, 12.30	N, 14.44
19	2,3-$(NH_2)_2$, 8-Cl	154-156 (Toluene)	46	$C_{13}H_{12}ClN_3O$	Calcd.	C, 59.66	H, 4.62	Cl, 13.55	N, 16.06
					Found	C, 60.15	H, 4.75	Cl, 13.28	N, 15.90

and multiplet, respectively.

The procedure described below for the preparations of the different functional phenyl ethers (**3-6**) and phenoxypyridines (**7-8**), respectively, are typical.

5-Chloro-2-(2,5-dichlorophenoxy)nitrobenzene (**3e**).

A mixture of 489 g. (3 moles) of 2,5-dichlorophenol and 579 g. (3 moles) of 2,5-dichloronitrobenzene was placed in a 1.5 l. flask, equipped with stirrer, thermometer, dropping funnel and a descending condensor. The mixture was heated to 120-125°, stirring commenced, and a solution of 200 g. of potassium hydroxide pellets (85%) in 130 ml. of water was added through the dropping funnel over a period of 3 hours. The temperature was then raised to 140-150° and maintained for a further 18 hours. Water and some volatile organic material slowly distilled and was collected through the descending condensor. The hot melt (90-100°) was poured into a stirred solution of 45 ml. of aqueous 30% sodium hydroxide in 4.5 l. of water. The initially formed oil solidified after several minutes into a mass of white crystals which were filtered and air dried. Crystallization from 1.5 l. of ethanol in the presence of decolorizing carbon yielded 756 g. (79%) of crystals.

4-Chloro-2-(2,5-dichlorophenoxy)nitrobenzene (**3g**) and 2,4-Bis(2,4-dichlorophenoxy)nitrobenzene (**11g**).

A mixture of 424.5 g. (2.6 moles) of 2,5-dichlorophenol and 500 g. (2.6 moles) of 2,4-dichloronitrobenzene was reacted in the presence of a solution of 173.6 g. of potassium hydroxyde (85%) pellets in 110 ml. of water as described for **3e**. Work-up and recrystallization from 3.5 l. of ethanol yielded 661 g. of crude product. Distillation of 40 g. gave 31.6 g. of **3g** (98% purity by gc). Crystallization of the residue from 100 ml. of isopropanol furnished 4.0 g. of **11g** (98.1% by gc).

4,5-Dichloro-2-(2,4,5-trichlorophenoxy)nitrobenzene (**3k**) and 5-chloro-2,4-bis(2,4,5-trichlorophenoxy)nitrobenzene (**11h**).

The mixture of **3k** and **11h** was prepared analogously from 1 mole of 2,4,5-trichloronitrobenzene and 1 mole of 2,4,5-trichlorophenol. Distillation yielded 150 g. of **3k** and 63 g. of **11h** which solidified on standing.

4,5-Dichloro-2-(2,4-dichlorophenoxy)nitrobenzene (**3h**) and 5-chloro-2,4-bis(2,4-dichlorophenoxy)nitrobenzene (**11i**).

The mixture of **3h** and **11i** was prepared from 169.9 g. (0.75 mole) of 2,4-dichlorophenol and 2,4,5-trichloronitrobenzene as described for **3e**. The resulting oil was distilled yielding **3h** which solidified on standing. The distillation residue was recrystallized from acetone in the presence of decolorizing carbon, yielding crystals (18.7 g.) of **11i**.

3,4-Dichloro-2-(2,4-dichlorophenoxy)nitrobenzene (**3i**) and 4-chloro-2,3-bis(2,4-dichlorophenoxy)nitrobenzene (**11k**).

The mixture of **3i** and **11k** was prepared analogously from 0.75 mole of 2,3,4-trichlorobenzene and 0.75 mole of 2,4-dichlorophenol. Distillation yielded **3i** and after crystallization of the distillation residue from acetone there was obtained 27 g. of **11k** as white crystals.

5-Chloro-2-(2,5-dichlorophenoxy)aniline (**4e**).

A solution of 497 g. (1.5 moles) of **3e** in 3 l. of dioxane was hydrogenated in the presence of 50 g. of Raney nickel over a period of 8 hours at atmospheric pressure. The catalyst was filtered from the solution which was evaporated to dryness. Distillation of the remaining oil yielded 402.8 g. (93%) of product.

5-Methyl-2-(2-bromophenoxy)-*N,N*-dimethylaniline (**5b**).

A solution of 86.5 g. (0.31 mole) of **4b** in 270 ml. of dimethyl methylphosphonate was heated under reflux for a period of 1 hour. The cooled solution was added to a mixture of 100 ml. of water and 110 ml. of concentrated aqueous ammonia and stirred for 1 hour. The product was extracted with 500 ml. of ether and the ether solution washed twice with 100 ml. of water. After drying over sodium sulfate, the ether was distilled off yielding 62.3 g. of yellow oil, which was purified *via* its hydrobromic acid salt as follows: a solution of 38.8 g. in 150 ml. of ether was saturated with hydrogen bromide; the precipitated salt was filtered and washed with 100 ml. of ether. It was then dissolved in a solution of 20 g. of sodium bicarbonate in 300 ml. of water at 60°, and the oil extracted with 300 ml. of ether. The ether solution was washed with water, dried and evaporated, leaving 15.6 g. of oily product.

5-Chloro-2-(2,5-dichlorophenoxy)-*N,N*-dimethylaniline (**5e**).

A solution of 57.7 g. (0.2 mole) of **4e** in 300 ml. of dimethyl methylphosphonate was heated under reflux for a period of 3 hours. The cold solution was added to a mixture of 1.5 l. of water and 29 ml. of concentrated aqueous ammonia, and stirred for 2 hours. Then the product was extracted with 1 l. of ether, and the ethereal extract washed three times with 300 ml. of water. The ether solution was dried over sodium sulfate, the solvent evaporated and the residual oil distilled, yielding 58 g. (91.7%) of product.

5-Methyl-2-(2-bromophenoxy)trimethylanilinium Methylsulfate (**6b**).

A solution of 24.5 g. (0.08 mole) of **5b** and 20.2 g. (0.16 mole) dimethyl sulfate in 100 ml. of chlorobenzene was heated at 100° for a period of 6.5 hours. Crystals were filtered from the solution, washed with 50 ml. of chlorobenzene, then with ether, and dried yielding 21.5 g. of product.

5-Chloro-2-(2,5-dichlorophenoxy)trimethylanilinium Methylsulfate (**6e**).

A solution of 22.15 g. (0.07 mole) of **5e** and 17.64 g. (0.14 mole) of dimethyl sulfate in 90 ml. of chlorobenzene was heated at 110° for a period of 40 minutes. The crystals were filtered from the solution through a glass sintered funnel, washed with 50 ml. of chlorobenzene, followed by 100 ml. of ether, and dried at 90°/12 torr yielding 27.3 g. (88%) of product.

2-Chloro-3-(2-nitro-4-chlorophenoxy)pyridine (**7a**).

A stirred mixture of 25.9 g. (0.2 mole) of 2-chloro-3-hydroxypyridine and 38.4 g. (0.2 mole) of 2,5-dichloronitrobenzene was heated at 120-125° and a solution of 13.17 g. of potassium hydroxide pellets (85%) in 10 ml. of water was added over a period of 2 hours. The temperature was then raised to 140-150° and maintained for 2 hours. The hot suspension was transferred to a mixer and blended with 300 ml. of water. Crystals were filtered from the solution and washed with 1 l. of water. Crystallization from 63 ml. of ethanol yielded 25.3 g. of product.

2-Chloro-6-methyl-3-(2-nitro-5,6-dichlorophenoxy)pyridine (**7e**) and 3-Chloro-2,4-bis(2-chloro-6-methyl-3-pyridyloxy)nitrobenzene (**12b**).

The mixture of **7e** and **12b** was analogously prepared from 0.3 mole of 2,3,4-trichloronitrobenzene and 0.3 mole of 2-chloro-3-hydroxy-6-methylpyridine. The work-up followed the procedure given for **8d** except that the crude product was suspended in 300 ml. of methanol yielding a mixture of **7e** and **12b**. Distillation gave **7e** and from the distillation residue 6.25 g. of **12b** was obtained after crystallization from acetone.

2-Chloro-3-(2-amino-4-chlorophenoxy)pyridine (**8a**).

A solution of 14.25 g. (0.05 mole) of **7a** in 75 ml. of dioxane was hydrogenated in the presence of 15 g. of Raney nickel. Work-up and distillation yielded 8.3 g. of product.

2-Chloro-6-methyl-3-(2-nitro-4,5-dichlorophenoxy)pyridine (**8d**) and 5-chloro-2,4-bis(2-chloro-6-methyl-3-pyridyloxy)nitrobenzene (**12a**).

The procedure was essentially analogous to that described for **3e**.

A mixture of 158.6 g. (0.7 mole) of 2,4,5-trichloronitrobenzene and 100.45 g. (0.7 mole) of 2-chloro-3-hydroxy-6-methylpyridine was heated at 120° and, with stirring, a solution of 46.12 g. of potassium hydroxide pellets (85%) in 32.3 ml. of water was added over a period of 1 hour. Then the temperature was increased to 135-140° and maintained for 18 hours. The dark brown melt was added to a mixture of 1 l. of water and 10.5 ml. of an aqueous 30% sodium hydroxide solution. The resinous precipitate was collected, dissolved in 1 l. of boiling acetone and the solution filtered from undissolved material. The filtrate was evaporated to dryness and the oily residue (222 g.) distilled. The fraction boiling at 205-220°/8 × 10^{-2} torr was collected, yielding 103 g. of **8d**.

The distillation residue (80.6 g.) was treated with decolorizing carbon in 240 ml. of boiling acetone and filtered. The filtrate was cooled and the crystals obtained were washed on the filter with 100 ml. of cold methanol, yielding 44.4 g. of **12a**.

2-Chloro-6-methyl-3-(2-amino-4-chlorophenoxy)pyridine (**8b**).

A solution of 194.4 g. (0.65 mole) of **7b** in 1 l. of dioxane was hydrogenated in the presence of 19 g. of Raney nickel at 25°. The catalyst was filtered from the solution and the solvent distilled off on a rotary evaporator, yielding a crystalline product which was washed with 500 ml. of petroleum ether.

2,8-Dichloro-10-methylphenoxazine (**9f**).

A solution of 288.5 g. (1 mole) of **4f** in 1.5 l. of dimethyl methylphosphonate was refluxed for a period of 114 hours. Then the cold reaction mixture was added to 7.5 l. of water containing 230 ml. of concentrated aqueous ammonia and stirred for 30 minutes. The crystals were filtered, washed with 5 l. of water and dried at 50-60°/30 torr, yielding 258 g. of product, m.p. 98-90°. For further purification, 120 g. of product was extracted in a soxhlet with 1250 ml. of petroleum ether yielding 94 g., m.p. 96-97.5°. The gas evolved during the reaction was condensed in a cold trap which was connected to the top of the reflux condensor, and surrounded by a mixture of dry ice and acetone. The ir spectrum (gas cell) showed the condensate to consist predominantly of dimethyl ether, by comparison with an authentic reference spectrum. Small amounts of methyl chloride were identified by the mass spectrum, and by weak absorptions in the infrared spectrum at 1340 cm^{-1} and 1363 cm^{-1}.

8-Chloro-10-methyl[1,4]benzoxazino[3,2-*b*]pyridine (**13a**).

A solution of 20 g. (0.08 mole) of **8a** in 100 ml. of dimethyl methylphosphonate was refluxed for a period of 1 hour. The cooled reaction mixture was added to 600 ml. of water and stirred for 10 minutes. Crystals were filtered from the solution, washed with water and dried at 60°/20 torr, yielding 11.2 g. of product (purity: 99.8% by gc). Recrystallization from 220 ml. of methanol gave 7.9 g. of product.

Phenoxazine (**15a**).

The procedure given below is representative for the demethylation of the compounds **15b,c,f**.

A mixture of 7.5 g. (0.038 mole) of **9a** and 30 g. of pyridinium hydrobromide was heated to 200° for a period of 40 minutes. Then 150 ml. of water was added to the cooled suspension, the precipitate filtered and washed with 500 ml. of water. Crystallization from a mixture of 50 ml. of ethanol and 25 ml. of water afforded 5.2 g. of **15a**; nmr (acetone-d_6): 7.23 (S, NH); 6.6-6.8 (m, 8H, ArH).

2,8-Dichloro-3,7-dinitro-10-methylphenoxazine (**16**).

A slurry of 55.35 g. (0.2 mole) of **9f** in 3 l. of acetic acid was heated to 50° to obtain a homogeneous solution. Then 64.8 g. (0.4 mole) of ferric chloride was added with stirring over a period of 15 minutes at 25°, followed by 55.2 g. (0.8 mole) of sodium nitrite. Stirring was continued for a further 20 hours at 50°. The crystals formed were filtered from the solution, washed with 500 ml. of acetic acid, followed by water and dried, yielding 71 g. of **16**. A sample of 0.5 g. was recrystallized from 5 ml. of nitrobenzene.

2,8-Dichloro-10-methyl-3-nitrophenoxazine (**16b**).

A.

To a solution of 5.32 g. (0.02 mole) of **9f** in 160 ml. of acetic acid, was added 3.24 g. (0.02 mole) of ferric chloride at 60°. The soluton was cooled to 25°, 3 g. (0.04 mole) of sodium nitrite added, and stirred for 30 minutes. The suspension was added to 800 ml. of water, the precipitated crystals were filtered and washed with 200 ml. of water yielding 6 g. of product. A sample of 5 g. was recrystallized from 60 ml. of chlorobenzene, yielding 3.4 g. of **16b**.

To a solution of 13.3 g. (0.05 mole) of **9f** in 400 ml. of acetic acid was added 7.5 g. (0.11 mole) of sodium nitrite at 15° and the mixture was stirred for 15 hours. The resulting suspension was added to 2 l. of water, the crystals filtered and washed with water, yielding 15 g. of **16b**.

3,7-Dichloro-10-methyl-1-nitrophenoxazine (**16c**).

To a solution of 2.66 g. (0.01 mole) of **9g** in 80 ml. of acetic acid was added 1.62 g. of ferric chloride, followed by 1.5 g. of sodium nitrite. The mixture was added after 1 hour to 400 ml. of water, the crystals filtered and washed with 200 ml. of water, yielding 2.58 g. of product. A portion of the crude product (2.38 g.) was chromatographed on a silica gel column, eluted with toluene-acetone-heptane (8:1:1) to afford 1.43 g. of **16c**, which was recrystallized from chlorobenzene.

3-Amino-2,8-dichloro-10-methylphenoxazine (**17a**).

A solution of 6.2 g. (0.02 mole) of **16b** in 250 ml. of tetrahydrofuran was hydrogenated in the presence of 0.7 g. of Raney nickel. The solvent was distilled from the filtered solution and the residue recrystallized from chlorobenzene.

3,7-Diamino-2,8-dichloro-10-methylphenoxazine (**17b**).

The hydrogenation of 3.56 g. (0.01 mole) of **16e** in 150 ml. of tetrahydrofuran was carried out as described for **17a**.

2-Amino-8-chloro-3-nitro-10-methylphenoxazine (**18**).

A suspension of 77.5 g. (0.24 mole) of **16b** and 1 g. of copper(I) chloride in 1200 ml. of ethanol which had previously been saturated with ammonia at 20° was placed in an autoclave and heated at 180° for a period of 10 hours. The resulting suspension was filtered; the residue was washed with 500 ml. of ethanol and dried to give 68.2 g. of product. Recrystallization from 900 ml. of nitrobenzene afforded 37.8 g. of **18**.

8-Chloro-2,3-diamino-10-methylphenoxazine (**19**).

A solution of 3.2 g. (0.01 mole) of **18** in 150 ml. of tetrahydrofuran was hydrogenated in the presence of 0.8 g. of Raney nickel. The catalyst was filtered and the filtrate evaporated to dryness. Recrystallization of 2 g. from 20 ml. of toluene afforded 1.2 g. of **19**.

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