prepared by methods essentially similar to those described above. Deviations in some cases were possible because of the physical properties of the products. The *p*-toluenesulfonates of the *o*-biphenylene derivatives, compounds 57, 59, and 60, are sparingly soluble in water. In these cases, high vacuum sublimation of triethylamine hydrochloride was not necessary; it was sufficient after the ether trituration stage, to dissolve the residue in hot water. These quaternary tosylates separated out on cooling substantially pure. In the case of compound 56, the residue from trituration with ether was partially dissolved in acetone. In this instance, the quaternary chloride separated.

It is also possible in most cases to remove the bulk of the triethylamine hydrochloride from the ether-triturated residue by extraction with acetone in which triethylamine hydrochloride is quite insoluble. In such cases the vacuum sublimation is still desirable but can be considerably abbreviated.

TUCKAHOE, N. Y.

[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE AND THE DEPARTMENT OF CHEMISTRY OF RENSSELAER POLYTECHNIC INSTITUTE]

Local Anesthetics. 3-Halo-4-dialkylaminoalkoxy-5-alkoxyanilines

D. F. PAGE[1] AND R. O. CLINTON

Received April 11, 1961

A number of 3-bromo- and 3-chloro-4-dialkylaminoalkoxy-5-alkoxyanilines were prepared. The lower members of the series are potent, short-acting local anesthetics. Intermediate 2-alkoxy-4-nitrophenols were made by the alkaline displacement of the 1-alkoxy group in 1,2-dialkoxy-4-nitrobenzenes.

We have previously reported from these laboratories a series of dialkylaminoalkyl 4-amino-2-alkoxybenzoates[2] which possess both a high degree of local anesthetic activity and a fair degree of antifibrillatory activity. Recent investigations in these areas have been directed toward the preparation of compounds with an intense but short-acting local anesthetic activity for application in the production of intradermal anesthesia.

The local anesthetic activity associated with alkyl 2-(dialkylaminoalkoxy)-4-aminobenzoates[3] and with basic aryl alkyl ethers[4] led us to prepare first some 4-dialkylaminoalkoxy-3-alkoxyanilines, which proved to be quite unstable (*cf.* Kaye *et al.*[5] and Herbst and Simonian[6]) even as the solid hydrochloride derivatives. The search for more stable compounds led to the preparation of a series of 3-halo-4-dialkylaminoalkoxy-5-alkoxyanilines.

The route to the 3-bromo- and 3-chloro-4-dialkylaminoalkoxy-5-alkoxyanilines was I–V (X = Br or Cl, n = 2 or 3, R = CH_3 to C_6H_{13}, NR_2' = various dialkylamino groups).

The route to 4-dialkylaminoalkoxy-3-alkoxyanilines was I–V (X = H). An alternate preparation of II (R = CH_3) was the nitrosation of guaiacol followed by oxidation.

The reduction of 1-(2-diethylaminoethoxy)-2-methoxy-4-nitrobenzene[7] gave the corresponding aniline which proved to be very unstable in air, even as the hydrochloride salt. As we felt that β-elimination might play a part in the observed instability of the 4-(2-dialkylaminoethoxy)-3-alkoxyanilines we attempted to increase stability by the use of a 4-(3-dialkylaminoalkoxy) side chain. The resulting series was only slightly more stable toward air oxidation.

In hope of improving stability by changing the orientation of the substituents, the preparation of 3-(2-diethylaminoethoxy)-4-alkoxyaniline (VI. R = CH_3, n-C_3H_7) and 2-(2-diethylaminoethoxy)-5-methoxyaniline hydrochlorides (VII) was next undertaken. The compound VI (R = CH_3) has been previously reported as an intermediate[8] with no mention of stability. The precursors of VI were prepared from the parent 2-alkoxyphenyl acetates. Nitration, saponification, and a Williamson ether synthesis gave the 1-(2-diethylaminoethoxy)-2-alkoxy-5-nitrobenzenes. The starting compounds for VII (Table V) were prepared in a sequence parallel to I–IV (X = H), utilizing 1,4-dialkoxy-2-

(1) Taken from material submitted by D. F. Page to the Department of Chemistry of Rensselaer Polytechnic Institute in partial fulfillment of the requirements for the Ph.D. degree.

(2) R. O. Clinton, U. J. Salvador, S. C. Laskowski, and M. Wilson, *J. Am. Chem. Soc.*, **74**, 595 (1952).

(3) R. O. Clinton, S. C. Laskowski, U. J. Salvador, and P. M. Carroll, *J. Am. Chem. Soc.*, **79**, 2290 (1957).

(4) G. E. Ullyot, U. S. Patent **2,612,503** (1952); E. L. Anderson, J. W. Wilson, and G. E. Ullyot, *J. Am. Pharm. Assn.*, **41**, 643 (1952) and references therein; A. H. Sommers and A. W. Weston, *J. Am. Chem. Soc.*, **73**, 5749 (1951); M. B. Moore, H. B. Wright, M. Vernsten, M. Freifelder, and R. K. Richards, *J. Am. Chem. Soc.*, **76**, 3656 (1954); M. B. Moore, Brit. Patent **710,511** (1954); H. B. Wright and M. B. Moore, *J. Am. Chem. Soc.*, **76**, 4396 (1954) and references therein; R. O. Noojin, *Postgrad. Med.*, **16**, 453 (1954); H. B. Wright and M. B. Moore, *J. Am. Chem. Soc.*, **75**, 1770 (1953). W. H. Houff and R. D. Schuetz, *J. Am. Chem. Soc.*, **75**, 2073 (1953); H. R. Ing and W. E. Ormerod, *J. Pharm. and Pharmacol.*, **4**, 21 (1952); W. F. Minor, R. R. Smith, and L. C. Chaney, *J. Am. Chem. Soc.*, **76**, 2993 (1954).

(5) I. A. Kaye, W. J. Burlant, and L. Price, *J. Org. Chem.*, **16**, 1421 (1951).

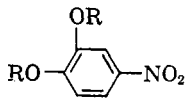
(6) R. M. Herbst and J. V. Simonian, *J. Org. Chem.*, **17**, 598 (1952).

(7) I. G. Farben, Brit. Patent **303,097** (1928).

(8) F. Mietzsch, U. S. Patent **1,727,480** (1929).

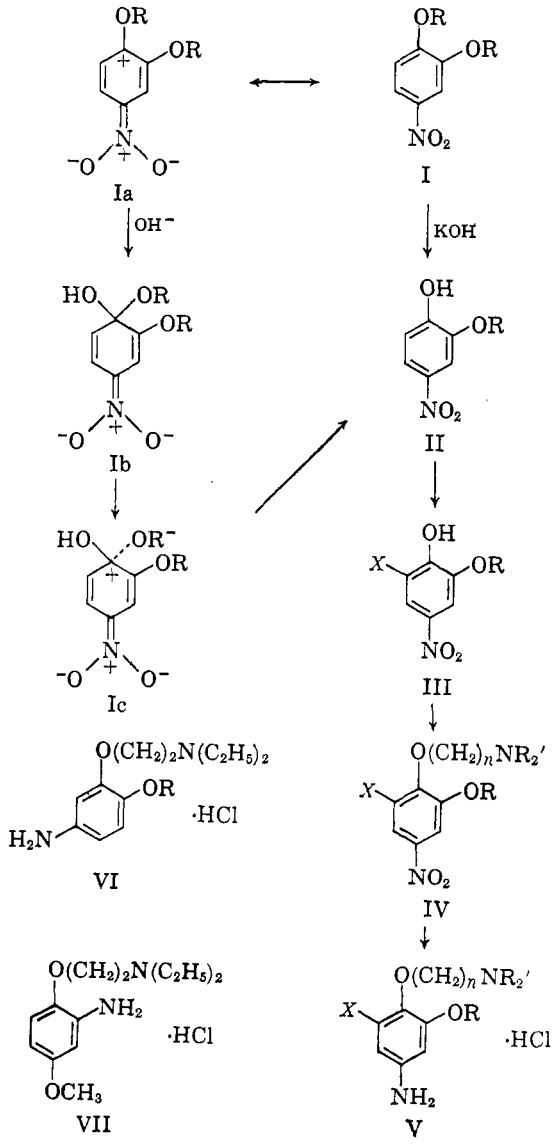
TABLE I

1,2-DIALKOXY-4-NITROBENZENES



R	Formula	M.P.	Recrystallized from[a]	Yield, %	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N_{Ti}
CH_3	$C_8H_9NO_4$	99.6–100.1°[b]	—	98.3						
C_2H_5	$C_{10}H_{13}NO_4$	74.0–74.5°[c]	A	94.8			6.64			6.78
n-C_3H_7	$C_{12}H_{17}NO_4$	61.6–62.4[d]	A	84.9			5.86			5.64
n-C_4H_9	$C_{14}H_{21}NO_4$	54.3–54.8°[e]	A	89.3			5.24			5.30
n-C_6H_{13}	$C_{18}H_{29}NO_4$	46.0–51.8[d]	A	94.1	66.84	9.04	4.33	66.53	8.53	4.22
$C_6H_5CH_2$	$C_{20}H_{17}NO_4$	98.8–99.5°[f]	B	92.9			4.18			4.03
n-C_8H_{17}	$C_{22}H_{37}NO_4$	61.0–61.8[d]	C	59	69.62	9.83	3.69	69.66	9.47	3.62
n-$C_{10}H_{21}$	$C_{26}H_{45}NO_4$	69.8–71.4[d]	D	93.1	71.68	10.41	3.22	71.48	10.26	2.63 3.70[g]

[a] A, methanol-water; B, ethanol; C, methanol; D, benzene-methanol. [b] Lit. m.p. 95–96°[24]; 97–98° (Ref. 28, p. 170). [c] Lit. m.p. 73–75° [O. Wisinger, *Monatshefte*, **21**, 1009 (1900)]. [d] Corrected m.p. [e] Lit. m.p. 56° [G. C. Hughes and F. Lyons, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 103 (1938)]. [f] Lit. m.p. 98° (ref. 15, p. 2879). [g] Dumas nitrogen determination.



nitrobenzenes (VIII) instead of 1,2-dialkoxy-4-nitrobenzenes (I). Reduction of the corresponding nitro compounds to give VI and VII resulted in bases unstable even as the solid hydrochloride salts. Thus, marked changes in orientation resulted in no appreciable increase in stability.

In the 4 - dialkylaminoalkoxy - 3 - alkoxyaniline series (V, X = H), it was thought that the introduction of a physiologically acceptable electron acceptor, as halogen, *meta* to the amino group, would offer added stability. The 3-bromo- and 3 - chloro - 4 - dialkylaminoalkoxy - 5 - alkoxyaniline hydrochlorides (V) proved to be quite stable. This inherent increase in stability might be due to resonance stabilization of the carbon-oxygen bond *para* to the amino group, or to the steric hindrance of the halogen in inhibiting oxidative attack at the same carbon atom.

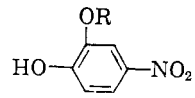
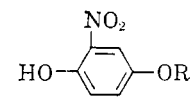
Bromination of 2-alkoxy-4-nitrophenols (II) to give the 2-bromo-6-alkoxy-4-nitrophenols (III) of Table III was carried out with bromine or pyridinium bromide perbromide in acetic acid. The latter was employed with 2-hexoxy-, 2-octoxy-, 2-decoxy-, and 2-benzyloxy-4-nitrophenols (II) in order to allow a higher reaction temperature (boiling acetic acid). With the latter compounds an equivalent of sodium acetate was present to neutralize hydrogen bromide as formed to prevent acid cleavage of the ether linkage.

Chlorination of II (R = CH_3 or C_2H_5) in acetic acid with excess chlorine gave 2-chloro-6-methoxy and -6-ethoxy-4-nitrophenol (III) (Table III). Attempted chlorination of II (R = CH_3) with N-chlorosuccinimide failed, and with sulfuryl chloride there was obtained at best only a low yield of III (R = CH_3) (*cf.* Fetscher and Bogert[9]).

(9) C. A. Fetscher and M. T. Bogert, *J. Org. Chem.*, **4**, 77 (1939).

TABLE II

ALKOXYNITROPHENOLS

R	Formula	Method[a]	Reaction Time	Isolation Procedure[a]	M.P.	Yield, %	Recryst. From[b]
2-Alkoxy-4-nitrophenols							
CH_3	$C_7H_7NO_4$	A	15 hr.[c]	1	100–101°[d]	73.4	u
		A	9 hr.	2	102–103	86.3	v
		A	18 hr.	3	101.5–102.5	98.2	u
		A	16 hr.	4	101.5–102.1	80.3	w
C_2H_5	$C_8H_9NO_4$	A	114 hr.[c]	1	95.0–95.7[e]	68.2	w
		A	94 hr.	2	94.5–95.5	63.2	w
		B	18 hr.[c]	6	94.0–95.5	76.5	w
		B	72 hr.	2	96.5–97.7	91.9	w
		F	66 hr.	6	94.5–95.1	54.6	u
		G	77 hr.[c]	6	90.0–93.5	<17	—
		H	94 hr.	9	Oil	<10	—
		J	4 days[c]	6	93.0–94.5	8.3	w
n-C_3H_7	$C_9H_{11}NO_4$	B	5 days	6	80.8–83.2[f]	94.4	w
		F	77 hr.[c]	6	80.0–81.0	46	w
n-C_4H_9	$C_{10}H_{13}NO_4$	B	5 days	6	40.4–41.6[g]	81.6	w
		B	96 hr.	2	38–39	87.3	w
		F	77 hr.[c]	6	Crude	<32.2	—
n-C_6H_{13}	$C_{12}H_{16}NO_4$	B	5 days	6	<20 crude	<17.5	—
		C	5 days	8	<20 crude	<73.7	—
		D	5 days	3	Oil	<51.6	—
	$C_{12}H_{15}NO_4K$	E	5 days	3	—[h]	38.8	x
$C_6H_5CH_2$	$C_{13}H_{11}NO_4$	A	61 hr.	1	Oil	<2	—
		B	24 hr.	6	79.7–80.5[i]	64.9	w
		B	40 hr.	2	80.0–82.0	58	w
n-C_8H_{17}	$C_{14}H_{20}NO_4K$	E	5 days	3	—[j]	33.5	x
n-$C_{10}H_{21}$	$C_{16}H_{24}NO_4K$	E	5 days	3	—[k]	34.1	x
4-Alkoxy-2-nitrophenols							
CH_3	$C_7H_7NO_4$	K	64 hr.	2	80.5–81.2[l]	88.4	y
		A	48 hr.	5	79.0–80.5	88.1	y
		B	67 hr.	6	80.4–81.7	37.7	z
C_2H_5	$C_8H_9NO_4$	A	52 hr.	2	Oil	<9	—
		B	8 days	7	80.9–81.5[m]	57.6	v
C_3H_7	$C_9H_{11}NO_4$	B	33 hr.	6	44.8–45.8[n]	11.1	w
		B	5 days	7	47–48	42.7	v

[a] See Experimental, *2-Alkoxy-4-nitrophenols.* [b] u, water; v, methanol-water; w, ethanol-water; x, ethanol; y, *i*-propyl alcohol-water; z, *i*-propyl alcohol. [c] Heated without stirring. [d] *Anal.* Calcd.: N, 8.29. Found: N_{Ti}, 8.20. Lit. m.p. 101–102°.[12] [e] Lit. m.p. 101°.[14] [f] Cor. m.p. *Anal.* Calcd.: N, 7.10; Found: N_{Ti}, 6.97. [g] Cor. m.p. *Anal.* Calcd.: N, 6.64; Found: N_{Ti}, 6.54. [h] *Anal.* Calcd.: K, 14.10; Found: K_{AP}, 14.13. [i] *Anal.* Calcd.: N, 5.72; Found: N_{Ti}, 5.51. Lit. m.p. 83–85° (ref. 15, p. 2879). [j] *Anal.* Calcd.: K, 12.80; N, 4.59; Found: K_{AP}, 12.83; N_D, 4.68. [k] *Anal.* Calcd.: K, 11.73; N, 4.20; Found: K, 11.74; N_D, 4.09. [l] Lit. m.p. 80° [T. Takahashi, N. Hattori, and M. Suyematsu, *J. Pharm. Soc. Japan*, 65, No. 5-6A, 9 (1945); *Chem. Abstr.*, 45, 8530f]. [m] Lit. m.p. 82° [T. Takahashi *et al.*, *op. cit.*]. [n] Cor. m.p. *Anal.* Calcd.: N, 7.10; Found: N_D, 6.93.

The attempted iodination of II (R = CH_3) with iodine monochloride failed.

A Williamson ether synthesis between III and the proper dialkylaminoalkyl chloride gave the 1-bromo- and 1-chloro-2-(dialkylaminoalkoxy)-3-alkoxy-5-nitrobenzenes (IV) (Table IV), which after a Béchamp reduction yielded the desired 3-bromo- and 3-chloro-4-dialkylaminoalkoxy-5-alkoxyanilines (V) (Table VII). Hydrogenation of IV (*X* = bromine) over palladium resulted in partial hydrogenolysis of the halogen. The fate of IV (*X* = chlorine) in a catalytic hydrogenation was not determined. However Najer[10,11] has shown that the chlorine atom in 2-chloro-1-[2-(morpholino)-ethoxy]- and -1-(2-diethylaminoethoxy)-4-nitrobenzene is not replaced during hydrogenation over palladium, while the chlorine in 2-chloro-4-nitrophenol undergoes partial hydrogenolysis.

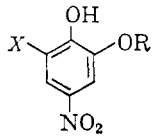
During the preparation of the 2-alkoxy-4-nitrophenols (II), it was of interest to investigate in some detail the alkaline displacement of the 1-alkoxy group in 1,2-dialkoxy-4-nitrobenzenes (I).

(10) H. Najer and P. Mabille, *Bull. soc. chim. France*, 645 (1958).

(11) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. soc. chim. France*, 108 (1956).

TABLE III

2-HALO-6-ALKOXY-4-NITROPHENOLS

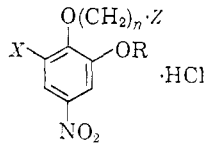


R	X	Formula	Corrected M.P.	% Yield	Method	Recryst. from[a]	Calcd. N	Calcd. X	Found N_{Ti}	Found X
CH_3	Br	$C_7H_6BrNO_4$	151.4–154.6° dec.[b]	86.8	A	r	5.65	32.22	5.60	32.14
C_2H_5	Br	$C_8H_8BrNO_4$	160.2–161.8 dec.	64.9	A	r, s	5.34	30.50	5.32	30.89
n-C_3H_7	Br	$C_9H_{10}BrNO_4$	116–118 dec.	43.9	A	r, s	5.07	28.94	5.05	29.03
n-C_4H_9	Br	$C_{10}H_{12}BrNO_4$	97.2–98.4	48.7	A	r	4.83	27.53	4.87	27.38
n-C_6H_{13}	Br	$C_{12}H_{16}BrNO_4$	84.2–88.2	70.2	B	t, r	4.40	25.12	4.37	24.90
$C_6H_5CH_2$	Br	$C_{13}H_{10}BrNO_4$	126.0–134.4	49.4	C	r, u	4.32	24.66	4.04	24.95
n-C_6H_{17}	Br	$C_{14}H_{20}BrNO_4$	69.8–70.6	22.1	B	r, t	4.05	23.08	4.03	22.82
n-$C_{10}H_{21}$	Br	$C_{16}H_{24}BrNO_4$	59.2–59.8	31.0	B	t	3.75	21.35	3.81	21.02
CH_3	Cl	$C_7H_6ClNO_4$	149.4–152.2 dec.	55.6	D	r	6.88	17.42	6.83	17.68
C_2H_5[c]	Cl	$C_8H_8ClNO_4$	154.4–158.8 dec.	74.8	D	r		16.32		16.25

[a] r, ethanol-water; s, *i*-propyl alcohol; t, petroleum ether (b.p. 90–100°); u, *i*-propyl alcohol water. [b] Lit. m.p. 150° dec. (ref. 30). Lit. m.p. 150–2° [T. Jones and R. Robinson, *J. Chem. Soc.*, 111, 918 (1917)].

TABLE IV

1-HALO-2-(DIALKYLAMINOALKOXY)-3-ALKOXY-5-NITROBENZENE HYDROCHLORIDES



Compound	X	R	Z	n	Formula·HCl	Corrected M.P.	Yield, %	Calcd., % N_{NO_3}	Calcd., % Cl^-	Found, % N_{Ti}	Found, % Cl^-
1	H	CH_3	$(C_2H_5)_2N$	2	$C_{13}H_{20}N_2O_4$	165.2–168.6	62	4.59	11.63	4.57	11.50
2	H	CH_3	$C_5H_{10}N$[a]	3	$C_{15}H_{22}N_2O_4$	156.3–160.4	71	8.47[c]	10.72	8.26[c]	10.64
3	Br	CH_3	$(C_2H_5)_2N$	2	$C_{13}H_{19}BrN_2O_4$	170.4–170.6	65.9	3.65	9.24	3.63	9.17
4	Br	C_2H_5	"	2	$C_{14}H_{21}BrN_2O_4$	167–168.2	79.3	3.53	8.92	3.32	8.90
5	Br	C_3H_7	"	2	$C_{15}H_{23}BrN_2O_4$	148.6–151.2	47.6	6.80[c]	8.61	7.11[c]	8.62
6	Br	C_4H_9	"	2	$C_{16}H_{25}BrN_2O_4$	98.2–100.0	72.4	6.58[c]	8.33	6.84[c]	8.24
7	Br	C_6H_{13}	"	2	$C_{18}H_{29}BrN_2O_4$	127.6–129.0	72.1	3.09	7.92	3.04	7.76
8	Br	$C_6H_5CH_2$	"	2	$C_{19}H_{23}BrN_2O_4$	165.8–167.0	90.8	3.05	7.72	2.99	7.69
9	Cl	CH_3	"	2	$C_{13}H_{19}ClN_2O_4$	170.4–171.8	51.2	4.13	10.46	4.05	10.32
10	Cl	C_2H_5	"	2	$C_{14}H_{21}ClN_2O_4$	170.0–174.4	83.1	3.97	10.03	3.94	10.10
11	Cl	CH_3	"	3	$C_{14}H_{21}ClN_2O_4$	162.8–164.4	90.4	3.97	10.03	3.94	9.88
12	Cl	CH_3	$(CH_3)_2N$	2	$C_{11}H_{15}ClN_2O_4$	173.4–175.4	46.9	4.51	11.39	4.51	11.38
13	Cl	CH_3	$(CH_3)_2N$	3	$C_{12}H_{17}ClN_2O_4$	179.0–181.6	58.8	4.31	10.91	4.33	10.94
14	Cl	C_2H_5	$(C_2H_5)_2N$	3	$C_{15}H_{23}ClN_2O_4$	165.0–166.2	75.2	3.81	19.31[d,e]	4.05	19.10[d]
15	Cl	CH_3	$C_6H_{12}N$[b]	2	$C_{15}H_{21}ClN_2O_4$	170.4–171.4	72.4	3.84	9.71	3.85	9.65
16	Cl	CH_3	$C_6H_{12}N$[b]	3	$C_{16}H_{23}ClN_2O_4$	153.2–156.4	54.4	3.70	9.36	3.70	9.28

[a] Piperidino. [b] 2-Methylpiperidino. [c] N_{total} by Dumas determination. [d] C_{total} by oxidative determination. [e] Compound prepared by Mr. U. J. Salvador of S.W.R.I.

Cardwell and Robinson[12] obtained 4-nitroguaiacol from 4-nitroveratrole by heating with potassium hydroxide, water, and methanol. The omission of methanol was shown to give a better yield, avoiding the formation of the byproduct 4,4′-azoxyveratrole.[13] By the latter procedure, Oliverio[14] also obtained 2-ethoxy-4-nitrophenol, in unreported yield, from 1,2-diethoxy-4-nitrobenzene, and asserted that the displacement proceeds equally well with other ethers of 4-nitropyrocatechol. Baker[15] and Balaban[16] found that, under the same conditions, no displacement occurred in 1,2-dibenzyloxy-4-nitrobenzene. In our experience (Table II), heating

(12) D. Cardwell and R. Robinson, *J. Chem. Soc.*, **107**, 258 (1915).

(13) F. Pollecoff and R. Robinson, *J. Chem. Soc.*, **113**, 647 (1918).

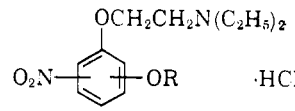
(14) A. Oliverio, *Gazz. chim. Ital.*, **73**, 196 (1943).

(15) W. Baker, A. Kirby, and L. Montgomery, *J. Chem. Soc.*, 2877 (1932).

(16) I. Balaban, *J. Chem. Soc.*, 1092 (1929).

TABLE V

OTHER 1-(2-DIETHYLAMINOETHOXY)ALKOXYNITROBENZENE HYDROCHLORIDES

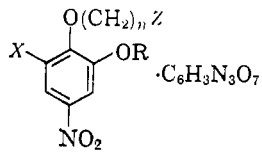


	Ring Substituent 2	4	5	Appearance	Formula·HCl	Corrected M.P.	Yield, %	Calcd., % N	Calcd., % Cl⁻	Found, % N_D	Found, % Cl⁻
17	CH_3O	H	NO_2	Almost colorless solid	$C_{13}H_{20}N_2O_4$	198.0–199.4°	59.4	9.18	11.63	9.23	11.62
18	C_3H_7O	H	NO_2	Light tan solid	$C_{15}H_{24}N_2O_4$	165.6–171.7	81.3	8.42	10.65	8.44	10.74
19	NO_2	CH_3O	H	Yellow-green plates	$C_{13}H_{20}N_2O_4$	135.4–137.6	85.7	4.59[a]	11.63	4.58[b]	11.56

[a] N_{NO_2}. [b] N_{Ti}.

TABLE VI

PICRATES



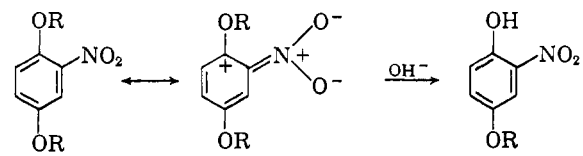
Compound	M.P.	N_{Ti}, % Calcd.	N_{Ti}, % Found
3	154–155.5°	9.72	9.67
4	152.5–154.5	9.51	9.37
5	124.6–125.6	9.27	9.28
6	117.6–119	9.07	9.04
7	118–119	8.66	8.69
8	149.0–150.3	8.58	8.58
9	165.5–167.2	10.53	10.62
10	149.5–150.4	10.25	10.38
12	178.5–180	11.12	11.10
13	128.5–129.5	10.82	11.02
14	115–116.5	10.00[a]	9.74
15	155.6–157.0	10.04	10.04
16	123.0–124.2	9.80	9.80

[a] Compound prepared by Mr. U. J. Salvador of S.W.R.I.

the proper 4-nitropyrocatechol ether (I) with aqueous potassium hydroxide, followed by acidification, gave a good yield of 4-nitroguaiacol, a smaller yield of 2-ethoxy-4-nitrophenol, and only a minute yield of impure 2-benzyloxy-4-nitrophenol. The preparation of the 2-propoxy-, 2-butoxy-, and 2-benzyloxy-4-nitrophenols in good yields required the use of an added solvent such as Methyl Cellosolve to increase the solubility of the starting material. Thus, it was found that 1,2-dibenzyloxy-4-nitrobenzene will undergo an alkaline displacement to give 2-benzyloxy-4-nitrophenol only under rigorous conditions. The preparation of the low-melting 2-hexoxy-, 2-octoxy-, and 2-decoxy-4-nitrophenols required the use of more concentrated alkali, and the addition of a higher boiling solvent as Cellosolve, in order to obtain even moderate yields of their crystalline potassium salts.

The alkaline displacement of the 1-alkoxy-group in 1,2-dialkoxy-4-nitrobenzenes (I) to give 2-alkoxy-4-nitrophenols (II) is a good preparative method for lower members of the series and is a reasonable, but slow, method for the higher homologs. High boiling point and polarity of any added solvent favor the reaction. The nucleophilic displacement of the 1-alkoxy group from the electron-poor carbon atom *para* to the nitro group is apparently impeded, in the case of the higher homologs, both by the hindrance of the large alkoxy-group to the incoming hydroxyl (Ib) and by the greater reluctance of the alkoxy group to ionize to the anion (Ic) in leaving the point of substitution.

In the case of 1,4-dialkoxy-2-nitrobenzenes (VIII), the alkaline displacement of the 1-alkoxy group to give 4-alkoxy-2-nitrophenols (IX) (Table II) generally gave poorer yields than with the corresponding nitropyrocatechol ethers, but nevertheless this is a reasonable preparative method for the



VIII VIIIa IX

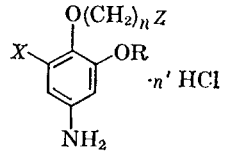
lower members of the series. For example, the production of 4-methoxy-2-nitrophenol (IX. R = CH_3) in good yield required only refluxing in aqueous potassium hydroxide, but even on heating in aqueous alkali with added Methyl Cellosolve, the 4-ethoxy- and 4-propoxy-2-nitrophenols (IX) were produced in lower yields than their corresponding pyrocatechol isomers (II).

Where the activation toward nucleophilic substitution in I and VIII is due in each case to a single nitro group *ortho* or *para* to the site of substitution, the lower rate of displacement of the 1-alkoxy group in VIII can be explained in part by the bulk of the 2-nitro group in shielding the site from the incoming hydroxyl more than does a methoxy, ethoxy, or propoxy group in I. That the site of substitution in VIII is not as reactive as in I is also due to the difficulty with which the nitro group in VIII may achieve coplanarity with the benzene ring (VIIIa) because of the adjacent alkoxy group, compared to the freedom of the nitro group in Ia.

The 3-halo-4-dialkylaminoalkoxy-5-alkoxyanilines (Table VII) all showed local anesthetic activity.

TABLE VII

3-HALO-4-DIALKYLAMINOALKOXY-5-ALKOXYANILINE AND 4-DIALKYLAMINOALKOXY-3-ALKOXYANILINE HYDROCHLORIDES



Compound	X	R	Z	n	n'	Formula	Corrected M.P.	Yield, %	Calcd., % C	Calcd., % H	Calcd., % Cl⁻	Found, % C	Found, % H	Found, % Cl⁻
1	H	CH_3	$C_5H_{10}N$[a]	3	1	$C_{15}H_{24}N_2O_2 \cdot HCl$	160.0–161.0	89.5	[c]		11.79	[c]		11.82
2	Br	CH_3	$(C_2H_5)_2N$	2	1	$C_{13}H_{21}BrN_2O_2 \cdot HCl$	220.8–224.6	80.7	44.14	6.27	10.02	44.24	6.36	10.02
3	Br	C_2H_5	"	2	1	$C_{14}H_{23}BrN_2O_2 \cdot HCl$	169.0–173.4	83.1	45.73	6.58	9.64	45.43	6.58	9.78
4	Br	C_3H_7	"	2	2	$C_{15}H_{25}BrN_2O_2 \cdot 2HCl$	146.4–indef.	84.5	43.08	6.51	16.96	42.92	6.27	16.91
5	Br	C_4H_9	"	2	2	$C_{16}H_{27}BrN_2O_2 \cdot 2HCl$	171.0–190.6	88.8	44.46	6.77	16.41	44.61	6.88	16.29
6	Br	C_6H_{13}	"	2	2	$C_{18}H_{31}BrN_2O_2 \cdot 2HCl$	193.0–196.0	80.8	46.97	7.21	15.41	47.13	7.56	15.36
7	Br	$C_6H_5CH_2$	"	2	2	$C_{19}H_{25}BrN_2O_2 \cdot 2HCl$	223.2–224.2 dec.	85.2	48.94	5.84	15.21	49.04	5.92	15.11
8	Cl	CH_3	$(C_2H_5)_2N$	2	1	$C_{13}H_{21}ClN_2O_2 \cdot HCl$	191.8–195.6	66.3	50.49	7.17	11.47	50.50	7.34	11.42
9	Cl	C_2H_5	$(C_2H_5)_2N$	2	1	$C_{14}H_{23}ClN_2O_2 \cdot HCl$	178.2–180.6	81.9	52.01	7.48	10.97	52.39	7.46	10.90
10	Cl	CH_3	$(C_2H_5)_2N$	3	1	$C_{14}H_{23}ClN_2O_2 \cdot HCl$	135.0–137.6	66.3	52.01	7.48	10.97	51.74	7.50	11.01
11	Cl	CH_3	$(CH_3)_2N$	2	1	$C_{11}H_{17}ClN_2O_2 \cdot HCl$	162.0–164.2	68	46.99	6.45	12.61	47.12	6.21	12.65
12	Cl	CH_3	$(CH_3)_2N$	3	1	$C_{12}H_{19}ClN_2O_2 \cdot HCl$	210.8–213.2	68.6	48.82	6.83	12.01	48.50	6.71	11.93
13	Cl	C_2H_5	$(C_2H_5)_2N$	3	1	$C_{15}H_{25}ClN_2O_2 \cdot HCl$	147.4–149.4	83.2	53.41	7.77	21.02[d,e]	53.75	8.08	21.05[d]
14	Cl	CH_3	$C_6H_{12}N$[b]	2	1	$C_{15}H_{23}ClN_2O_2 \cdot HCl$	208.8–216.2	65.3	53.73	7.22	10.58	54.00	7.12	10.59
15	Cl	CH_3	$C_6H_{12}N$[b]	3	1	$C_{16}H_{25}ClN_2O_2 \cdot HCl$	169.2–172.4	62	55.01	7.50	10.15	54.92	7.67	10.00

[a] Piperidino. [b] 2-Methyl(piperidino). [c] N_k. Calcd.: 9.31; Found: 9.34. [d] Cl_{total} by oxidative determination. [e] Compound prepared by Mr. U. J. Salvador of S.W.R.I.

Of particular interest in intradermal anesthesia, because of relatively high activity and low irritancy and toxicity (in comparison with Procaine), were compounds number 4, 8, 9, and 13.[17]

Acknowledgment. D. F. Page wishes to express his thanks to Prof. J. B. Cloke and the Chemistry Department of Rensselaer Polytechnic Institute for their cooperation in admitting this work, carried out at Sterling-Winthrop Research Institute, as part of a degree program.

EXPERIMENTAL[18]

1,2-Dialkoxybenzenes. The alkyl benzenesulfonates not commercially available were prepared by the method of Hückel[19] as modified by Clinton.[20]

1,2-Diethoxybenzene. Pyrocatechol was alkylated under nitrogen with diethyl sulfate to give a steam-volatile, almost colorless, crystalline product in 62% yield, m.p. 41.3–42.1° (from methanol-water) (lit. m.p. 45°).[21]

1,2-Dipropoxybenzene. Procedure A. Pyrocatechol was treated under nitrogen with *n*-propyl benzenesulfonate according to Slotta and Frank[22] to give 26.3% of colorless liquid, boiling 114–118° (21 mm.), n_D^{25} 1.4964 (lit. n_D^{27} 1.4950).[23]

Procedure B. Over 0.5 hr., 343.4 g. (1.72 moles) of *n*-propyl benzenesulfonate was added under nitrogen to a stirred solution of 188.9 g. (1.72 moles) of pyrocatechol and 111.5 g. (1.72 moles) of potassium hydroxide in 215 ml. of water and 650 ml. of ethanol at 46–80°. After 1 hr. of reflux, 13.0 g. of potassium hydroxide in water was added followed by 11 hr. at reflux. To the partly cooled solution was added 98.5 g. of potassium hydroxide in water, followed by a second, equal portion of propyl benzenesulfonate added over 50 min. at 41–76°. After 1 hr. at reflux, 15.0 g. of potassium hydroxide, in water, was added followed by 11 hr. at reflux. The mixture was cooled and the layers were separated. The aqueous layer was extracted with ether. The combined organic layers were washed with dilute alkali, with saturated salt solution, and were dried over potassium hydroxide pellets. The ether was distilled through a 16-in. Vigreux head and the residue was distilled to give 238.4 g. (71.6%) of colorless liquid boiling 142–148° (30 mm.), n_D^{25} 1.4963.

1,2-Dibutoxybenzene. Procedure A. The slow addition of 154.2 g. (0.72 mole) of *n*-butyl benzenesulfonate to 39.64 g. (0.36 mole) of pyrocatechol and 46.9 g. (0.72 mole) of potassium hydroxide in ethanol-water at 46–70° (1 hr. at reflux); the addition of 5.0 g. of potassium hydroxide in water (11 hr. at reflux); separation of the layers; extraction with ether of the diluted water-ethanol phase; washing the extracts with potassium carbonate solution; drying; and distillation gave 50.11 g. (62.5%) of colorless liquid boiling at 149–157° (14–15 mm.), n_D^{25} 1.4912–1.4922 (lit. n_D^{27} 1.4911).[23]

1,2-Dihexoxybenzene. Procedure A. The slow addition of 232.6 g. (0.96 mole) of *n*-hexyl benzenesulfonate to 44.04 g. (0.40 mole) of pyrocatechol, and 52.2 g. (0.80 mole) of potassium hydroxide in ethanol-water at 38–64° (1.5 hr. at reflux); the addition of 19.6 g. (0.30 mole) of potassium hydroxide in water; and 12 hr. at reflux were followed by steam distillation. Mainly ethanol and *n*-hexyl alcohol were removed from the reaction mixture. The residue was extracted with ether. Distillation gave 64.19 g. (57.6%) of pale yellow liquid boiling 186–197° (12 mm.), n_D^{25} 1.4872–1.4880 (lit. n_D^{27} 1.4849).[23]

1,2-Dioctoxybenzene (*Procedure A*), as with the above homolog, was obtained in 59.8% yield as a pale yellow oil boiling 173–189° (0.5 mm.) which would solidify in an ice bath (lit. m.p. 26.5°).[21]

1,2-Didecoxybenzene (*Procedure A*) was obtained as above as a waxy solid from the steam distillation residue. Recrystallization from benzene methanol gave 79.2% of fluffy, almost colorless solid, m.p. 38.5–39.0° (lit. m.p. 41°).[21]

1,2-Dibenzyloxybenzene. Under nitrogen, 110.1. g. (1.00 mole) of pyrocatechol, 278.2 g. (2.20 moles) of benzyl chloride, 148.5 g. (1.40 moles) of sodium carbonate, 16.6 g. (0.10 moles) of potassium iodide, 8 ml. of water, and 900 ml. of ethanol were stirred at reflux over 12 hr. After standing for 6 hr., the warmed suspension was filtered, washing the cake with hot absolute ethanol. The cake was slurried with 500 ml. of hot ethanol. The combined filtrates were evaporated to 400 ml. and were chilled. The precipitate was collected, washed with cold ethanol, and was recrystallized from 400 ml. of ethanol to give 130.3 g. (44.8%) of fine colorless crystals, m.p. 58–9° (lit. m.p. 63–4°).[15]

1,4-Dipropoxybenzene. Procedure B. As with the isomeric pyrocatechol, 100.1 g. of hydroquinone was alkylated with *n*-propylbenzene sulfonate in a flask with a subliquid, nitrogen entry tube. The crude product was filtered from the cooled reaction mixture. Recrystallization from methanol-water gave 97.5 g. (55.3%) of light tan plates, m.p. 50–51.5° (lit. m.p. 50°).[23]

1,2-Dialkoxy-4-nitrobenzenes (Table I). 4-Nitroveratrole was prepared from veratrole and nitric acid (sp. gr. 1.42) in acetic acid and water by the method of Clark.[24]

General method for the rest of the series as exemplified by 1,2-dibutoxy-4-nitrobenzene. Over 1.5 hr., 11.12 g. (0.05 mole) of 1,2-dibutoxybenzene in 25 ml. of glacial acetic acid was added to a solution of 6.7 ml. (0.105 mole) of nitric acid (sp. gr. 1.42) in 25 ml. of acetic acid, chilled to 0–17°. After 2 hr. of stirring without cooling, the solution was quenched in 500 ml. of water. The solid was filtered and was recrystallized from methanol-water, to give 11.92 g. of fine, pale-yellow needles, m.p. 54.3–54.8°.

1,4-Dialkoxy-2-nitrobenzenes. 1,4-Diethoxy-2-nitrobenzene. In the general method for the isomeric 1,2-dialkoxy-4-nitrobenzenes, 60.48 g. (0.40 mole) of 1,4-diethoxybenzene gave 81.9 g. (96.9%) of bright-yellow solid (from methanol-water) m.p. 48.9–49.8° (lit. m.p. 47°).[25]

1,4-Dipropoxy-2-nitrobenzene. In the general method 38.85 g. (0.20 mole) of 1,4-dipropoxybenzene gave an orange-yellow oil (volatile with steam). The oil was extracted with methylene chloride, the solvent was evaporated and the residue was distilled to give 35.5 g. (74.2%) of pale-orange liquid boiling at 164–5° (2.8 mm.), n_D^{25} 1.5236.

2-Alkoxy-4-nitrophenols (Table II). The general method was that of Pollecoff and Robinson[13] in which the 1,2-dialkoxy-4-nitrobenzene was stirred at reflux with twice its weight of potassium hydroxide in twenty parts of water

(17) F. P. Luduena, J. O. Hoppe, D. F. Page, and R. O. Clinton, *J. Med. Pharm. Chem.*, **3**, 547 (1961); E. Gonzales and F. P. Luduena, *J. Med. Pharm. Chem.*, **3**, 557 (1961).

(18) Analyses were performed by Mr. K. D. Fleischer and his staff. Melting points and boiling points are uncorrected, unless otherwise specified. The former were taken on a Fisher-Johns apparatus. N_{Ti} = nitro nitrogen by titration with titanous chloride. N_D = Dumas nitrogen determination. N_{AP} = basic nitrogen by titration with perchloric acid in glacial acetic acid solution. K_{AP} = potassium ion as in N_{AP}.

(19) W. Hückel, O. Neuenhoffer, A. Gercke, and E. Frank, *Ann.*, **477**, 143 (1930).

(20) Ref. 2, p. 596.

(21) R. Nodzu *et al.*, *J. Pharm. Soc. Japan*, **72**, 546 (1952); *Chem. Abstr.*, **47**, 2730*i*.

(22) K. H. Slotta and W. Frank, *Ber.*, **63B**, 685 (1930).

(23) K. R. Irani, N. L. Phalnikar, N. Z. Patel, H. R. Chipalkati, and K. S. Nargund, *J. Univ. Bombay*, **18**, Part 5, Sec. A, Sci. No. 27, 10 (1950): *Chem. Abstr.*, **45**, 1974*d*.

(24) E. P. Clark, *J. Am. Chem. Soc.*, **53**, 3434 (1931).

(25) K. H. Klaassens and C. J. Schoot, *Rec. trav. chim.*, **72**, 179 (1953).

(8% alkali), until a clear, deep red solution resulted. In the case of the higher alkoxy compounds, an equal volume of organic solvent was added to increase their solubility. In spite of the added solvent, and a higher proportion of alkali, which was also employed, the reaction was seldom complete.

The modifications of the displacement, noted in Table II, follow. The nitro compound was heated: A. in twenty parts of water with two parts of potassium hydroxide (8% alkali); B. in twenty parts of water, an equal volume of Methyl Cellosolve, and two parts of alkali (8% alkali); C. in twenty parts of water, an equal volume of Methyl Cellosolve, and five parts of alkali (18% alkali); D. in twenty parts of water, an equal volume of Methyl Cellosolve, and seven parts of alkali (24% alkali); E. in twenty parts of water, an equal volume of Cellosolve, and seven parts of alkali (24% alkali); F. in twenty parts of water, an equal volume of ethanol, and two parts of alkali (8% alkali); G. in twenty parts of water, an equal volume of dioxane, and two parts of alkali (8% alkali); H. in twenty parts of water, an equal volume of 1,2-dimethoxyethane, and two parts of alkali (8% alkali); J. in sixteen parts of water, an equal volume of bis-1,1-(2-methoxyethoxy)ethane and two parts of alkali (10% alkali); K. in thirteen parts of water and two parts of alkali (12% alkali).

The various procedures employed in the isolation of the phenolic products from the alkaline reaction mixtures are: (1) Filtration hot; acidification; filtration and/or extraction; and recrystallization; isolated as the free phenol. (2) Steam distillation; acidification of the residue or of a solution of the filtered potassium salt; filtration and/or extraction; and recrystallization; isolated as the free phenol. (3) Filtration hot; filtration cold and recrystallization of the potassium salt; acidification of the filtrates; filtration and/or extraction; and recrystallization; isolated as the potassium salt and free phenol. (4) Filtration cold and recrystallization of the potassium salt; acidification of the salt and filtrates; and recrystallization; isolated as the free phenol. (5) Steam distillation and as in (3). (6) Removal of the organic solvent; filtration hot and/or extraction; acidification; filtration; and recrystallization; isolated as the free phenol. (7) Removal of the organic solvent and as in (3). (8) Removal of the organic solvent; extraction; acidification; extraction of product; isolated as the crude phenol. (9) Evaporation of the solvents; steam distillation; acidification; and extraction; isolated as the crude phenol.

An example of the procedure is the preparation, by method B (2), of *2-ethoxy-4-nitrophenol*. Under reflux, 63.3 g. (0.30 mole) of 1,2-diethoxy-4-nitrobenzene, the specified amounts of potassium hydroxide, water, and Methyl Cellosolve were stirred over 72 hr. although the reaction was practically complete within 12 hr. (dilution of a small sample of the deep red solution with water gave no precipitate). The mixture was steam distilled, the residue was chilled and the potassium salt was filtered. An aqueous solution of the salt was filtered hot, acidified and filtered, to give 39.68 g. of yellow rods and needles (recrystallized from ethanol-water), m.p. 96.5–97.7°.

The original alkaline filtrate was evaporated to 1.5 l. and was acidified. The solid was filtered, sucked dry, and was recrystallized from absolute ethanol-water (filtering the large amount of potassium chloride from the ethanolic solution before adding water) to give an additional 10.85 g. of phenol, light tan crystals, m.p. 95.5–97.5°.

Alternate route to 4-nitroguaiacol. 4-Nitrosoguaiacol. In the method of Marvel and Porter,[26] 124.1 g. (1.00 mole) of redistilled guaiacol, dissolved in dilute sodium hydroxide, was nitrosated with sodium nitrite and dilute sulfuric acid. Recrystallizing from benzene–ethyl acetate–petroleum ether (b.p. 90–100°) gave, in two crops, 56.71 g. (37.1%) of 4-nitrosoguaiacol, m.p. 161–167° dec. (lit. m.p. 165°, dec.[27]).

4-Nitroguaiacol. 4-Nitrosoguaiacol was oxidized with potassium ferricyanide[27] in 67% yield to give material identical with that prepared by an alkaline displacement from 4-nitroveratrole.

4-Alkoxy-2-nitrophenols (Table II). The methods and work up procedures are those noted under the preparation of 2-alkoxy-4-nitrophenols, but starting from the corresponding 1,4-dialkoxy-2-nitrobenzenes.

2-Alkoxy-5-nitrophenols. 2-Propoxyphenol. Pyrocatechol was monoalkylated with *n*-propyl benzenesulfonate under nitrogen by the method of Slotta and Frank[22] in 41% yield to give material boiling at 110–111° (15 mm.), n_D^{25} 1.5192.

2-Propoxyphenyl acetate. To 121.76 g. (0.800 mole) of 2-propoxyphenol in 520 ml. of 10% sodium hydroxide, plus an equal amount of ice, was added 104 g. (1.02 mole) of acetic anhydride. After stirring over 12 min., the suspension was extracted with benzene. The extracts were washed with bicarbonate and saturated salt solutions, the benzene was distilled, and the residue was distilled through an 8-in. Hempel column to give 112 g. (72%) of colorless liquid boiling at 140.4–140.8° (11 mm.), n_D^{25} 1.4956.

2-Methoxy-5-nitrophenyl acetate. Nitrating 49.85 g. of 2-methoxyphenyl acetate with fuming nitric acid according to Drake *et al.*[28] gave crude, 39.77 g. (62.7%) and, on recrystallization from ethanol, 35.2% of pale-yellow needles, m.p. 100.5–101.5° (lit. m.p. 101°).[29]

2-Methoxy-5-nitrophenol. Saponifying 38.65 g. of crude 2-methoxy-5-nitrophenyl acetate gave 18.53 g. (59.8%) of fine, light-yellow solid, m.p. 104–105.1° (lit. m.p. 104°).[28]

5-Nitro-2-propoxyphenyl acetate and 5-nitro-2-propoxyphenol. Nitrating 97.11 g. of 2-propoxyphenyl acetate in the above manner gave, crude, 81 g. of yellow-tan 5-nitro-2-propoxyphenyl acetate, which was saponified as above and was recrystallized from benzene to give 31.07 g. (31.5%) of light tan, crystalline 5-nitro-2-propoxyphenol, m.p. 85.4–87.4° (cor.).

Anal. Calcd. for $C_9H_{11}NO_4$: N, 7.10. Found: N_{Tl}, 7.07.

2-Halo-6-alkoxy-4-phenols (Table III). *Method A.* The method was that of Drake *et al.*[30] An example is the preparation of *2-bromo-6-ethoxy-4-nitrophenol.* To 14.40 g. (0.079 mole) of 2-ethoxy-4-nitrophenol in 120 ml. of acetic acid, stirred and heated on a steam bath under reflux, was added 1.38 g. (0.087 mole) of bromine, in 170 ml. of acetic acid, over 3 hr. After stirring, hot, over 6 hr., the partly decolorized solution was quenched in 800 ml. of ice water with stirring. The tan solid was filtered, washed with water, recrystallized from ethanol-water with Darco, and was recrystallized from isopropyl alcohol, to give 13.33 g. of light, yellow-tan needles.

2-Bromo-6-hexoxy-4-nitrophenol. Method B. To a solution of 3.27 g. (0.0088 mole) of pyridinium bromide perbromide (86%, recrystallized from acetic acid) and 0.2 ml. of 30% hydrogen bromide in acetic acid, in 80 ml. of acetic acid, stirred under reflux on a steam bath, was added a solution of 2.22 g. (0.008 mole) of 2-hexoxy-4-nitrophenol potassium salt, in 45 ml. of acetic acid, over 1 hr. After another hour of stirring, hot, the red solution was concentrated to 100 ml. and was quenched in 600 ml. of ice water containing 1 g. of sodium bisulfite. The tan solid was filtered and was recrystallized from petroleum ether (b.p. 90–100°) and then from ethanol-water to give 1.79 g. of fine, tan plates.

6-Benzyloxy-2-bromo-4-nitrophenol. Method C. To a solution of 4.90 g. (0.02 mole) of 2-benzyloxy-4-nitrophenol and 0.5 ml. of 30% hydrogen bromide in acetic acid, in 45 ml. of acetic acid, stirred under reflux on a steam bath, was added a hot solution of 8.18 g. (0.022 mole) of pyridinium bromide perbromide (86%) and 1.64 g. (0.02 mole) of fused sodium acetate in 180 ml. of acetic acid over 0.5 hr. After 1.5 hr. of stirring, the solution was concentrated to *ca.* 50

(26) H. Gilman, *Org. Syntheses*, Coll. Vol. I, 403 (1932).
(27) H. Rupe, *Ber.*, 30, 2446 (1897).
(28) N. Drake, H. Harris, and C. Jaeger, *J. Am. Chem. Soc.*, 70, 169 (1948).
(29) F. Reverdin and P. Crépieux, *Ber.*, 39, 4232 (1906).
(30) Ref. 28, p. 170.

ml. The residue was quenched in 1.8 l. of ice water containing 2 g. of sodium bisulfite. The red-tan solid was filtered and was recrystallized twice from ethanol-water and from *i*-propyl alcohol-water to give 3.22 g. of light yellowish brown prisms.

2-Chloro-6-ethoxy-4-nitrophenol. Method D. Chlorine gas was run rapidly into a stirred solution of 5.49 g. (0.03 mole) of 2-ethoxy-4-nitrophenol in 55 ml. of acetic acid, over 1.25 hr. at 30–35°, warming in a water bath after the first few minutes. After 1 hr. of stirring, warm, the chilled suspension was filtered and the solid was recrystallized from ethanol-water to give 4.88 g. of fine, yellow solid.

Higher temperature chlorinations resulted in a mixture of polychlorinated products.

1-Dialkylaminoalkoxy-2-alkoxy-4-nitrobenzene, 1-halo-2-(dialkylaminoalkoxy)-3-alkoxy-5-nitrobenzene and other 1-(2-diethylaminoethoxy)alkoxynitrobenzene hydrochlorides (*Tables* IV *and* V).

The general method involved the condensation of a dialkylaminoalkyl chloride with the sodium or potassium salt of a phenol by heating in toluene until the orange or red color of the salt was discharged (16–120 hr.), followed by conversion to the hydrochloride salt.[31]

The dialkylaminoalkyl chlorides were prepared in dried toluene solution from the corresponding hydrochlorides, where commercially available. The remainder were prepared from the corresponding dialkylaminoalkanols[32] by reaction with thionyl chloride.[33]

An example for the preparation of all except compounds number 1, 2, and 19 is *1-chloro-2-(3-diethylaminopropoxy)-3-methoxy-5-nitrobenzene hydrochloride.* To a stirred suspension of sodium ethoxide (from 2.30 g. (0.10 mole) of sodium and 50 ml. of absolute ethanol) in 190 ml. of C. P. toluene, was added 20.35 g. (0.10 mole) of 2-chloro-6-methoxy-4-nitrophenol. Ethanol-toluene was again distilled to a head temperature of 110°. To the partly cooled, orange suspension was added 16.46 g. (0.11 mole) of 3-diethylaminopropyl chloride in 40 ml. of toluene. The mixture was stirred at reflux over 52 hr. The brown suspension was filtered and the cake washed with hot benzene. The filtrate was evaporated to dryness *in vacuo* three times, twice with added toluene, leaving 33.3 g. of red-brown oil. The base in ether was treated with a slight excess of ethereal hydrogen chloride. The crude, yellow hydrochloride salt was filtered, taken up in water and was converted to the base with dilute alkali. The base was extracted with ether. The extracts were washed with water and with saturated salt solution followed by drying over Drierite plus Darco. The hydrochloride was precipitated, filtered, and was recrystallized from ethanol-ether (both absolute) to give 31.92 g. of fine, almost colorless, slightly hygroscopic solid.

Compounds 1,2, and 19 were prepared in a similar manner, but using equivalent amounts of the red, crystalline potassium salt of the alkoxynitrophenol and the alkyl chloride in toluene.

3-Halo-4-dialkylaminoalkoxy-5-alkoxyaniline and 4-dialkylaminoaminoalkoxy-3-alkoxyaniline hydrochlorides (*Table* VII). The 1-(2-diethylaminoethoxy)-2-methoxy-4-nitrobenzene on reduction with iron-hydrochloric acid, hydrogenation over palladium, or neutral reduction with zinc and calcium chloride in ethanol-water gave 4-(2-diethylaminoethethoxy)-3-methoxyaniline which was readily oxidized in air even as the hydrochloride salt.

The only nonhalogen-containing aniline, isolated as a relatively stable salt, was *3-methoxy-4-[3-(piperidino)propoxy]aniline hydrochloride.* In a Parr apparatus, 11.59 g. (0.035 mole) of 2-methoxy-1-[3-(piperidino)propoxy]-4-nitrobenzene hydrochloride and 0.90 g. of 10% palladium on charcoal in 200 ml. of commercial absolute ethanol were hydrogenated at room temperature over 2.5 hr., when the uptake had stopped at the theoretical amount. The filtered, straw-colored solution was concentrated *in vacuo* under nitrogen. The red concentrate was diluted with ether. The crude, purple product was filtered and the solid was recrystallized from ethanol-ether to give 9.49 g. of fine light purple solid, which darkened further on standing.

Low pressure catalytic hydrogenation over palladium of the bromine-containing nitro compounds resulted in partial hydrogenolysis of the bromine. The general method for the rest of the compounds in Table VII is shown in the following examples:

3-Bromo-5-butoxy-4-(2-diethylaminoethoxy)aniline dihydrochloride. Under nitrogen, 5.53 g. (0.013 mole) of 1-bromo-3-butoxy-2-(2-diethylaminoethoxy)-5-nitrobenzene hydrochloride in 90 ml. of ethanol-water (1:1) was added to a stirred suspension of 4.36 g. (0.078 mole) of iron powder and 0.4 ml. of concd. hydrochloric acid in 130 ml. of ethanol-water (1:1) at reflux, over 35 min. After 3 hr. of heating and stirring, 2.6 g. of sodium bicarbonate, in water, was added. The hot suspension was filtered and the cake was washed with hot ethanol. The combined filtrates were evaporated *in vacuo* under nitrogen. The residue, suspended in water, was made strongly basic with dilute alkali and was extracted with ether. The ether was washed with water and saturated salt solution, followed by drying over Drierite. The hydrochloride was precipitated with a slight excess of ethereal hydrogen chloride. Filtration and recrystallization from ethanol-ether gave 4.99 g. of almost colorless crystals.

In some cases, the monohydrochloride was specifically desired for testing or the dihydrochloride apparently lost part of a mole of hydrogen chloride on drying at moderate temperature *in vacuo*. The monohydrochlorides were prepared.

3-Chloro-4-(2-diethylaminoethoxy)-5-ethoxyaniline hydrochloride. As above, 17.66 g. (0.05 mole) of 1-chloro-2-(2-diethylaminoethoxy)-3-ethoxy-5-nitrobenzene hydrochloride, 16.76 g. (0.30 mole) of iron powder, 1.0 ml. of concd. hydrochloric acid, and 750 ml. of ethanol-water gave 16.93 g. of pale purple, recrystallized dihydrochloride salt, m.p. 155–163°. Of the dihydrochloride, 8.75 g., in water, was converted to the base, which was extracted with ether. The extracts were washed and dried over Drierite and Darco. The ethereal solution was added to a solution of the remaining dihydrochloride in absolute ethanol. The solid was filtered and recrystallized from ethanol-ether to give 13.22 g. of crystalline, pale-purple monohydrochloride.

3'-Chloro-4'-(2-diethylaminoethoxy)-5'-methoxyacetanilide hydrochloride. The corresponding aniline hydrochloride, 8.5 g., and excess acetic anhydride warmed in pyridine gave 9.40 g. (96.4%) of fine, colorless crystals, m.p. 220.4–221.4° (cor.) (from ethanol-ether).

Anal. Calcd. for $C_{15}H_{23}ClN_2O_3 \cdot HCl$: C, 51.29; H, 6.89; Cl^-, 10.09. Found: C, 51.21: H, 7.14; Cl^-, 10.01.

3'-Bromo-4'-(2-diethylaminoethoxy)-5'-ethoxyacetanilide hydrochloride. In the above manner, 3.67 g. of the corresponding aniline hydrochloride gave 3.66 g. (89.3%) of fine almost colorless crystals, m.p. 161.7–164.0° (cor.) (from ethanol-ether).

Anal. Calcd. for $C_{16}H_{25}BrN_2O_3 \cdot HCl$: C, 46.90; H, 6.40; Cl^-, 8.65. Found: C, 46.61: H, 6.33: Cl^-, 8.37.

RENSSELAER, N. Y

(31) Ref. 3, p. 2294.

(32) R. O. Clinton, U. J. Salvador, and S. C. Laskowski, *J. Am. Chem. Soc.*, 71, 3367 (1949).

(33) J. P. Mason and H. W. Block, *J. Am. Chem. Soc.*, 62, 1445 (1940).