partial hydrolysis of this isoquinolone derivative to *o*-acetylphenylacetic acid.

o-Acetylphenylacetic acid azine. The keto acid, 0.6 g., reacted with hydrazine hydrochloride, 0.4 g., with 0.8 g. of sodium acetate present, to give, after recrystallization from ethanol, 0.38 g. of *o*-acetylphenylacetic acid azine, m.p. 209–210°.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.15; H, 5.68. Found: C, 67.98; H, 5.64.

When the azine was heated at 220°, gas evolution occurred, and a low yield of colorless crystals was obtained by chromatography from the viscous residue. The product was identified by mixture melting point as 1-methyl-3H-2,3-benzodiazepin-4(5H)one.

o-Acetylphenylacetic acid 1-methyl-1-phenylhydrazone. 1-Methyl-1-phenylhydrazine was prepared by nitrosating *N*-methylaniline and subsequently reducing with zinc and acetic acid.[3] *o*-Acetylphenylacetic acid and 1-methyl-1-phenylhydrazine were mixed and allowed to stand for 8 hr. The resulting viscous mixture was extracted with ether and the ether solution was extracted with 2% sodium hydroxide solution. Acidification gave a yellow solid, *o*-acetylphenylacetic acid 1-methyl-1-phenylhydrazone, which was recrystallized from aqueous ethanol, m.p. 117–118°. Attempts to produce this compound by reaction in buffered aqueous solution were not successful.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.35; H, 6.39; neut. equiv., 282. Found: C, 72.01; H, 6.37; neut. equiv., 272.

Attempts to cyclize this phenylmethylhydrazone to an aminoisoquinolone were not successful.

o-Acetylphenyldimethylacetic acid. 3,3-Dimethyl-1-indanone was prepared by the method of Koelsch and LeClaire.[4] Upon several repetitions, the required intermediate oxidation of methyl β-phenylisobutyl ketone to β-phenylisovaleric acid was not uniformly satisfactory.

3,3-Dimethyl-1-indanone was converted to 1,3,3-trimethyl-1-indanol (b.p. 104–108°/25 mm.), by reaction with methylmagnesium iodide and acidification of the resulting alkoxide. The indanol (0.089 mole) was dehydrated to 1,1,3-trimethylindene, b.p. 196–197°, 12.4 g., by refluxing for 15 hr. with 25% sulfuric acid. Recovery of the product employed steam distillation and extraction with benzene.

1,1,3-Trimethylindene (0.079 mole) was added dropwise during 1 hr. to a stirred solution, at 55°, of 24.6 g. of sodium dichromate and 68 ml. of concd. sulfuric acid in 375 ml. of water. Stirring was continued until all the dichromate had reacted (8 hr.). The product separated as an oil which was filtered, washed with water, and allowed to stand in air until solidification appeared to be complete. *o*-Acetylphenyldimethylacetic acid was obtained by precipitation with excess hydrochloric acid from a solution of the crude product in 5% aqueous sodium hydroxide; yield, 0.026 mole, m.p. 105–107°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.80, H, 6.80. Found: C, 69.56; H, 6.68.

The attempt to synthesize the phenylhydrazone of this acid by the standard procedure gave light yellow plates, m.p. 179–181°, which were apparently *o*-acetylphenyldimethylacetic acid phenylhydrazone phenylhydrazide, most probably the β-phenylhydrazide.

Anal. Calcd. for $C_{24}H_{26}N_4O$: C, 74.60; H, 6.74; N, 14.51. Found: C, 74.36; H, 6.79; N, 14.13.

Attempts to convert the phenylhydrazone phenylhydrazide to a benzodiazepinone were not successful.

Methyl o-acetylphenylacetate. *o*-Acetylphenylacetic acid was esterified by refluxing for 4 hr. a solution of 5.0 g. in 55 ml. methanol with 5 drops of concd. sulfuric acid. Removal of methanol by distillation left an oil residue which solidified under water and was recrystallized from aqueous ethanol; yield, 1.4 g., m.p. 57–59°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.70; H, 6.25. Found: C, 68.58; H, 6.33.

o-Acetylphenylacetic acid hydrazone hydrochloride. *o*-Acetylphenylacetic acid phenylhydrazone was refluxed in methanol, with a trace of sulfuric acid, for 4.5 hr. Solvent was removed by distillation and hydrazine hydrate in equivalent amount was added, dissolved in methanol. The resulting solution was refluxed for 4 hr. Excess hydrochloric acid caused separation of a white solid, m.p. 200° dec., which was not identified. From the filtrates a product was separated, m.p. 194° dec., which was identical with previously synthesized *o*-acetylphenylacetic acid hydrazone hydrochloride (m.p. 202–205° dec.), mixture m.p. 202° dec.

ANN ARBOR, MICH.

(3) W. W. Hartman and L. J. Roll, *Org. Syntheses*, XIII, 66, 82 (1933).

(4) C. F. Koelsch and C. D. LeClaire, *J. Org. Chem.* 6, 516 (1941).

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION, SMITH KLINE & FRENCH LABORATORIES]

Analogs of Phenothiazines. II.[1] Phenoxazine and Phenoselenazine Analogs of Phenothiazine Drugs

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Received July 27, 1960

A general synthesis of 2-substituted phenoxazines was developed. The preparation of phenoselenazine and phenoxazine analogs of pharmacologically active 10-aminoalkylphenothiazines is reported. Spectral data on the intermediate 2-substituted phenoxazines and phenoselenazines are reported.

During the past decade a number of phenothiazine derivatives have been found to be useful therapeutic agents (see Table I). A study of compounds related to the potent antihistaminic drug, promethazine, led to the discovery of the tranquilizing and antiemetic properties of promazine and chlorpromazine.[2]

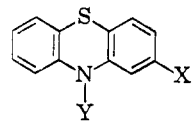
More potent therapeutic agents have been derived from the latter drug by replacement of the

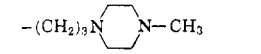
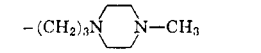
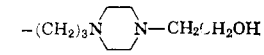
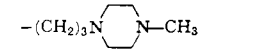
(1) Presented in part at 138th National Meeting, American Chemical Society, New York, N. Y., Sept. 12, 1960. Paper I of this series: P. N. Craig, B. M. Lester, A. J. Saggiomo, C. Kaiser, and C. L. Zirkle, *J. Org. Chem.*, **26**, 135 (1961).

(2) P. Viaud, *J. Pharm. and Pharmacol.*, **6**, 361 (1954).

TABLE I

10-AMINOALKYLPHENOTHIAZINE DRUGS

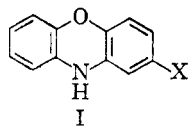


No.	X	Y	Generic Name
1	H	$-CH_2CH(CH_3)N(CH_3)_2$	Promethazine
2	H	$-(CH_2)_3N(CH_3)_2$	Promazine
3	H	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	Trimeprazine
4	Cl	$-(CH_2)_3N(CH_3)_2$	Chlorpromazine
5	Cl		Prochlorperazine
6	$SO_2N(CH_3)_2$		Thioperazine
7	Cl		Perphenazine
8	CF_3	$-(CH_2)_3N(CH_3)_2$	Trifluopromazine
9	CF_3		Trifluoperazine

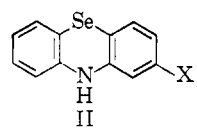
chlorine atom by other groups and/or the dimethylamino group by piperazine moieties; e.g., compounds 5–9,[3] Table I.

The pharmacology of some of these compounds has been reviewed by Viaud.[2]

As part of an extensive investigation of the structural requirements for effective tranquilizing and antiemetic activities in this class of compounds, we prepared a series of analogs of the phenothiazine derivatives, listed above, derived from phenoxazines Ia — Id and phenoselenazines IIa — IIc.



I



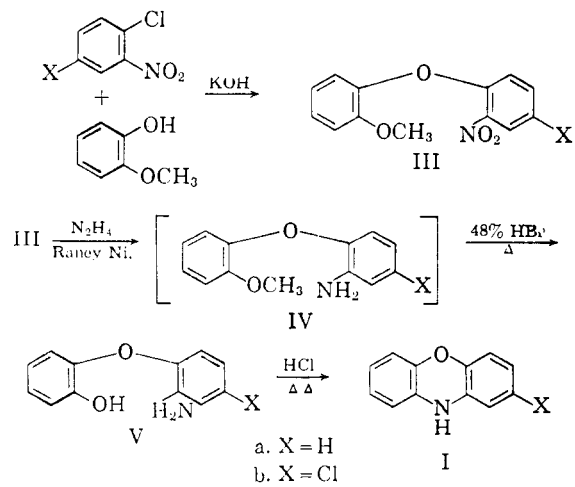
II

a. X = H
b. X = Cl
c. X = CF_3
d. X = $SO_2N(CH_3)_2$

The literature on aminoalkyl derivatives of phenoxazine and phenoselenazine is fragmentary. Statements have been made that 10-(2-dimethylaminoethyl)phenoxazine has a low order of antihistaminic activity[4] and that "selenium analogs of promethazine and chlorpromazine show antihistaminic activity similar to that of their sulfur analogs."[5] However, chemical characterization of these derivatives or of 2-chlorophenoxazine (Ib) has not been reported. One 10-substituted phenoxazine, 10-β-(imidazolylethyl)phenoxazine, has been described in the patent literature.[6] 2-Chlorophenoselenazine (IIb) has been described by Müller, Buu-Hoï, and Rips.[5]

Although several methods for the preparation of phenoxazine have been reported,[7] we found them to be incapable of extension to the preparation of substituted phenoxazines. Therefore, alternative routes were devised for the preparation of these compounds. A route based upon the work of Cullinane, Davey and Padfield[7] was found to give consistent results for the preparation of phenoxazine and 2-chlorophenoxazine (Scheme A).

SCHEME A



(3) P. N. Craig, E. A. Nodiff, J. J. Lafferty, and G. E. Ullyot, *J. Org. Chem.*, 22, 709 (1957); H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, 79, 4375 (1957). Handbook of Toxicology, Vol. IV, p. 51. W. B. Saunders Co., 1959; R. M. Jacob and G. L. Regnier, U. S. Patent 2,894,947 (July 14, 1959); R. J. Horclois, U. S. Patent 2,902,484 (Sept. 1, 1959).

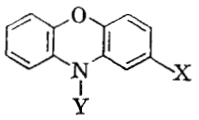
(4) D. Bovet and F. Bovet-Nitti, *Structure et Activité pharmacodyamique des Médicaments du Systéme Nerveux Végétatif*, S. Karger and S. A. Bale, 1948, p. 773.

(5) P. Müller, N. P. Buu-Hoï, and R. Rips, *J. Org. Chem.*, 24, 37 (1959) [See ref. 2].

(6) K. Miescher and A. Marxer, U. S. Pat. 2,485,212 (Oct. 18, 1949).

TABLE II

10-AMINOALKYLPHENOXAZINES

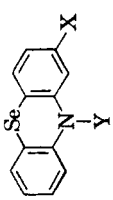


No.	Y	X	Yield, %	B.P. (mm.)	Salt	M.P.	Empirical Formula	Carbon		Hydrogen	
								Calcd.	Found	Calcd.	Found
1	$-CH_2CH_2N(CH_3)_2$	H	97	152–154 (0.2)	HCl	239–240	$C_{16}H_{19}ClN_2O$	66.08	66.12	6.59	6.53
2	$-(CH_2)_3N(CH_3)_2$	H	79	155 (0.2)	HCl	97–98	$C_{17}H_{21}ClN_2O$	66.98	66.98	6.94	7.22
3	$-CH_2CH(CH_3)N(CH_3)_2$[a]	H	90[b]	151–158 (0.2)	HCl	181–183	$C_{17}H_{21}ClN_2O$	66.98	67.28	6.94	6.99
4	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	H	96	165–170 (2.0)	HCl	140–148	$C_{18}H_{23}ClN_2O \cdot {}^1/_4H_2O$[d]	66.86	67.05	7.33	7.54
5	$-(CH_2)_3N(CH_3)_2$	Cl	85	178–180 (0.3)	HCl	222.5–223.5	$C_{17}H_{20}Cl_2N_2O$	60.18	60.14	5.94	5.68
6	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	Cl	86	190–195 (1)	HCl	190–194	$C_{18}H_{22}Cl_2N_2O$	61.19	61.11	6.28	6.46
7	$-(CH_2)_3$-N⟨ ⟩N-CH_3	Cl	68	215–225 (33.5)	Dimaleate	194–195	$C_{28}H_{32}ClN_3O_9$	56.99	57.10	5.47	5.71
8	$-(CH_2)_3N(CH_3)_2$	CF_3	68	165–180 (0.2–1)	HCl	230–236	$C_{18}H_{20}ClF_3N_2O$	57.99	57.91	5.41	5.58
9	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	CF_3	97	148–150 (0.5)	HCl	209–214	$C_{19}H_{21}ClF_3N_2O$	58.99	58.76	5.73	6.04
10	$-(CH_2)_3$-N⟨ ⟩N-CH_3	CF_3	80	205 (0.5)	Di-HCl	255 dec.	$C_{21}H_{26}Cl_2F_3N_3O$	54.31	54.02	5.64	5.94
11	$-(CH_2)_3$-N⟨ ⟩NH	CF_3	47	193–196 (0.0025)	—	—	$C_{20}H_{22}F_3N_3O$	63.65	63.33	5.88	6.19
								Nitrogen Calcd.: 8.46. Found: 8.68			
12	$-(CH_2)_3$-N⟨ ⟩N-CH_2CH_2OH	CF_3	90[c]	—	Di-HCl	237 dec.	$C_{22}H_{29}Cl_2F_3N_3O_2$	53.44	53.42	5.71	6.03
13	$-(CH_2)_3$-N⟨ ⟩N-CH_3	$SO_2N(CH_3)_2$	49	—	Dimaleate	202–203	$C_{30}H_{38}N_4O_{11}S$	54.37	54.60	5.78	6.10
14	$-(CH_2)_3$-N⟨ ⟩N-CH_2CH_2OH	$SO_2N(CH_3)_2$	23	—	Dimaleate	164–165	$C_{31}H_{40}N_4O_{12}S$	53.75	53.40	5.82	6.40
								Nitrogen Calcd.: 8.09. Found: 8.02			

[a] This compound is assumed to have structure shown by analogy to the phenothiazine analog [compare P. Charpentier *et al.*, *Compt. rend.*, **232**, 2232 (1951)]. [b] Only 33% obtained in crystalline form. [c] Prepared from preceding compound. [d] Paper chromatogram indicated purity to be 99%.

TABLE III

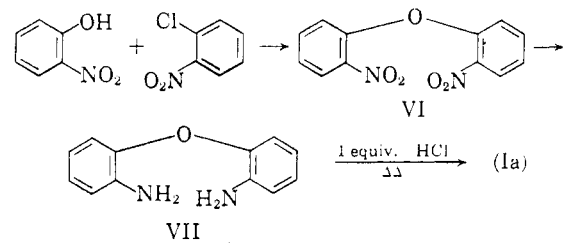
10-AMINOALKYLPHENOSELENAZINES



Y	X	Yield, %	B.P., Mm.	Salt	M.P.	Empirical Formula	Carbon		Hydrogen	
							Calcd.	Found	Calcd.	Found
$-(CH_2)_3N(CH_3)_2$	H	88	185–190 (0.2)	Maleate	134–135	$C_{21}H_{24}N_2O_4Se$	56.38	56.56	6.26	6.52
$-(CH_2)_3N(CH_3)_2$	Cl	82	204–207 (0.3–0.4)	Maleate	129–130	$C_{21}H_{23}ClN_2O_4Se$	52.34	52.57	4.81	4.79
$-(CH_2)_3$-N(CH$_3$)-CH$_3$	Cl	75	210–215 (0.08)	Di-HCl	229–230.5	$C_{20}H_{26}Cl_3N_3Se$	48.65	48.54	5.31	5.60
$-(CH_2)_3N(CH_3)_2$	CF_3	47	165–170 (0.1)	HCl	182.5–183.5	$C_{13}H_{20}ClF_3N_2Se$	49.61	49.63	4.63	4.63
$-(CH_2)_3$-N(CH$_3$)-CH$_3$	CF_3	25	198–210 (0.05–0.10)	Dimaleate	182–183	$C_{29}H_{32}F_3N_3O_8Se$	50.73	50.64	4.70	4.83

A second, but highly unsatisfactory, procedure (Scheme B) for preparing phenoxazine involved ring closure of 2,2′-diaminodiphenyl ether (VII), an approach that has been used for the synthesis of carbazole and other nitrogen heterocycles.

SCHEME B

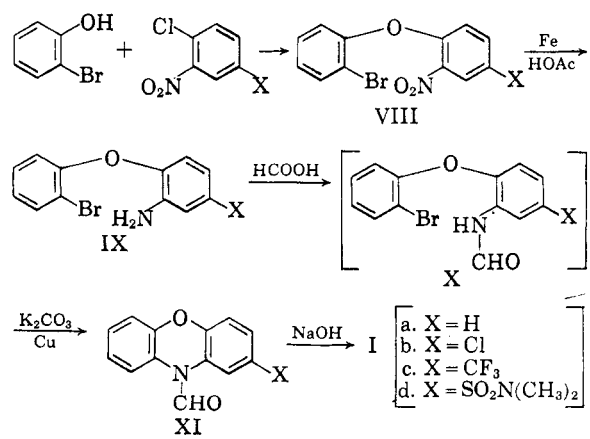


The condensation of 2-chloronitrobenzene with 2-nitrophenol gave the dinitrodiphenyl ether VI in very poor yield as reported by Cullinane, *et al.*[7] Reduction of VI afforded the diamine VII and ring closure of the latter, accomplished by heating its monohydrochloride at 250° in a Carius tube, gave phenoxazine (Ia) in 32% yield.

The best route to phenoxazines was found in the sequence of reactions shown in Scheme C. By this method which is similar to a general procedure for preparing phenothiazine derivatives,[8] 2-trifluoromethylphenoxazine (Ic) was readily obtained, while attempts to prepare it by Scheme A were unsatisfactory. Compounds Ia, b & d also were easily prepared by Scheme C.

In tables IV and V spectral data on the phenoxazines and phenoselenazines[9] used in this work

SCHEME C



(7) A. Bernthsen, *Ber.*, **20**, 943 (1887); F. Kehrmann, *Ann.*, **322**, 1 (1902); F. Kehrmann and A. A. Neil, *Ber.*, **47**, 3102 (1914); N. M. Cullinane, H. G. Davey, and H. J. H. Padfield, *J. Chem. Soc.*, 716 (1934); H. Gilman and L. O. Moore, *J. Am. Chem. Soc.*, **79**, 3485 (1957).

(8) P. J. C. Buisson, P. Gailliot, and J. Gaudechon, U. S. Patent **2,769,002** (October 30, 1956).

(9) The phenoselenazine intermediates used for preparing the aminoalkyl derivatives listed in Table III were synthesized by Dr. G. B. Butler and co-workers of Peninsular ChemResearch Inc., Gainesville, Fla., who will report elsewhere the preparation of 2-trifluoromethylphenoselenazine.

TABLE IV

ULTRAVIOLET SPECTRAL DATA[a]

Compound	λ_{max} mμ—(Log ε)	
Phenothiazine	254 (4.66)	318 (3.68)
Phenoxazine	239 (4.66)	318 (3.93)
Phenoselenazine	257 (4.56)	316 (3.75)
2-Chlorophenothiazine	258 (4.78)	322 (3.84)
2-Chlorophenoxazine	239 (4.73)	324 (4.01)
2-Chlorophenoselenazine	259 (4.57)	322 (3.70)
2-Trifluoromethylphenothiazine	262 (4.62)	324 (3.61)
2-Trifluoromethylphenoxazine	240 (4.62)	318 (3.87)
2-Trifluoromethylphenoselenazine[9]	263 (4.56)	322 (3.68)
2-Dimethylsulfonamidophenothiazine	267 (4.53)	330 (3.53)
2-Dimethylsulfonamidophenoxazine	247 (4.69)	322 (3.94)

[a] Obtained with a Cary Model 11 Spectrophotometer.

are compared with those on the corresponding phenothiazine derivatives.

Alkylation of the phenoxazines and phenoselenazines gave the 10-dialkylaminoalkyl derivatives listed in Tables II and III. The results of the pharmacological evaluation of these compounds will be reported elsewhere.

EXPERIMENTAL[10]

Phenoxazine (Ia) *by scheme A. 2-Methoxy-2'-nitrodiphenyl ether* (IIIa). A mixture of 47.5 g. of potassium hydroxide, 12 ml. of water, 79 g. of 2-chloronitrobenzene and 106 g. of guaiacol was stirred under reflux at a temperature of 115° for 3 hr. The reaction mixture was then treated with dilute sodium hydroxide and extracted with benzene. Fifty-three

(10) All melting points uncorrected.

TABLE V

INFRARED SPECTRAL DATA[a]

Phenoxazine	2.95(W); 5.20(W); 5.30(W); 5.64(W); 5.95(W); 6.11(M); 6.28(S); 6.64(V.S.); 6.81(M); 7.08(S); 7.69(V.S.); 7.77(M); 8.10(W); 8.30(M); 8.76(W); 8.97(S); 9.70(M); 10.90(S); 11.40(W); 11.65(W); 12.10(S); 13.59(V.V.S)
2-Chlorophenoxazine	2.98(M); 5.39(W); 5.61(W); 5.85(W); 6.14(M); 6.30(S); 6.66(V.S.); 6.90(M); 7.26(M); 7.70(S); 7.98(W); 8.15(W); 8.36(M); 8.42(M); 8.70(W); 8.96(S); 9.12(M); 9.22(S); 9.70(W); 10.84(S); 11.65(S); 12.02(M); 12.42(V.S.); 13.46(V.S.)
2-Trifluoromethylphenoxazine	2.97(M); 5.19(W); 5.34(W); 5.61(W); 5.79(W); 6.13(M); 6.20(M); 6.30(S); 6.62(V.S.); 6.87(V.S.); 7.45(V.S.); 7.60(V.S.); 7.67(S); 7.76(S); 8.00(S); 8.14(V.S.); 8.35(S); 8.65(S); 8.90(S); 9.05(S); 9.15(S); 9.37(V.S.); 9.81(W); 10.33(W); 10.75(V.S.); 10.87(V.S.); 11.54(V.S.); 12.10(V.S.); 13.30(V.S.); 13.81(W)
2-Dimethylsulfonamidophenoxazine	3.00(M); 3.10(W); 3.50(W); 5.61(W); 5.75(W); 5.85(W); 6.12(W); 6.30(S); 6.70(V.S.); 6.90(S); 7.25(M); 7.47(S); 7.55(S); 7.70(S); 7.79(S); 7.97(W); 8.08(W); 8.26(M); 8.45(M); 8.72(S); 8.91(M); 9.10(W); 9.26(M); 9.55(W); 9.72(W); 10.55(W); 10.77(W); 11.45(S); 11.99(W); 12.16(S); 13.37(V.S.)
Phenoselenazine	3.00(W); 5.30(W); 5.37(W); 5.65(W); 6.11(W); 6.26(S); 6.37(S); 6.83(V.S.); 6.90(S); 7.12(W); 7.65(S); 7.84(W); 7.95(M); 8.12(W); 8.66(W); 8.86(W); 9.45(W); 9.75(S); 10.32(W); 10.74(M); 10.81(M); 11.44(M); 11.66(M); 11.71(M); 11.93(W); 13.08(V.S.); 13.35(V.S.); 13.46(V.S.); 13.97(V.S.)
2-Chlorophenoselenazine	3.01(W); 5.28(W); 5.36(W); 5.63(W); 5.90(W); 6.28(S); 6.39(S); 6.65(W); 6.84(V.S.); 7.01(S); 7.34(M); 7.70(S); 7.87(W); 8.01(W); 8.16(M); 8.66(W); 8.96(W); 9.17(V.S.); 9.48(W); 9.75(M); 10.85(V.S.); 11.41(W); 11.70(V.S.); 11.85(V.S.); 12.46(V.S.); 13.45(V.S.); 13.52(V.S.)
2-Trifluoromethylphenoselenazine	2.99(W); 5.15(W); 5.30(W); 5.60(W); 5.86(W); 6.24(S); 6.34(M); 6.54(M); 6.77(V.S.); 6.97(V.S.); 7.10(W); 7.19(V.S.); 7.50(V.S.); 7.80(M); 8.15(S); 8.60(V.S.); 9.05(V.S.); 9.25(V.S.); 9.74(W); 10.31(W); 10.73(V.S.); 11.54(V.S.); 11.94(W); 12.24(V.S.); 13.38(V.S.)

[a] Obtained with a Perkin-Elmer Model 21 Spectrophotometer; Nujol mull technique.

grams of guaiacol was recovered from the alkaline solution upon acidification. The benzene solution was dried over magnesium sulfate and evaporated. The residue was vacuum distilled until a vapor temperature of 150° (0.2 mm.) was reached. The distillate (recovered 2-chloronitrobenzene) weighed 23.5 g., and the residue (crude 2-methoxy-2'-nitrodiphenyl ether) weighed 87.5 g. (71% yield).

2-Amino-2'-methoxydiphenyl ether (IVa). The crude nitrodiphenyl ether (IIIa) was reduced by the hydrazine reduction method of Balcom and Furst.[11] The reaction product was dissolved in dilute hydrochloric acid, the resulting solution was made alkaline with sodium hydroxide, and the mixture was extracted with benzene. Upon evaporation of the benzene solution, crude IVa was obtained.

2-Amino-2'-hydroxydiphenyl ether (Va). Crude IVa was heated with excess 48% hydrobromic acid containing a trace of 50% hypophosphorous acid until no more methyl bromide was evolved (vapor temperature of 123–124°). The dark solution was diluted with two volumes of water, treated with decolorizing carbon and filtered. Upon neutralization of the filtrate with ammonium hydroxide, an oil separated which solidified to form gray crystals; m.p. 106–110°. The yield from crude IIIa was 66%.

Phenoxazine. Ring closure was effected by heating the aminophenol (Va) with concentrated hydrochloric acid in a Carius tube at 195° for 72 hr. Changing the time of heating at this temperature, as well as changing the reaction temperature, resulted in poorer yields. The reaction was worked up by diluting the tube contents with water and extracting the resulting mixture with benzene. Evaporation of the organic extract gave the crude phenoxazine, which was vacuum distilled (b.p. 142–150°/0.1 mm.) and then recrystallized from hexane to give platelets, m.p. 154.5–156° (35% conversion). Upon acidification of the aqueous acid layer about 50% of Va was recovered.

2-Chlorophenoxazine (Ib) *by Scheme A.* Condensation of 2,5-dichloronitrobenzene and guaiacol, carried out as described above for the preparation of IIIa, gave crude 4-chloro-2'-methoxy-2-nitrodiphenyl ether (IIIb); b.p. 163–168° (0.5 mm.) in 94% yield (based on recovery of guaiacol and 2,5-dichloronitrobenzene). 2-Amino-4-chloro-2'-hydroxydiphenyl ether (Vb) was obtained from crude IIIb in 66% yield by the methods used for the preparation of IVa and Va. The analytical sample was obtained from ethanol as colorless needles, m.p. 138–139°.

Anal. Calcd. for $C_{12}H_{10}ClNO_2$: C, 61.15; H, 4.28. Found: C, 61.15; H, 4.50.

Heating the aminophenol Vb with hydrochloric acid in a Carius tube at 195° for 15 hr. gave Ib. The reaction mixture was worked up as described for the preparation of Ia. 2-Chlorophenoxazine was distilled and recrystallized; b.p. 155–160° (0.2 mm.); platelets from hexane, m.p. 144.5–145.5°; 58% yield (based on recovery of starting aminophenol Vb).

Anal. Calcd. for $C_{12}H_8ClNO$: C, 66.22; H, 3.71; N, 6.44. Found: C, 66.33; H, 3.96; N, 6.70.

Phenoxazine by Scheme B. 2,2'-Dinitrodiphenyl ether (VI) was obtained in 7% yield by the procedure of Cullinane, *et al.*[7]; m.p. 113° (lit.[7] m.p. 116°). In our hands the reaction mixture had a pronounced tendency to overheat, rapidly char and erupt. Reduction of VI to give 2,2'-diaminodiphenyl ether (VII) was accomplished over a Raney nickel catalyst at 60° and 50 p.s.i. of hydrogen. The diamine (m.p. 59–60°) was converted to the dihydrochloride salt; m.p. 240–250° dec. A mixture of 2.4 g. (0.0088 mole) of the dihydrochloride and 2.0 g. (0.010 mole) of the free base (m.p. 59–60°) was heated in a Carius tube to 250° for 6 hr. The contents of the tube were dissolved in hot ethanol and the solution was filtered to remove insoluble matter. The filtrate was concentrated to 150 ml. and diluted to 500 ml. with 1% hydrochloric acid. The resulting solution was extracted five times with benzene; the combined extracts were concentrated to 50 ml. and diluted to 200 ml. with ethanol. Addition of 50 ml. of 15% hydrochloric acid precipitated the crude phenoxazine; m.p. 145–150°. Reprecipitation from ethanol by 15% hydrochloric acid gave 1.1 g. (32%) of light gray crystalline product; m.p. 150–153°, which was identified as phenoxazine by its infrared and ultraviolet spectra.

2-Trifluoromethylphenoxazine (Ic) *by Scheme C. 2-Bromo-2'-nitro-4'-trifluoromethyldiphenyl ether* (VIIIc). A mixture of 68 g. of *o*-bromophenol, 88.5 g. of 4-chloro-3-nitrobenzotrifluoride and 5 cc. of water was stirred at room temperature in a flask equipped with a thermometer, stirrer, and reflux condenser. Twenty-three grams of potassium hydroxide pellets was added in several portions, and the reaction temperature rose to 90°. The mixture was stirred at about 105° for 3 hr. It was then treated with dilute sodium hydroxide and extracted with benzene. Twenty-six grams of *o*-bromophenol was recovered upon acidification of the aqueous layer. The benzene layer was dried over magnesium sulfate, evaporated, and the residue was vacuum distilled, yielding 21 g. of 4-chloro-3-nitro-benzotrifluoride, b.p. 80° (0.5 mm.), and 98.5 g. of product as a yellow oil, b.p. 140–160° (0.5–1.0 mm.); 70% yield, corrected to 94% yield, based on recovery of starting material.

Anal. Calcd. for $C_{13}H_7BrF_3NO_3$: C, 43.12; H, 1.95. Found: C, 43.20; H, 2.04.

2'-Amino-2-bromo-4'-trifluoromethyldiphenyl ether (IXc): A mixture of 87 g. of VIIIc, 400 ml. of water and 105 g. of iron filings was heated at reflux, and 210 g. of acetic acid was added over a period of 3 hr. The mixture was refluxed for 1 hr., 300 cc. of benzene added, and the mixture was filtered. The filter cake was washed with benzene, and the filtrate was separated. The benzene layer was evaporated, and the residue vacuum distilled, yielding 72 g. of a pale yellow, mobile liquid, b.p. 140–150°/0.3 mm. (90% yield). Infrared analysis indicated that no nitro compound was present.

Anal. Calcd. for $C_{13}H_9BrF_3N$: C, 47.01; H, 2.73. Found: C, 46.95; H, 2.92.

2-Trifluoromethylphenoxazine (Ic). Fifteen grams of 88% formic acid was added to 61 g. of the aminodiphenyl ether (IXc). Water was distilled until the liquid temperature was 155°, and then the last traces of water and formic acid were removed under reduced presssure. Seventeen grams of potassium carbonate, 1 g. of cupric carbonate, and 75 cc. of xylene were added. A water separator was attached to the reflux condenser, and the mixture was refluxed 18 hr. at a liquid temperature of 150–155°. About 1.5 ml. of water was collected in the separator. A solution of 8 g. of sodium hydroxide in 50 cc. of water was added, and the mixture was refluxed 2 hr. The mixture was diluted with water and benzene and the layers were separated while still hot. The solvent was evaporated and the residue was distilled; b.p. 160–165° (1 mm.). The solid distillate was recrystallized from hexane, yielding 34 g. of white platelets; m.p. 149–152° (73% yield). A small sample was recrystallized from hexane for analysis (m.p. 150–152°).

Anal. Calcd. for $C_{13}H_8F_3NO$: C, 62.15; H, 3.21. Found: C, 61.98; H, 3.27.

2-Dimethylsulfonamidophenoxazine (Id). Scheme C was used for this preparation without isolation and characterization of the intermediate compounds. A mixture of 35 g. (0.13 mole) of 4-chloro-3-nitro-*N,N*-dimethylbenzenesulfonamide, 25.9 g. (0.15 mole) of 2-bromophenol and 1 ml. of water was stirred and heated to 50°. Solid potassium hydroxide (8.4 g.) was added gradually as the temperature was raised to 135°, and stirring was continued for 2 hr. The cooled mixture was diluted with benzene and water, stirred, and the layers were separated. Evaporation of the benzene layer and recrystallization of the residue from hexane-acetone gave 34 g. of crude 2-bromo-2'-nitro-4'-dimethylsulfonamidodiphenyl ether (VIIId); m.p. 120–121°. A stirred mixture of the above compound, 175 ml. of water, and 47 g. of iron filings was treated dropwise at reflux with 100 ml. of glacial acetic acid. The cooled mixture was filtered, and the

(11) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, 75, 4334 (1953).

filter cake was extracted with boiling benzene and acetone (1 to 1 mixture). Concentration and cooling of the extracts gave 25.6 g. of crude 2'-amino-2-bromo-4'-dimethylsulfonamidodiphenyl ether (IXd). This compound was heated at 100° with 63 g. of 88% formic acid until the excess formic acid had evaporated.

The residue (Xd) was taken up in 30 ml. of xylene, and the xylene was removed by distillation at atmospheric pressure to remove traces of formic acid. The residual gum was stirred at reflux for 18 hr. with 8.6 g. of potassium carbonate, 1 g. of copper carbonate and 40 ml. of xylene. Excess water and benzene were added to the cooled mixture and the organic layer was evaporated to leave a gum. Crystallization from benzene-hexane (1 to 3) gave 8.2 g. of 2-dimethylsulfonamidophenoxazine (Id) (19% overall yield); m.p. 184–185°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.91; H, 4.86; N, 9.65; S, 11.04. Found: C, 58.18; H, 5.24; N, 9.44; S, 10.81.

Phenoxazine and 2-chlorophenoxazine by Scheme C: The condensation of 2-bromophenol with 2-chloronitrobenzene and with 2,5-dichloronitrobenzene, carried out as described for the preparation of VIIIc, afforded 2-bromo-2'-nitrodiphenyl ether (40% conversion) and 2-bromo-4'-chloro-2'-nitrodiphenyl ether (50% conversion), respectively. Since the analogous condensation to form the trifluoromethyl derivative, VIIIc, was accomplished with a 70% conversion, the presence of an electron-attracting group para to the reactive chlorine atom appears to aid the condensation reaction, as expected.[12] Reduction of nitrodiphenyl ethers with iron and acetic acid proceeded smoothly to give IXa and IXc in approximately 90% yields. Ring-closure of Xa and Xc by the method described for the preparation of Ic resulted in the preparation of phenoxazine (68% yield) and 2-chlorophenoxazine (62% yield).

2-Amino-2'-bromodiphenyl ether (IXa) was obtained as a yellow oil; b.p. 140–155° (0.2–0.4 mm.).

2-Bromo-4'-chloro-2'-nitrodiphenyl ether (VIIIb), b.p. 165° (0.2 mm.), solidified on long standing at room temperature; light yellow needles (from ethanol); m.p. 73.5–74°.

Anal. Calcd. for $C_{12}H_7BrClNO_3$: C, 43.86; H, 2.15. Found: C, 43.86; H, 2.28. Reduction of VIIIb to 2'-amino-2-bromo-4'-chloridiphenyl ether (IXb) by means of iron and acetic acid gave IXb as a pale yellow oil; b.p. 150–170°/0.2–1.0 mm.

Alkylation of phenoxazines and phenoselenazines. Sodamide in benzene or toluene was stirred at reflux with 0.9 molar ratio of the phenoxazine or phenoselenazine for 0.25–2 hr. After addition of 1.2 molar ratio of the dialkylaminoalkyl chloride, stirring at reflux was continued for 4 to 18 hr. Water was added, the layers were separated, and dilute hydrochloric acid was used to extract the organic layer. Neutralization with excess sodium hydroxide liberated the free base, which was taken up in benzene. Removal of the solvent was followed by distillation of the free base in a sausage flask. The free base was converted to the desired salt by standard techniques, and the salt was purified to a constant melting point by recrystallization from suitable solvents, such as ethanol-ether, methanol, acetone, etc.

The hydroxyethylpiperazinylpropyl analogs (compounds 12 and 14, Table II) were prepared by the method previously described.[13]

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

The Synthesis and Properties of Iodopyrazines

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The lack of reactivity of chloro- and bromopyrazines towards the preparation of organometallic derivatives stressed the desirability of preparing iodopyrazines. Using a methyl ethyl ketone solution of sodium iodide and hydriodic acid, it was possible to prepare eight iodopyrazines, by displacement of the chlorine from variously substituted chloropyrazines, in 30–60% yield. Treatment of the isodiazotate salt of 2-amino-3,6-dimethylpyrazine (XI) with hydriodic acid, according to a procedure described by Chichibabin for the preparation of iodopyridine, afforded 2-amino-3,6-dimethyl-5-iodopyrazine (XIII). Similarly, the isodiazotate salt of 2-amino-3-methylpyrazine (X) afforded 2-amino-3-methyl-5-iodopyrazine (XVI). It could be demonstrated that the isodiazotate salts were reduced to the corresponding amines, which in the subsequent workup were iodinated. The isodiazotate salt of aminopyrazine (IX) afforded iodopyrazine, but in poor yield.

The convenient synthesis of 2-hydroxypyrazines published by Jones[3] and its subsequent modification by Karmas and Spoerri[4] led also to improved methods for the preparation of chloro- and bromopyrazines. Thus a variety of 2-chloropyrazines were synthesized by the reaction of hydroxypyra-

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