The sirup was diluted with methanol, ether was added, and the mixture was refrigerated for crystallization. Crystals occasionally were removed from the sides of the flask. After 8–12 days, the crystallizate was filtered off, washed with a cold mixture of ethanol and ether, and dried in a desiccator; yield, 7.6 g., $[\alpha]^{20}_{\mathrm{D}} -75.3°$ (*c* 1.3, water), m.p. 136–139°, undepressed when mixed with authentic L-fucose.

The noncrystallizing syrup was chromatographically examined, using irrigants A, B, and C and spray reagents I, II, and III. Only three spots could be detected; they were identical with those for fucose, galactose, and xylose.

The other samples of fucoidan were treated with methanolic hydrogen chloride under the same conditions. The yields of crystalline L-fucose usually were very similar. The noncrystallizing residues from all samples showed evidence of the presence of fucose, galactose, and xylose. In addition to those sugars, one experiment using unpurified fucoidan and another one using quadruply reprecipitated fucoidan gave evidence of the presence of a trace of mannose.

Identification of D-Galactose and D-Xylose.—The noncrystallizing residue was placed on a cellulose column, 55 × 650 mm., and irrigant A was applied. The first fraction contained only L-fucose; this was followed by fractions containing a mixture of L-fucose and D-xylose, then of D-xylose only, and finally of D-galactose. The fractions containing D-xylose and D-galactose were concentrated separately to sirups, diluted with water, and treated with some Amberlite IR-120-(H^+) cation-exchange resin and activated carbon. After filtration, they were concentrated *in vacuo* to a very small volume. Ethanol was added and both solutions were kept in the refrigerator for crystallization. The crystals were filtered off on a fritted-glass funnel, washed with a cold mixture of ethanol and water, and dried in a desiccator over calcium chloride.

The hexose had $[\alpha]^{20}_{\mathrm{D}} + 79.2 \pm 1.3°$ (*c* 1.4, water), m.p. 161–163° and, after recrystallizing from ethanol-water, 165–166°, undepressed when admixed with authentic D-galactose.

The data for the pentose were $[\alpha]^{20}_{\mathrm{D}} +17.5 \pm 2.3°$ (*c* 0.6, water), m.p. 140–142.5°, undepressed when admixed with authentic D-xylose.

Quantitative Determinations.—The fractions containing L-fucose were concentrated *in vacuo*. The sirup obtained was diluted with water, treated with some Amberlite IR-120-(H^+) and activated carbon, filtered, concentrated to a smaller volume, and adjusted to 100 ml. with water. L-Fucose was determined by oxidation with Fehling solution (see Lane and Eynon[17]). The table values were corrected for L-fucose, 0.74 g. of L-fucose having the reducing power of 1 g. of D-glucose.

The fractions containing D-galactose were concentrated to a sirup and, after dilution with water and treatment with activated carbon and Amberlite IR-120-(H^+), adjusted to 100 ml. with water. D-Galactose was determined by oxidation with Fehling solution. The reducing power of 0.855 g. of D-galactose was found to be equivalent to that of 1 g. of D-glucose, and the values were corrected on this basis.

All fractions containing D-xylose and a mixture of D-xylose and L-fucose were combined, concentrated to a sirup, diluted with water, treated with Amberlite IR-120-(H^+) and activated carbon, and adjusted to 100 ml. with water. L-Fucose was determined as previously described.[16] The amount of D-xylose was found by subtraction of the calculated reducing power of L-fucose from the total reducing power determined by oxidation with Fehling solution. These values were, however, reliable only if the quantities of D-xylose and L-fucose were of a similar order of magnitude. The yields of D-xylose given in Table I were obtained by a chromatographic method. Spots of five different, known mixtures of D-xylose and L-fucose were placed on a paper strip together with a spot of the sample to be determined. The paper was developed in irrigant A and sprayed with spray reagent I. The size of the red spots from D-xylose was determined by cutting out the spots and weighing them. The weight was plotted on a curve against the amount of D-xylose, and the value for the unknown yield of D-xylose was taken from this curve. For each sample, five chromatograms were prepared to obtain one average value. The accuracy of the method was tested by using known amounts of D-xylose and L-fucose instead of the unknown samples. The method was found to be reliable within a limit of error of about ±7%.

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(17) J. H. Lane and L. Eynon, *Soc. Chem. Ind.* (London), **42**, 32T–37T (1923).

A New Type of Smiles Rearrangement of *N*,*N*-Dialkyl-*N'*-[2-(*o*-bromophenoxy)phenyl]-1,3-propanediamines to 2-[*N*-(3-Dialkylaminopropyl)-*o*-bromoanilino]phenols[1a]

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A new type of Smiles rearrangement of *N*,*N*-dialkyl-*N'*-[2-(*o*-bromophenoxy)phenyl]-1,3-propanediamines (III) to the isomeric 2-[*N*-(3-dialkylaminopropyl)-*o*-bromoanilino]phenols (IV) has been studied in some detail. Cyclization of the latter constitutes a new ring closure by which 10-(3-dialkylaminopropyl)phenoxazines have been obtained. Phenoxazine analogs of chlorpromazine, methoxypromazine, and prochlorperazine were prepared.

The first paper in this series[1b] described two new syntheses of 2-chloro-10-(3-dimethylaminopropyl)-phenoxazine (Ia, Table I). These methods were designated as the *o*-phenoxyaniline route (A_1) and the modified Turpin reaction (route B). We now wish to report a novel "Smiles type" rearrangement of *N*,*N*-dialkyl-*N'*-[2-(*o*-bromophenoxy)-phenyl]-1,3-propanediamines (III) to the isomeric 2-[*N*-(3-dialkylaminopropyl)-*o*-bromoanilino]-phenols (IV). These rearranged products (IV) also afforded the desired phenoxazines (I) on ring closure; this is designated the 2-(*o*-bromoanilino)-

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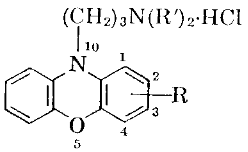
(1) (a) Presented in part before the Division of Organic Chemistry at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 9–14, 1962; (b) G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 2797 (1961).

TABLE I

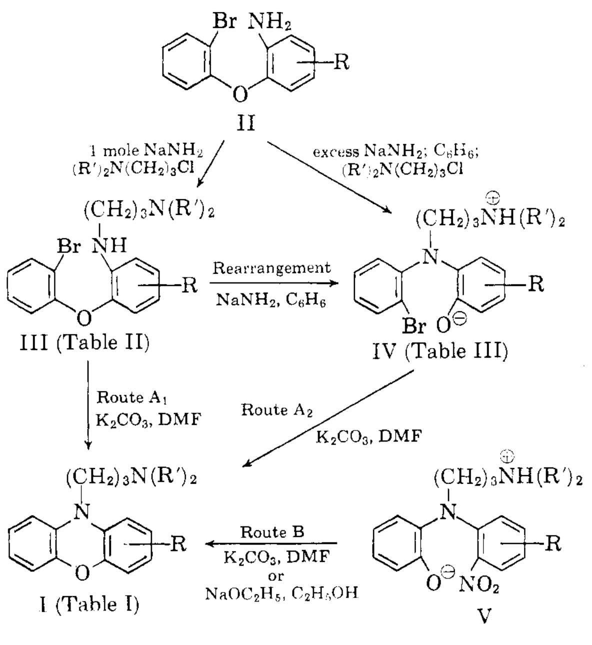
10-(3-DIALKYLAMINOALKYL)PHENOXAZINES (I)



Cpd. no.	R	$N(R')_2$	Pre-cursor/ route	% Yield[a] base/ salt	Base b.p., °C./mm.	Salt m.p., °C.	Salt	Empirical formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
Ia	2-Cl	$N(CH_3)_2$	IVa[b]/A_2	92[b]/91	176–180[c]/0.5	220–222	HCl	$C_{17}H_{20}Cl_2N_2O$	60.2	59.9	5.94	6.01	20.9	20.8	8.25	8.41
Ib	2-CH_3O	$N(CH_3)_2$	IIIb/A_1	36/26	166–169/0.1[d]	190–191	HCl	$C_{18}H_{23}ClN_2O_2$	64.6	64.5	6.92	7.14	10.6	10.6	8.37	8.30
Ib	2-CH_3O	$N(CH_3)_2$	IVb/A_2	48/37	168–172/0.1[e]	191–192	HCl	$C_{18}H_{23}ClN_2O_2$	64.6	64.8	6.92	7.24	10.6	10.6	8.37	8.69
Ic	2-Cl	$N(CH_2CH_2)_2NCH_3$	IIIc/A_1	52/21	198–200/0.25[f]	266–269[f]	2HCl	$C_{20}H_{26}Cl_3N_3O$	55.8	55.5	6.08	6.22	24.7	25.0	9.75	9.81
Ic	2-Cl	$N(CH_2CH_2)_2NCH_3$	IVc/A_2	49/34	188–194/0.05	267–269	2HCl	$C_{20}H_{26}Cl_3N_3O$	55.8	55.3	6.08	6.28	24.7	24.8	9.75	9.71
Id	4-Cl	$N(CH_3)_2$	IIId/A_1	83[g]/75	168–173/0.2[h]	174–175	HCl	$C_{17}H_{19}ClN_2O$[i]	67.4	67.1[i]	6.32	6.54	11.7	11.9	9.26	9.30
Id	4-Cl	$N(CH_3)_2$	IVd/A_2	82[g]/76	[g,h]	174–175	HCl	$C_{17}H_{20}Cl_2N_2O$	60.2	60.2	5.94	6.00	20.9	20.9	8.25	8.32
Ie	2-CH_3O	$N(CH_2CH_2)_2NCH_3$	IIIe/A_1	48/40	205–215/0.2	265–267	2HCl	$C_{21}H_{27}N_3O_2$[i]	71.4	71.1[i]	7.65	7.73			11.9	11.6
Ie	2-CH_3O	$N(CH_2CH_2)_2NCH_3$	IVe/A_2	51/40	205–215/0.2	264–267	2HCl	$C_{21}H_{29}Cl_2N_3O_2$	59.2	59.2	6.86	7.02	16.7	16.5	9.86	10.1
If	2-CF_3	$N(CH_3)_2$	IIIf/A_1	63/43[j]	144–145/0.1[k]	233–235[k]	HCl	$C_{18}H_{19}ClF_3N_2O$	64.5	64.2	5.71	6.06	17.0[l]	16.5	8.35	8.41
Ig[m]	2-Cl[m]	$N(CH_3)_2$[m]	IVg[m]/A_2[m]	74/76	160–162/0.3[n]	190–193	HCl	$C_{17}H_{20}Cl_2N_2O$[m]	60.2	60.0	5.94	6.10	20.9	20.9	8.25	8.35
Ih	3-Cl	$N(CH_3)_2$	Va[p]/B	18[q]/12	175–180/0.4[r]	183–184	HCl	$C_{17}H_{20}Cl_2N_2O$	60.2	59.8	5.94	6.29	20.9	21.2	8.25	8.28
Ii	1-Cl	$N(CH_3)_2$	Vb[s]/B	22[q]/18	[g]	158–159	HCl	$C_{17}H_{20}Cl_2N_2O$	60.2	60.0	5.94	6.34	20.9	21.2	8.25	8.45

[a] Yields of purified products are based on weight of precursor. [b] Comparable yields were obtained without the use of Cu as catalyst, *e.g.* $\text{IIIa} \xrightarrow[90\%]{A_1} \text{Ia} \xleftarrow[91\%]{A_2} \text{IVa}$. [c] n^{25}_D 1.614. [d] n^{25}_D 1.592. [e] n^{25}_D 1.596. [f] Lit.,[2] b.p. 215–225°/33.5 mm., prepared by a different method. Lit.,[2] m.p. of dimaleate, 194–195°. [g] Purified by chromatography. [h] n^{25}_D 1.608. [i] Free base. [j] n^{25}_D 1.555. [k] Lit.,[2] b.p. 165–180°/0.2–1.0 mm.; m.p. 230–236°. [l] Fluorene analysis. [m] Side chain is $-CH_2CH(CH_3)N(CH_3)_2$. [n] n^{25}_D 1.620. [p] Intermediate Va was isolated from reaction mixture containing Ih. [q] Over-all yield based on weight of starting material. [r] n^{25}_D 1.601. [s] Vb could not be isolated from the reaction mixture.

phenol route (A_2: IV → I). *N*-Alkylation of II with either 3-chloro-*N*,*N*-dimethylpropylamine or 1-(3-chloropropyl)-4-methylpiperazine and *one* equivalent of sodium amide in anhydrous benzene yielded the expected *N'*-[2-(*o*-bromophenoxy)-phenyl]-*N*,*N*-dialkyl-1,3-propanediamines (III) as previously described.[1b] In contrast, when these *N*-alkylations were carried out in the presence of *more than one* equivalent of sodium amide, a mixture of two products was frequently obtained. In addition to the expected *N'*-[2-(*o*-bromophenoxy)-phenyl]-*N*,*N*-dialkyl-1,3-propanediamines (III), the isomeric 2-[*N*-(3-dialkylaminopropyl)-*o*-bromoanilino]phenols (IV) were also isolated, generally as the sodium salts. For example, treatment of 2-(*o*-bromophenoxy)-5-chloroaniline[1b] with 3-chloro-*N*,*N*-dimethylpropylamine and *two* equivalents of sodium amide in benzene gave over 90% of the rearranged product, 2-[*o*-bromo-*N*-(3-dimethylaminopropyl)anilino]-4-chlorophenol (IVa) Treatment of chromatographically purified *N'*-[2-(*o*-bromophenoxy)-5-chlorophenyl]-*N*,*N*-dimethyl-1,3-propanediamine (IIIa)[1b] with *one or more* equivalents of sodium amide in benzene also gave the same rearranged product, as the partially hydrolyzed sodium salt, in 85% yield, and the free phenol (IVa) in 74% over-all yield. IVa showed absorption bands in the 3.7–4.3 μ region attributed to a phenolic group in a zwitterionic interaction with the side chain dimethylamino moiety as described in our previous paper.[1b] The sodium salt derived from IVa did not absorb in this region. It readily hydrolyzed in water. IVa formed a virtually insoluble hydrochloride and an *O*-acetate which showed no absorption in the 3.7–4.3-μ region, but showed carbonyl absorption at 5.68 μ. A number of structures analogous to IIIa and IVa were studied, and, in each case, rearrangement was obtained. These results are summarized in Table III. Further investigation of the properties of IVa indicated that the rearranged products (IV) were obtainable only when a nonpolar solvent, benzene, was employed. This suggests that the initially formed phenolate salts of IV are not sufficiently ionized to permit further reaction of the phenoxide moiety with the *o*-bromine atom (ring closure).



Treatment of IVa with potassium carbonate in *N*,*N*-dimethylformamide (DMF) with or without copper powder yielded 2-chloro-10-(3-dimethylaminopropyl)phenoxazine (Ia) in better than 90% yield after refluxing for several hours. The sodium salt of IVa also gave 65% ring closure in refluxing dimethylformamide after one hour. Copper was also unnecessary for the analogous ring closure of IIIa to Ia (route A_1). Samples of Ia obtained by these routes were identical in every respect, and also identical with material prepared from Va ($R = 5\text{-Cl}$; $R' = CH_3$; route B).[1b] Ia has also been prepared by Olmsted, *et al.*,[2] by an independent route. A variety of other compounds of type IV all gave facile ring closure to the phenoxazine derivatives (I); these results are summarized in Table I. The conversion of II to IV (through III using excess sodium amide) followed by ring closure to I has been of distinct preparative value for our phenoxazines since isolation and purification of compounds of type IV, which are generally solids, was much easier than tedious high vacuum distillation of viscous oils of type III. A further detailed study of the ring closure of IVa to Ia indicated that a base, potassium carbonate, was required, and a polar solvent (DMF *vs.* benzene) favored the reaction.

The data described above indicate that the rearrangement of III to IV in the presence of sodium amide and benzene is analogous to the Smiles rearrangement.[3] The recently reported[4] rearrangement of isodehydrodigallic acid dimethyl ester (a) to normal-dehydrodigallic acid dimethyl ester (b) in hot water is postulated to proceed by an anal-

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(2) M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, **26**, 1901 (1961).

(3) (a) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951), also see references therein; (b) J. F. Bunnett, *Quart. Rev.*, **12**, 1 (1958).

(4) W. Mayer and H. Scheuermann, *Angew. Chem.*, **71**, 382 (1959): In this example, the electron-withdrawing properties of the ester moiety (Ring A) should be similar to those of the nitro group usually present in compounds undergoing the Smiles rearrangement.[3] This example is somewhat unusual in that a basic catalyst (to increase the nucleophilic reactivity of the attacking group) is not necessary.

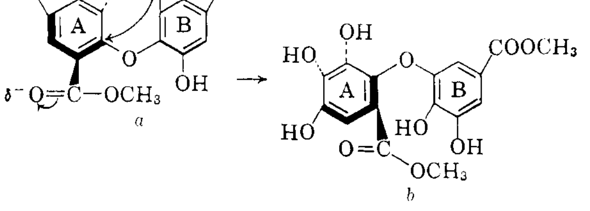
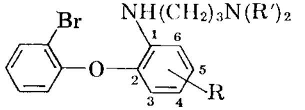


TABLE II

N,N-DIALKYL-N'-[2-(o-BROMOPHENOXY)PHENYL]-1,3-PROPANEDIAMINES (III)

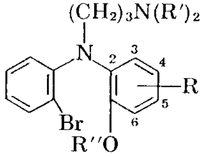


Cpd. no.	R	N(R')$_2$	% Yield	M.p., °C. or b.p., °C./mm.	Empirical formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
IIIa	5-Cl	$N(CH_3)_2$	[a]												
IIIb	5-CH_3O	$N(CH_3)_2$	40[b]	186–190/0.2[c]	$C_{18}H_{23}BrN_2O_2$	57.0	57.2	6.12	6.40	21.1	20.9			7.39	7.07
IIIc	5-Cl	$N(CH_2CH_2)_2NCH_3$	60[d]	46–48	$C_{20}H_{25}BrClN_3O$	53.7[e]	53.6	5.86	5.87	17.9	17.8	7.92	8.31	9.39	9.69
IIId	3-Cl	$N(CH_3)_2$	74[f]	180–182[g]	$C_{17}H_{22}BrCl_3N_2O$[g]	44.7	44.3	4.85	4.97	17.5	17.3	23.3	23.3	6.13	6.20
IIIe	5-CH_3O	$N(CH_2CH_2)_2NCH_3$	50[h]	104–105	$C_{21}H_{28}BrN_3O_2$	58.1	58.2	6.50	6.60	18.4	17.8			9.68	9.37
IIIf	5-CF_3	$N(CH_3)_2$	42	150–153/0.3[i]	$C_{18}H_{20}BrF_3N_2O$	51.8	52.2	4.83	5.11	19.2	18.7	[j]		6.71	6.81

[a] Reported in our first paper (see ref. 1b). [b] Yield corrected for recovery of starting material. Also obtained 31% of isomeric "phenolic" product IVb (Table III). [c] n^{25}_D 1.586. [d] Prepared with one equivalent of $NaNH_2$; with two equivalents the yield was 27% of IIIc and 26% of IVc (Table III). [e] Analysis of hemihydrate. [f] Free base; purified by chromatography. [g] Dihydrochloride. [h] Also obtained 29% of isomeric "phenolic" product IVe (Table III). [i] n^{25}_D 1.546. [j] Fluorine analysis; Calcd.: 13.7. Found: 13.8.

TABLE III

2-[N-(3-DIALKYLAMINOPROPYL)-o-BROMOANILINO]PHENOLS (IV)

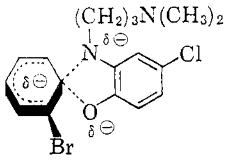


Cpd. no.	R	N(R')$_2$	R″	% Yield	Salt	M.p., °C.	Empirical formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found	Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
IVa	4-Cl	$N(CH_3)_2$	H	60–92	...	161–163	$C_{17}H_{20}BrClN_2O$	53.2	53.0	5.25	5.37	20.8	20.8	9.24	9.40	7.30	7.29
	4-Cl	$N(CH_3)_2$	H	94	HCl	215–217	$C_{17}H_{21}BrCl_2N_2O$	48.6	48.7	5.04	5.19	19.0	19.1	16.9	16.8	6.67	6.74
	4-Cl	$N(CH_3)_2$	CH_3CO	68	HCl	186–188	$C_{19}H_{23}BrCl_2N_2O_2$[a]	49.4	49.4	5.02	5.23	17.3	17.6	15.3	15.3	6.05	5.92
IVb	4-CH_3O	$N(CH_3)_2$	H	31[b]	...	157–159	$C_{18}H_{23}BrN_2O_2$	57.0	56.8	6.12	6.44	21.1	21.3			7.39	7.57
IVc	4-Cl	$N(CH_2CH_2)_2NCH_3$	H	26[c]	...	176–178	$C_{20}H_{25}BrClN_3O$	54.8	55.0	5.74	6.05	18.2	17.9	8.09	8.33	9.58	9.70
	4-Cl	$N(CH_2CH_2)_2NCH_3$	CH_3CO	35	2HCl	237–239	$C_{22}H_{29}BrCl_3N_3O_2$	47.7	47.5	5.29	5.49	14.4	14.5	19.2	19.4	7.59	7.73
IVd	6-Cl	$N(CH_3)_2$	H	52	...	182–184	$C_{17}H_{20}BrClN_2O$	53.2	53.1	5.25	5.35	20.8	21.1	9.24	9.25	7.30	7.35
IVe	4-CH_3O	$N(CH_2CH_2)_2NCH_3$	H	29[d]	...	152–153	$C_{21}H_{28}BrN_3O_2$	58.1	58.1	6.50	6.83	18.4	18.8			9.68	9.31
IVg[e]	4-Cl[e]	$N(CH_3)_2$[e]	H	78	...	145–147	$C_{17}H_{20}BrClN_2O$[e]	53.2	53.0	5.25	5.36	20.8	21.1	9.24	9.30	7.30	7.26
	4-Cl[e]	$N(CH_3)_2$[e]	H	82	HCl	171–173	$C_{17}H_{21}BrCl_2N_2O$[e]	48.6	48.2	5.04	4.98			8.44[f]	8.24	6.67	6.72
	4-Cl[e]	$N(CH_3)_2$[e]	CH_3CO[g]	75	HCl	187–189	$C_{19}H_{23}BrCl_2N_2O_2$[e]	49.4	49.8	5.02	5.37			7.67[f]	7.85	6.05	6.17

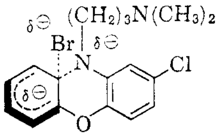
[a] CH_3CO, Calcd.: 9.31. Found: 9.29. [b] Yield corrected for recovery of starting material. Also obtained 40% of IIIb (Table II). [c] Yield corrected for recovery of starting material. Also obtained 27% of IIIc (see footnote c, Table II). [d] Also obtained 50% yield of IIIe. [e] Side chain is $-CH_2CH(CH_3)N(CH_3)_2$ (isomeric with IVa). [f] Ionic chlorine. [g] CH_3CO, Calcd.: 9.31. Found: 9.02.

ogous mechanism. Rearrangements of III to IV appear to be the first examples of Smiles rearrangements with a halogen as the activating group, which must exert its effect through a predominantly inductive mechanism. In classical Smiles rearrangements[3] the activation is usually provided by the predominantly resonance effects of an *ortho-* or *para-*nitro group. Failure of 2-(*o*-bromophenoxy)-5-chloroaniline (II, R = 5-Cl) to rearrange or cyclize (to give 2-chlorophenoxazine) upon treatment with sodium amide in boiling xylene for nineteen hours was described in our previous report.[1b] These findings suggest that *N*-alkylation must precede the rearrangement. The nitrogen anion from alkylated derivatives III would be expected to be slightly more basic (with concomitant increased nucleophilic reactivity) than that from the unalkylated derivatives II. This might contribute to the markedly different behavior observed when II and III were subjected to identical rearrangement conditions. Other factors such as steric considerations and the presence of an extra proton on the nitrogen anion of II may also be important.

The steric requirements for these rearrangements have been emphasized by Bunnett.[3] A five-membered cyclic transition state is readily formed in which the two aromatic rings (A and B) are perpendicular to each other (see VI). The nitrogen anion, with its high nucleophilic reactivity, appears to be required for rearrangement. Potassium carbonate, a weaker base which presumably did not produce this nitrogen anion in dimethylformamide, gave the phenoxazine derivative Ia in good yield from IIIa (route A_1). The steric requirements for this ring closure are probably not very different from the rearrangement. This ring closure (route A_1) would be expected to take place through a six-membered transition state (see VII) in which rings A and B are also virtually perpendicular to each other. The ring closure of IV to I (route A_2) also requires a similar six-membered cyclic transition state. Both of these ring closure routes are, therefore, sterically similar to the rearrangement.



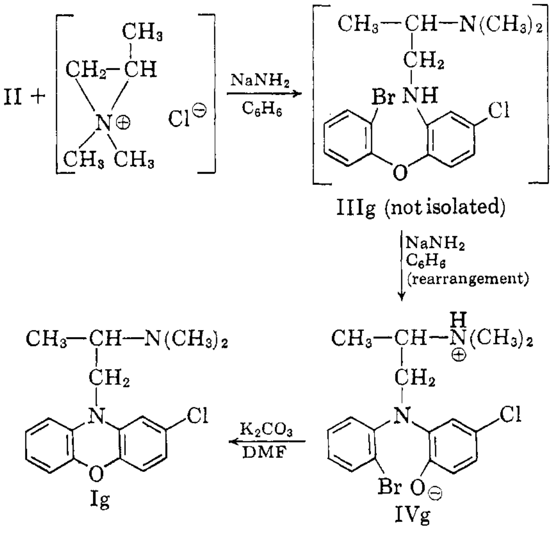
VI



VII

The apparent need for a highly nucleophilic nitrogen anion to initiate the Smiles rearrangement has already been discussed. However, the ring closure reaction of IIIa took place without such a requirement, as potassium carbonate and copper in dimethylformamide gave very good results. The alkyl–anilino group was apparently sufficiently nucleophilic to cause ring closure and the carbonate was primarily an acid acceptor to neutralize the liberated hydrogen bromide. The poor cyclization of II, (R = 5-Cl) to 2-chlorophenoxazine is also explainable along these lines. The weaker basic (and nucleophilic) character of the unsubstituted anilino group in II (R = 5-Cl) gave a less facile ring closure.[1b] It did not form a hydrochloride readily, while IIIa formed a dihydrochloride very easily.[1b] Another noteworthy point is derived from the behavior of the anion produced from IIIa with sodium amide in benzene. Evidence for competitive ring closure directly to Ia was not observed in benzene. Only the rearranged 2-(*o*-bromoanilino)phenol (IVa) was isolated in excellent yield. Electrostatic repulsions between two electron-rich moieties, the nitrogen anion and the bromine atom, may be sufficient to more effectively inhibit formation of a six-membered transition state leading to ring closure, compared with a five-membered transition state leading to rearrangement. On the other hand, neither rearrangement nor ring closure of the N-anion from II (R = 5-Cl) were obtained, following treatment with sodium amide in benzene. Failure of this rearrangement reaction is then attributed to the lesser nucleophilic reactivity of the anilino anion compared with an alkyl–anilino anion. Repulsion between the bromine and the nitrogen anion may have also prevented ring closure.

The possibility that ring closure of III (and II) with potassium carbonate in dimethylformamide actually proceeds by rearrangement and subsequent ring closure (III → IV → I) has been considered. This seems unlikely in view of published data on Smiles rearrangements[3] which indicate that a highly nucleophilic, anionic moiety is usually required as the attacking group in cases where activation at the site of displacement is minimal. Additional experimental data are needed to clarify these points.



The reaction of 2-(*o*-bromophenoxy)-5-chloroaniline with two equivalents of sodium amide and 2-chloro-*N*,*N*-dimethylpropylamine, which presumably reacted through the cyclic immonium intermediate[5] gave IVg in 78% yield. The structures of IVg and Ig are postulated as 2-dimethylaminopropyl derivatives by analogy with the reaction of 2-chloro-*N*,*N*-dimethylpropylamine and phenothiazine under similar conditions[6] to give 10-(2-dimethylaminopropyl)phenothiazine, promethazine, as proved by subsequent degradation studies.[6] IVg was first obtained in early experiments when a faulty batch of 3-chloro-*N*,*N*-dimethylpropylamine which must have contained 2-chloro-*N*,*N*-dimethylpropylamine was used. Comparison of the n.m.r. spectra of Ia and Ig (from IVg) then clearly indicated that Ig must have a methyl branch in the side chain.

The n.m.r. spectra of Ig and IVg are consistent with the structure assigned for the side chain. The CH and CH_2 patterns in Ig are readily distinguished by integration values corresponding to one and two protons, respectively. Their chemical shifts depend on their positions relative to the two nitrogen atoms which have markedly different basicities. Protons (CH or CH_2) adjacent to the less basic nitrogen atom appear downfield from those adjacent to the more basic nitrogen. Comparison with the n.m.r. spectra of promethazine and isomeric pairs of *N*-dimethylaminopropylanilines[7] and *N*-dimethylaminopropylpropionanilides[7] also supports this assignment. The n.m.r. data are summarized in Table IV.

1-Chloro- and 3-chloro-10-(3-dimethylaminopropyl)phenoxazine (Ii and Ih, respectively) were prepared according to route B discussed in our previous paper.[1b] The reaction of *o*-(3-dimethylaminopropylamino)phenol[1b] with 1,2-dichloro-3-nitrobenzene and sodium methylate in alcohol afforded the ring-closed phenoxazine derivative, 1 - chloro - 10 - (3 - dimethylaminopropyl)phenoxazine (Ii), directly without isolation of the intermediate, 2-[6-chloro-*N*-(3-dimethylaminopropyl)-2-nitroanilino]phenol.

Experimental

Melting Points.—All melting points are uncorrected and were determined in a Hershberg melting point apparatus.

Yields.—Unless otherwise specified, the yields reported are those determined after purification of the products either by chromatography, distillation and/or recrystallization to constant melting point.

***o*-Halophenyl 2-Nitrophenyl Ethers.**—Generally, *o*-halophenyl 2-nitrophenyl ethers were prepared by pyrolytic condensation of sodium *o*-bromophenolate and a 1-chloro-2-nitrobenzene derivative according to the procedure described for the preparation of *o*-bromophenyl 4-chloro-2-nitrophenyl ether.[1b] The fusion mixture was usually prepared by dissolving equimolar quantities of sodium methoxide, *o*-bromophenol and a 1-chloro-2-nitrobenzene derivative in absolute alcohol. The solution was evaporated to dryness on a water bath under vacuum, and the residue was heated at 190–200° for several hours.

1-(*o*-Bromophenoxy)-4-methoxy-2-nitrobenzene.—A 0.5-mole reaction heated at 200° for 8 hr., gave 96 g. of crude product. After distillation, 65 g. (40% yield), b.p. 184–186°/0.3 mm., $n^{25}D$ 1.622 was obtained.

Anal. Calcd. for $C_{13}H_{10}BrNO_4$: C, 48.2; H, 3.10; Br, 24.7; N, 4.32. Found: C, 48.0; H, 3.34; Br, 24.3; N, 4.27.

***o*-Bromophenyl α,α,α-Trifluoro-2-nitro-*p*-tolyl Ether.**—A 0.25-mole reaction, heated at 195° for 5 hr., gave 72% of distilled product, b.p. 139–142°/0.5 mm., $n^{25}D$ 1.562, which was analytically pure (lit.,[2] b.p. 140–160°/0.5–1.0 mm.).

***o*-Bromophenyl 2-Chloro-6-nitrophenyl Ether.**—A 0.2-mole reaction, heated at 190° for 2 hr., gave 38% of pure product, m.p. 80–82°, after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_7BrClNO_3$: C, 43.9; H, 2.15; Br, 24.3; Cl, 10.8; N, 4.26. Found: C, 44.3; H, 2.10; Br, 24.3; Cl, 10.7; N, 4.25.

2-(*o*-Bromophenoxy)anilines (II).—These intermediates were prepared by the general procedure described in our first paper[1b]: A mixture of the 2-nitrophenyl ether with approximately 4 moles of stannous chloride dihydrate in anhydrous ether was treated with anhydrous hydrogen chloride.

6-(*o*-Bromophenoxy)-*m*-anisidine.—From 0.056 mole of 1-(*o*-bromophenoxy)-4-methoxy-2-nitrobenzene the product was obtained in 56% yield after recrystallization from ethanol, m.p. 80–82°.

Anal. Calcd. for $C_{13}H_{12}BrNO_2$: C, 53.1; H, 4.11; Br, 27.2; N, 4.76. Found: C, 53.0; H, 4.45; Br, 27.4; N, 5.00.

6-(*o*-Bromophenoxy)-α,α,α-trifluoro-*m*-toluidine.—From 0.16 mole of *o*-bromophenyl α,α,α-trifluoro-2-nitro-*p*-tolyl ether the product was obtained by treating the crude residue with water and extraction into ether. The yield of distilled product, b.p. 110–118°/0.45 mm., $n^{25}D$ 1.569, was 90%. This compound was recently prepared by reduction with iron and acetic acid (lit.,[2] b.p. 140–150°/0.3 mm.).

2-(*o*-Bromophenoxy)-3-chloroaniline and Hydrochloride.—From 0.04 mole of *o*-bromophenyl 2-chloro-6-nitrophenyl ether the pure hydrochloride, m.p. 175–190°, was obtained by passing hydrogen chloride into an ethereal solution of the base followed by recrystallization from alcohol–ether (70% yield). The free base, m.p. 64–67°, was reisolated from the hydrochloride and recrystallized from ethanol.

Anal. Calcd. for $C_{12}H_9BrClNO$: C, 48.3; H, 3.04; Br, 26.8; Cl, 11.9; N, 4.69. Found: C, 48.4; H, 3.18; Br, 26.6; Cl, 12.1; N, 4.66.

***N*,*N*-Dialkyl-*N*′-[2-(*o*-bromophenoxy)phenyl]-1,3-propanediamines (III; Table II).**—The *N*,*N*-dialkyl-*N*′-[2-(*o*-bromophenoxy)phenyl]-1,3-propanediamines were prepared by treating 2-(*o*-bromophenoxy)anilines with one molar equivalent of sodium amide and 3-chloro-*N*,*N*-dimethylpropylamine[8] or 1-(3-chloropropyl)-4-methylpiperzine[9] in benzene as described in our first paper.[1b] When more than one equivalent of sodium amide was used, in certain cases, the isomeric 2-[*N*-(3-dialkylaminopropyl)-2-bromoanilino]phenols (IV; Table III) were also produced.

2-[*N*-(3-Dialkylaminopropyl)-2-bromoanilino]phenols (IV; Table III).—The 2-[*N*-(3-dialkylaminopropyl)-2-bromoanilino]phenols (IV) were produced together with the isomeric *N*,*N*-dialkyl-*N*′-[2-(*o*-bromophenoxy)phenyl]-1,3-propanediamines (III; Table II) under the conditions described for the preparation of the latter (III), but employing two or more molar equivalents of sodium amide. Alternately, the

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(5) E. M. Schultz, C. M. Robb, and J. M. Sprague, *J. Am. Chem. Soc.*, **69**, 188 (1947).

(6) P. Charpentier, *Compt. rend.*, **225**, 306 (1947).

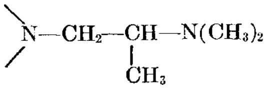
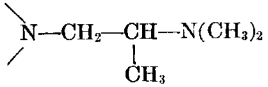
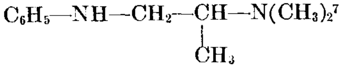
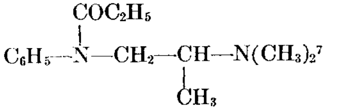
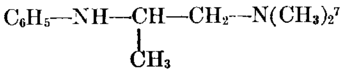
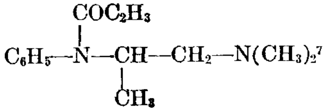
(7) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 476 (1961).

(8) A. Marxer, *helv. Chim. Acta*, **24**, 209E (1941).

(9) O. Hromatka, I. Grass, and F. Sauter, *Monatsh.*, **87**, 701 (1956).

TABLE IV

N.M.R.[a] CHARACTERISTICS: τ VALUES,[b] DESCRIPTION OF MULTIPLICITY, COUPLING CONSTANT (J)[c]

Compound (side chain)	$-CH_2-$ (2 protons)[d]	$-\overset{|}{CH}-$ (1 proton)	$-N(CH_3)_2$ (6 protons)	$>CH-CH_3$ (3 protons)	Other features
Ig,  $>N-CH_2-\underset{\underset{CH_3}{\vert}}{CH}-N(CH_3)_2$	6.55,[e] doublet, J = 6 c.p.s.	6.7–7.2,[f] multiplet (4 or more peaks)	7.75, singlet	9.02, doublet, J = 6 c.p.s.	Aromatic protons, 3.4–3.6
Promethazine[6]  $>N-CH_2-\underset{\underset{CH_3}{\vert}}{CH}-N(CH_3)_2$	6.0–6.6, multiplet (2 quartets)	6.7–7.2, multiplet (4 or more peaks)	7.64, singlet	8.93, doublet, J = 7 c.p.s.	Aromatic protons, 2.8–3.1
 $C_6H_5-NH-CH_2-\underset{\underset{CH_3}{\vert}}{CH}-N(CH_3)_2$[7]	Complex peak (3 protons), 6.9–7.6, greatest intensity at 7.12		7.79, singlet	9.07, doublet, J = 4 c.p.s.	Aromatic protons, 2.8–3.6; NH, 5.7, wide peak
 $C_6H_5-\overset{\overset{COC_2H_5}{\vert}}{N}-CH_2-\underset{\underset{CH_3}{\vert}}{CH}-N(CH_3)_2$[7]	6.1–6.4, quartet	7.0–7.5, multiplet (4 or more peaks)	7.80, singlet	9.08, doublet, J = 6 c.p.s.	Aromatic protons, 2.5–2.9; CH_3 (propionyl), 8.97, triplet, J = 7.5 c.p.s. CH_2 (propionyl), 7.7–8.2, multiplet
 $C_6H_5-NH-\underset{\underset{CH_3}{\vert}}{CH}-CH_2-N(CH_3)_2$[7]	7.3–8.1, multiplet (4 or more peaks)	6.3–6.8, multiplet (4 or more peaks)	7.79, singlet	8.83, doublet, J = 6 c.p.s.	Aromatic protons, 2.7–3.5
 $C_6H_5-\overset{\overset{COC_2H_5}{\vert}}{N}-\underset{\underset{CH_3}{\vert}}{CH}-CH_2-N(CH_3)_2$[7]	7.3–8.3, multiplet (approx. 8 peaks), superimposed with propionyl CH_2	4.6–5.1, multiplet (4 or more peaks)	7.75, singlet	8.97, doublet, J = 7 c.p.s.	Aromatic protons, 2.5–3.0; CH_3 (propionyl), 9.00, triplet, J = 7.5 c.p.s. CH_2 (propionyl), 7.3–8.3, multiplet, superimposed with side chain CH_2

[a] Spectra were measured on Varian Associates HR-60 and A-60 spectrometers at 60 Mc. (approx. 20% in $CDCl_3$) and calibrated against tetramethylsilane. [b] P.p.m. relative to tetramethylsilane (τ = 10.00). [c] C.p.s. at 60 Mc. [d] Relative values obtained from electronic integration of area under the curve for the appropriate regions. [e] Single τ values represent chemical shifts for the origin of the well defined singlet, doublet, and triplet peaks. [f] Complex and partially obscured multiplet peaks are described by the range of τ values corresponding to integration for the appropriate number of protons.

"phenolic" isomers (IV) were prepared from III with one or more equivalents of sodium amide.

2-[*o*-Bromo-*N*-(3-dimethylaminopropyl)anilino]-4-chlorophenol (IVa). (a) ***N*-Alkylation of 2-(*o*-Bromophenoxy)-5-chloroaniline and Two Equivalents of Sodium Amide.**—A mixture of 36.2 g. (0.121 mole) of 2-(*o*-bromophenoxy)-5-chloroaniline,[1b] 10.5 g. (0.243 mole) of sodium amide (90% pure) and 14.7 g. (0.121 mole) of 3-chloro-*N*,*N*-dimethylpropylamine in 400 ml. of anhydrous benzene was allowed to react under the general conditions previously described.[1b] The cooled reaction mixture was filtered and the insoluble product (A) was washed with ether on the filter.[10] The ether washings were added to the benzene filtrate and the solution was evaporated to dryness. The residue (B) was saved. The product (A), free of ether, was added in small portions[10] to 600 ml. of rapidly stirred water. After 1.5 hr. the crude product (IVa) was collected by filtration and washed with water until washings were no longer alkaline, and air-dried. The yield was 31 g. (67%), m.p. 158–160°. Additional product was obtained from residue B as follows: Residue B was triturated with 300 ml. of cold ether and filtered and the precipitate was treated with water as above to give an additional 2.6 g. of IVa. The ethereal filtrate was treated with 200 ml. of 1 *N* hydrochloric acid and the mixture kept overnight at room temperature. IVa hydrochloride, 5.6 g., separated and was collected (the acidic filtrate, C, consisting of ether and aqueous layers, was saved) and converted to the free base by the addition of excess potassium carbonate to a rapidly stirred suspension of the salt. An additional 4.7 g. of IVa was obtained. The total crude yield was 38.3 g. (82.5%). Recrystallization from 250 ml. of alcohol afforded 28 g. (73% recovery) of analytically pure product, m.p. 161–163°. Additional material was recoverable from the mother liquor.

The ether phase, from filtrate C, was separated, washed with water, dried, and evaporated. A residue, 0.6 g., of unchanged 2-(*o*-bromophenoxy)-5-chloroaniline, identified by its infrared spectrum, was collected. The aqueous acidic phase from filtrate C was washed with ether and made alkaline with potassium carbonate. The precipitate was extracted into two 150-ml. portions of ether, from which 3.5 g. (7.5% yield) of *N'*-[2-(*o*-bromophenoxy)-5-chlorophenyl]-*N*,*N*-dimethyl-1,3-propanediamine (IIIa)[1b] was obtained on evaporation. This material was the only product obtained when the above reactants were allowed to react in the presence of *one* equivalent of sodium amide.[1b]

Compounds IVb, c, e were prepared by analogous procedures, and the alkylated but unrearranged intermediates. IIIb, c, e were also isolated from their respective reaction mixtures (see Tables II and III for details).

(b) **From *N'*-[2-(*o*-Bromophenoxy)-5-chlorophenyl]-*N*,*N*-dimethyl-1,3-propanediamine and One Equivalent of Sodium Amide.**—A mixture of 11.2 g. (0.0292 mole) of *N'*-[2-(*o*-bromophenoxy)-5-chlorophenyl]-*N*,*N*-dimethyl-1,3-propanediamine (IIIa),[1b] and 1.26 g. (0.0292 mole) of sodium amide (90% pure) in 125 ml. of anhydrous benzene was allowed to react as previously described.[1b] The insoluble product was filtered, washed on the filter with benzene, and air-dried. The infrared spectrum showed weak absorption in the 3.7–4.3-μ region, indicating that the sodium salt of IVa was partially hydrolyzed during work-up. The benzene filtrates were combined and evaporated under vacuum. Trituration of the residue with 50 ml. of cold ether and filtration afforded a second crop. The two fractions were combined and hydrolyzed in water by stirring for 0.5 hr. IVa was collected and air-dried to give 10.1 g. (90% yield) of material, m.p. 159–161°. Addition of 50 ml. of 1 *N* hydrochloric acid to the ether filtrate afforded 0.3 g. of the hydrochloride corresponding to 0.27 g. of free base. Total crude yield was 92%. The recrystallized product melted at 161–163°.

Compound IVd was prepared in an analogous fashion from the purified intermediate IIId obtained by alkylation using one mole of sodium amide (see Tables II and III for details).

2-[*o*-Bromo-*N*-(3-dimethylaminopropyl)anilino]-4-chlorophenol Hydrochloride.—A solution of the free base (IVa), 5.2 g. (13.5 mmoles) in 150 ml. of ether was quickly extracted with two 100-ml. portions of 1 *N* hydrochloric acid. The combined acidic extracts soon deposited the insoluble hydrochloride salt (Table III). It was purified by recrystallization from alcohol.

2-[*o*-Bromo-*N*-(3-dimethylaminopropyl)anilino]-4-chlorophenol Acetate Hydrochloride.—A mixture of 4.0 g. (10.2 mmoles) of 2-[*o*-bromo-*N*-(3-dimethylaminopropyl)anilino]-4-chlorophenol (IVa) and several drops of pyridine in 30 ml. of acetic anhydride was heated on a steam bath for 1.5 hr. The reaction mixture was evaporated to dryness, the residue was dissolved in alcohol, and the solution was again evaporated to dryness. The residue was taken up in 15 ml. of alcohol and treated with one equivalent of alcoholic hydrogen chloride. Ether was added to the cloud point (approximately 90 ml.). On standing for several days, 3.9 g. of product, m.p. 180–184°, was obtained, and recrystallized once again from alcohol–ether.

O-Acetates from IVc and IVg were obtained in a similar manner (see Table III).

2-[*o*-Bromo-*N*-(2-dimethylamino-2-methylethyl)anilino]-4-chlorophenol (IVg).—A mixture of 2-(*o*-bromophenoxy)-5-chloroaniline, 17.0 g. (0.057 mole), and 7.4 g. (0.171 mole) of sodium amide (90% pure under mineral oil) in 125 ml. of anhydrous benzene was heated under reflux and stirred for 2.5 hr., and then treated with 9.0 g. (0.057 mole) of 2-chloro-*N*,*N*-dimethylpropylamine hydrochloride in small portions. Heating and stirring were continued for another 18 hr. The reaction mixture was cooled and filtered. The insoluble product was washed with ether on the filter, and air-dried to give IVg (as Na salt). A sample of this salt was recrystallized from alcohol, m.p. 229–232° (anal. pure). Hydrolysis of IVg (Na salt) in water and recrystallization from 150 ml. of alcohol afforded the free base (Table III).

2-Chloro-10-(3-dimethylaminopropyl)phenoxazine Hydrochloride (Ia). From IVa (Route A_2). (a)—A mixture of 9.6 g. (0.025 mole) of IVa, 4.6 g. (0.033 mole) of potassium carbonate and 1.0 g. of copper powder in 100 ml. of *N*,*N*-dimethylformamide was heated under reflux for 48 hr. The cooled reaction mixture was filtered and the filtrate was evaporated to dryness under vacuum. The residue, 8.5 g., was dissolved in 100 ml. of ether and washed with water; sodium chloride was used to break the emulsion, and after most of the phase was separated, the remaining mixture was filtered through a "Celite" (diatomaceous earth) bed. The filtrate was washed several times with water and dried over anhydrous magnesium sulfate. Evaporation of the ethereal solution afforded 7.0 g. of substantially pure free base. A portion was converted to the hydrochloride which was recrystallized twice from alcohol–ether with charcoal (see Table I). Mixed melting points with samples prepared[1b] from routes A_1 and B were not depressed. The infrared spectra of the base and hydrochloride were identical with the corresponding spectra of these materials previously reported.[1b]

This procedure was also used for the preparation of compounds I, b–e and Ig (see Table I).

(b) **From IVa and Potassium Carbonate in Dimethylformamide without Copper.**—Heating under reflux 2.5 g. (6.5 mmoles) of IVa and 0.45 g. (3.3 mmoles) of potassium carbonate in 25 ml. of dimethylformamide for 1 hr. afforded approximately 85% of Ia (free base), estimated by ultraviolet at $\lambda_{max}^{CH_3OH}$ 328 mμ. No change in yield was observed (by UV) after 7 hr. of heating. The development of absorption maxima at 241 and 328 mμ (characteristic of Ia)

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[10] Anhydrous ether was used since the crude product contained some unaltered sodium amide. As a safety precaution the work-up of this reaction was done in a hood behind a protective shield.

and the disappearance of maxima at 275 mμ (shoulder) and 296 mμ (characteristic of IVa) were observed after varied heating periods.

(c) **From IVa (Na Salt) in Dimethylformamide without Copper.**—Heating 3.4 g. (8.8 mmoles) of IVa and 0.40 g. (9.2 mmoles) of sodium amide overnight in 40 ml. of benzene afforded only the sodium salt of IVa. The solvent was decanted from the cooled reaction mixture, and IVa (sodium salt) was heated under reflux in 25 ml. of dimethylformamide. After 1 hr. of heating approximately 65% of Ia (free base) was formed, estimated by ultraviolet at $\lambda_{max}^{CH_3OH}$ 328 mμ. Approximately 80% of Ia was formed after 4.5 hr. of heating. The reaction mixture was heated for 23 hr., but no significant change in yield was observed after 7 hr. The product, Ia (free base), 2.4 g. (91% yield) was isolated from the reaction mixture as described above.

(d) **From IVa and Potassium Carbonate in Benzene without Copper.**—IVa, 2.5 g. (6.5 mmoles), and 0.45 g. (3.3 mmoles) of potassium carbonate were heated under reflux in 25 ml. of benzene. After 4.5 hr. of heating no conversion to Ia was observed (by ultraviolet). Approximately 80% of Ia was formed after 22 hr. of heating, estimated by ultraviolet at $\lambda_{max}^{CH_3OH}$ 328 mμ. There was no significant change in yield after 41 hr. of heating.

(e) **From *N*′-[2-(*o*-Bromophenoxy)-5-chlorophenyl]-*N*,*N*-dimethyl-1,3-propanediamine[1b] (IIIa); Route A$_1$ without Copper.**—IIIa, 5.2 g. (0.014 mole) and 2.0 g. (0.015 mole) of potassium carbonate in 40 ml. of dimethylformamide were heated under reflux with stirring for 48 hr.[11] The reaction mixture was worked up as described above (see a) to give 3.8 g. (90% yield) of Ia (free base). Infrared and ultraviolet spectra of this product as well as the hydrochloride were identical with those prepared by the above procedures.

3-Chloro-10-(3-dimethylaminopropyl)phenoxazine Hydrochloride (Ih), from Va; Route B.[1b]—A reaction mixture of 26.7 g. (0.075 mole) of *o*-(3-dimethylaminopropylamino)-phenol dihydrobromide,[1b] 14.4 g. (0.075 mole) of 1,4-dichloro-2-nitrobenzene and 12.8 g. (0.225 mole) of sodium methylate (95% pure) in 500 ml. of absolute alcohol was heated under reflux for 20 hr. and the cooled reaction mixture was filtered. The filtrate was evaporated to dryness, and the residue was dissolved in 500 ml. of ether and was extracted with 500 ml. of 1 *N* hydrochloric acid in several portions. The combined acidic extracts were washed with ether, made alkaline with potassium carbonate, and extracted several times with ether. The combined ethereal extracts were washed with water, dried over magnesium sulfate, and evaporated to dryness. The residual oil, 9.2 g. (40% yield), was dissolved in 200 ml. of petroleum ether (b.p. 60–90°) and allowed to stand at room temperature for 2 days. The supernatant was decanted from 0.3 g. of a black tar, and the clear solution was cooled for 0.5 hr. in a Dry Ice–acetone bath. This caused a red crystalline solid to separate (Va; see below). The cooled petroleum ether solution was decanted and the supernatant allowed to stand for several days (no more of Va separated during this time). The solution was evaporated to dryness under vacuum. The residual oil was dissolved in ether, decanted from a small amount of an insoluble gum and again evaporated to dryness. The residue, 7.1 g. (31% yield), was distilled and 4.1 g. of purified base was obtained (see Table I).

Compound Ii was also obtained by an analogous procedure (see Table I).

***o*-[4-Chloro-*N*-(3-dimethylaminopropyl)-2-nitroanilino]-phenol (Va).**—The red crystalline solid obtained during the synthesis of Ih (above) was recrystallized from 5 ml. of hot alcohol with a charcoal treatment and 100 ml. of petroleum ether (b.p. 60–90°) to give 1.3 g. (4.7% yield) of crystalline product, m.p. 167–172°. A second recrystallization from 10 ml. of alcohol yielded 0.9 g. (3.3%) of analytically pure material, m.p. 172–173°.

Anal. Calcd. for $C_{17}H_{20}ClN_3O_3$: C, 58.4; H, 5.76; Cl, 10.1; N, 12.0. Found: C, 58.1; H, 5.92; Cl, 10.4; N, 11.8.

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[11] The optimum reaction time for this cyclization was not studied in detail as that from IVa. The actual time for cyclization may be much less, paralleling IVa → Ia.

An Analog Computer for Pyrrole, Porphyrin, and Chlorophyll Strains[1]

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An analog computer made up of specially prepared springs has been constructed to examine distortions in the pyrrole and porphyrin systems. The model permits estimation of changes in bond angles produced by changes in hybridization, those caused by the introduction of a small chelating atom into the center of the porphyrin system, the sliding motion produced by van der Waals repulsions of the central hydrogens, the "wrist action" caused by the introduction of an N-methyl group in the porphyrin ring, and the distortions produced by closure of the isocyclic ring in chlorophyll derivatives.

The usual Stuart-Brieglieb models of porphyrins are adequate to indicate that crowding exists in the γ-position of chlorophyll porphyrins and some chlorins. These models are incapable of showing tensions and warpages in molecules due to strains, however. To permit an assessment of the strains caused by the introduction of large and small groups and by the closure of the isocyclic ring in chlorophyll, phylloerythrin, and similar compounds, a simple analog computer has been constructed.

The principle used in the construction of our computer is based on observations by Kettering, Shutts, and Andrews.[2] The vibrating models

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[1] Porphyrin Studies. XXIII. Paper XXII, P. E. Wei, A. H. Corwin, and R. Arellano, *J. Org. Chem.*, **27**, 3344 (1962).

[2] C. F. Kettering, L. W. Shutts, and D. H. Andrews, *Phys. Rev.*, **36**, 531 (1930).