The amino alcohol, isolated as described above, was dissolved in Et_2O and treated with HCl gas to precipitate the amorphous hydrochloride. This crude salt was dissolved in 100 ml of $CHCl_3$ and 5 g of benzoyl chloride was added. The reaction was allowed to stand for 10 min, and then the solvents were removed *in vacuo*. The resulting oil, after standing for another 3 days, was warmed on the steam bath for 0.5 hr. The mixture was suspended in Et_2O and washed (K_2CO_3, H_2O). The Et_2O solution, dried over K_2CO_3, was removed *in vacuo*. The resulting yellow syrup (11.3 g) showed no OH absorption in the ir but a strong ester carbonyl.

The oil was reconverted to the hydrochloride in Et_2O as before. Removal of the solvents left a dry foam. Part of this foam (2 g) was converted to a maleate salt, but though crystalline, it was highly hygroscopic.

The remainder of the foam was chromatographed on 200 g of silicic acid (Mallinckrodt chromatography grade 200 mesh, Me_2CO washed and dried). The column was eluted with $CHCl_3$. The first 2.25 l. removed noncrystalline materials. The next 1.25 l. eluted 5.6 g of a solid which when crystallized twice from MeOH–Et_2O produced 4.0 g of ester hydrochloride XV (lost solvent at 102–103°, remelted 207–209°). Liberated as the free base and recrystallized from EtOH–H_2O, it melted at 77–78°.

The remainder of the material eluted from the column weighed 1.8 g, which on recrystallization from MeOH–Et_2O produced 0.9 g of isomer XVII, mp 230–232° (free base mp 91–93°). The ir and nmr spectra were consistent with the proposed structures XV and XVII.

Pharmacology.—Adult male mice weighing 18–24 g were used in all the pharmacological testing. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[10] See Table I for a summary of the pharmacological results.

HCl Writhing Test (HWT).—Groups of four mice were injected subcutaneously with the test compound and 45 min later, 0.01 ml/g of a 0.1% aqueous solution of HCl was administered intraperitoneally. The mice were then observed for 10 min for prevention of writhing. The results are expressed as the ratio of the number of mice protected to the number of mice tested.

Acknowledgments.—We wish to sincerely thank Dr. A. D. Rudzik and Mr. Phil Shea for obtaining the pharmacological test data.

(10) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

Synthesis and Antiinflammatory Screening of Phenoxazine-1-carboxylic Acids

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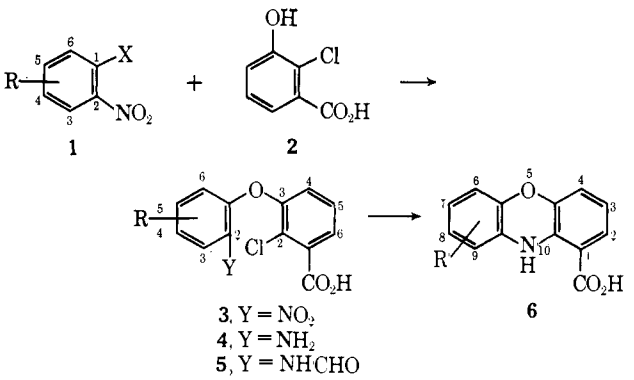
The title compounds (**6a–x**) were prepared in four steps from 1-halo-2-nitrobenzenes (1) and 2-chloro-3-hydroxybenzoic acid (**2**). Antiinflammatory activity was determined using the guinea pig uv erythema assay and the carrageenin filter paper granuloma assay in adrenalectomized rats. In these assays the most active compound, **6d**, was less active than the isosteric 8-trifluoromethylphenothiazine-1-carboxylic acid.

The recent finding in our laboratories that 8-trifluoromethylphenothiazine-1-carboxylic acid[1] has interesting antiinflammatory activity in experimental animals prompted us to investigate the isosteric phenoxazine compound. When this too had interesting biological activity further chemical studies were planned in which two goals were established: (1) to prepare a wide variety of 8-substituted phenoxazine-1-carboxylic acids, and (2) to investigate the effect on biological activity of moving the trifluoromethyl group from positions 6–9 in phenoxazine-1-carboxylic acid.

Early attempts to prepare **6d** using the Smiles rearrangement in an effort to utilize the procedure developed for the preparation of the phenothiazine-1-carboxylic acids[1] were unsuccessful. Under these reaction conditions the intermediate, 2-amino-4-trifluoromethylphenol, lost fluoride ion and apparently polymerized.[2] Therefore, a route used previously with success in our laboratories[3] was employed for the preparation of the compounds reported (Scheme I).

If, in addition to the nitro group, **1** contained a second electron-withdrawing group *ortho* or *para* to the halogen being displaced, diphenyl ether formation proceeded readily. With an electron-releasing group in the same positions the reaction proceeded poorly or failed. Only with DMF as a solvent were yields usually satisfactory (even with DMF 4-chloro-3-nitroanisole failed to react). If the fluoro compound (**1**, X = F) was available yields were improved and bis(2-methoxyethyl) ether (diglyme) could be substituted for DMF (*e.g.*, **3k**, Table I). The nitrodiphenyl ethers (**3**) are listed in Table I.

SCHEME I

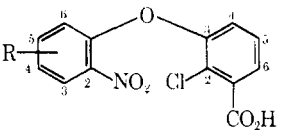


Reduction of **3** gave the amines **4** (Table II) which were formylated to give **5** (Table III). For the most part, these reactions were straightforward. However, in a few instances (**4b** and **v** and **5a**, **e**, **u**, **v**, and **w**) we were unable to obtain analytically pure samples, although impure **4b** could be converted to analytically pure **5b**. Attempts to hydrolyze purified **5b** to **4b** resulted in the concomitant hydrolysis of the trifluoromethyl group and the isolation of an amino diacid (**4**, R = 3-CO_2H). Ring closure and hydrolysis of the N-formyl group of **5** to yield **6** (Table IV) were usually effected simultaneously in refluxing DMF in the presence of copper bronze. Under these conditions

(1) B. M. Sutton and J. H. Birnie, *J. Med. Chem.*, **9**, 835 (1966).
(2) M. R. Pettit and J. C. Tatlow, *J. Chem. Soc.*, 3852 (1954).
(3) M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, **26**, 1901 (1961).

TABLE I

2-CHLORO-3-(2-NITROPHENOXY)BENZOIC ACIDS



Compd 3	R	Method	Mp, °C[a]	Recrystn solvent	% yield	Formula	Analyses
a	H	*b*	177–178	C_6H_6	95	$C_{13}H_8ClNO_5$	C, H, N
b	3′-CF_3	B	208–209	C_6H_6	60	$C_{14}H_7ClF_3NO_5$	C, H, Cl, N
c	4′-CF_3	C	209–210	C_6H_6	76		C, H, N
d	5′-CF_3	A	176–177	C_6H_6	62		C, H, N
e	6′-CF_3[c]	B	170–172	Aq MeOH	17		C, H, Cl, N
f	4′-Cl	A or B	204–205	C_6H_6	30	$C_{13}H_7Cl_2NO_5$	C, H, Cl, N
g	5′-Cl	A	213–214	EtOAc	40		C, H, Cl, N
h	6′-Cl	A or B	201–202	C_6H_6	61		C, H, Cl, N
i	4′-F	A	195–196	C_6H_6	81	$C_{13}H_7ClF_3NO_5$	C, H, N
j	5′-F	A	173–174	C_6H_6–cyclohexane	70		C, H, Cl, N
k	4′-CH_3	B or D[d]	173–175	50% aq EtOH	27[e]	$C_{14}H_{10}ClNO_5$	C, H, Cl, N
l	4′-SCH_3	B	180–182	$CHCl_3$	42	$C_{14}H_{10}ClNO_5S$	C, H, Cl, N
m	4′-SCF_3	B	196–197	C_6H_6	84	$C_{14}H_7ClF_3NO_5S$	C, H, Cl, N
n	4′-OCF_3	B	205–206	$CHCl_3$	66	$C_{14}H_7ClF_3NO_6$	C, H, Cl, N
o	4′-C_6H_5	B	232–233	EtOAc	39	$C_{19}H_{12}ClNO_5$	C, H, N
p	4′-$COCH_3$	D	162–164	C_6H_5Me	43	$C_{15}H_{10}ClNO_6$	C, H, Cl, N
q	4′-COC_6H_5	D	188–190	C_6H_5Me	51	$C_{20}H_{12}ClNO_6$	C, H, Cl, N
r	4′-CN	B	220–222	MeOH–H_2O	58	$C_{14}H_7ClN_2O_5$	C, H, Cl, N
s	4′-SO_2CH_3	D	244–245	THF–petr ether	92	$C_{14}H_{10}ClNO_7S$	C, H, Cl, N
t	4′-SO_2CF_3	A	163–164	C_6H_6	86	$C_{14}H_7ClF_3NO_7S$	C, H, Cl, N
u	4′,5′-Cl_2	A	179–180	C_6H_6	67	$C_{13}H_6Cl_3NO_5$	C, H, Cl, N
v	4′-SO_2NHCH_3	D	197–199	MeOH–H_2O	65	$C_{14}H_{11}ClN_2O_7S$	C, H, Cl, N
w	4′-$SO_2N(CH_3)_2$	D	180–181	EtOAc	62	$C_{15}H_{13}ClN_2O_7S$	C, H, Cl, N
x	4′-CO_2H	B	262–263	*i*-PrOH	77	$C_{14}H_8ClNO_7$	C, H, Cl, N
y	4′-$CONH_2$	B	252–254	*n*-BuOH	93	$C_{14}H_9ClN_2O_6$	C, H, Cl, N
z	4′-SO_2NH_2	D	228–229	THF–hexane	64	$C_{13}H_9ClN_2O_7S$	C, H, Cl, N

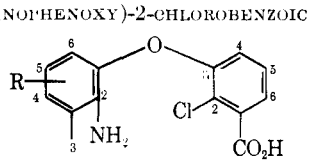
[a] Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected. [b] See specific directions in Experimental Section. [c] The intermediate 2-bromo-3-nitrobenzotrifluoride required in this synthesis was prepared by Mr. A. Saggiomo of the Temple University Research Institute from 2-bromo-3-nitrobenzoic acid and SF_4. [d] If **1** (X = Cl) was used, method B was employed; if 1 (X = F) was used, method D was employed. [e] Yield when 1 (X = F) was used.

5y was not converted cleanly to 8-carboxamidophenoxazine-1-carboxylic acid but was always contaminated with **6x**. Also, under these conditions **5n** and **t** did not lead to **6n** and **t**. However, **6n** and **t** were prepared using diglyme in place of DMF. From the preparation of 8-sulfamylphenoxazine-1-carboxylic acid a product was isolated which appeared chemically and spectrally to be the desired compound. It was homogeneous on thin layer chromatograms in two solvent systems but gave poor elemental analyses. Consequently, it was not included in Table IV and was not tested.

Metalation of phenoxazines with *n*-butyllithium and carbonation of the resulting lithio compounds was considered as an alternative route to **6**. Gilman and

TABLE II

3-(2-AMINOPHENOXY)-2-CHLOROBENZOIC ACIDS



Compd 4	R	Mp, °C[a]	Recrystn solvent	% yield	Formula	Analyses
a	H	199–201	*i*-PrOH–H_2O	65	$C_{13}H_{10}ClNO_3$	C, H, N
b	3′-CF_3	*b*		91	$C_{14}H_9ClF_3NO_3$	
c	4′-CF_3	138–139	C_6H_6	79		C, H, Cl, N
d	5′-CF_3	147–148	CCl_4	74		C, H, N
e	6′-CF_3	212–213	MeOH–H_2O	76		C, H, Cl, N
f	4′-Cl	182–183	C_6H_6	77	$C_{13}H_9Cl_2NO_3$	C, H, Cl, N
g	5′-Cl	154–155	EtOAc–C_6H_6	91		C, H, Cl, N
h	6′-Cl	158–159	EtOAc–cyclohexane	77		C, H, Cl, N
i	4′-F	130–131	EtOAc–C_6H_6	63	$C_{13}H_9ClFNO_3$	C, H, Cl, N
j	5′-F	178–179	EtOAc–C_6H_6	36		C, H, Cl, N
k	4′-CH_3	134–136	CCl_4	42	$C_{14}H_{12}ClNO_3$	C, H, Cl, N
l	4′-SCH_3	120–122	C_6H_6	40	$C_{14}H_{12}ClNO_3S$	C, H, Cl, N

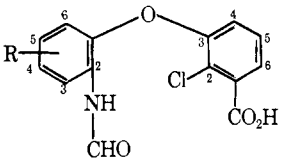
TABLE II (*Continued*)

Compd **4**	R	Mp, °C[a]	Recrystn solvent	% yield	Formula	Analyses
m	4′-SCF_3	142–143	C_6H_6	80	$C_{14}H_9ClF_3NO_3S$	C, H, Cl, N
n	4′-OCF_3	117–118	C_6H_6–cyclohexane	60	$C_{14}H_9ClF_3NO_4$	C, H, Cl, N
o	4′-C_6H_5	227–228	EtOAc–C_6H_6	94	$C_{19}H_{14}ClNO_3$	C, H, Cl, N
p	4′-$COCH_3$	203–205	EtOAc–petr ether	66	$C_{15}H_{12}ClNO_4$	C, H, Cl, N
q	4′-COC_6H_5	177–179	EtOAc–petr ether	88	$C_{20}H_{14}ClNO_4$	C, H, Cl, N
r	4′-CN	187–189	MeOH–H_2O	67	$C_{14}H_9ClN_2O_3$	C, H, Cl, N
s	4′-SO_2CH_3	191–193	H_2O	76	$C_{14}H_{12}ClNO_5S$	C, H, Cl, N
t	4′-SO_2CF_3	176–177	EtOAc–C_6H_6	79	$C_{14}H_9ClF_3NO_5S$	C, H, Cl, N
u	4′,5′-Cl_2	205–206	C_6H_6	64	$C_{13}H_8Cl_3NO_3$	C, H, Cl, N
v	4′-SO_2NHCH_3	*b*			$C_{14}H_{13}ClN_2O_5S$	
w	4′-$SO_2N(CH_3)_2$	202–204	EtOH–H_2O	87	$C_{15}H_{15}ClN_2O_5S$	C, H, Cl, N
x	4′-CO_2H	261–263	MeOH	78	$C_{14}H_{10}ClNO_5$	C, H, Cl, N
y	4′-$CONH_2$	259–260	*n*-BuOH	61	$C_{14}H_{11}ClN_2O_4$	C, H, Cl, N
z	4′-SO_2NH_2	208–210	H_2O	55	$C_{13}H_{11}ClN_2O_5S$	C, H, Cl, N

[a] Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected. [b] See text.

TABLE III

2-CHLORO-3-(2-FORMAMIDOPHENOXY)BENZOIC ACIDS



Compd **5**	R	Mp, °C[a]	Recrystn solvent	% yield	Formula	Analyses
a	H	180–182		98	$C_{14}H_{10}ClNO_4$	*b*
b	3′-CF_3	186–187	Me_2CO–$CHCl_3$	52	$C_{15}H_9ClF_3NO_4$	C, H, Cl, N
c	4′-CF_3	200–201	C_6H_5Me	87		C, H, N
d	5′-CF_3	178–179	C_6H_6	86		C, H, N
e	6′-CF_3	165–167		68		*b*
f	4′-Cl	229–230	EtOH–C_6H_6	98	$C_{14}H_9Cl_2NO_4$	C, H, Cl, N
g	5′-Cl	198–200	EtOAc–C_6H_6	75		C, H, Cl, N
h	6′-Cl	154–155	C_6H_6	96		C, H, Cl, N
i	4′-F	214–216	EtOAc–C_6H_6	88	$C_{14}H_9ClFNO_4$	C, H, Cl, N
j	5′-F	197–198	EtOAc–C_6H_6	91		C, H, Cl, N
k	4′-CH_3	198–199	MeOH	67	$C_{15}H_{12}ClNO_4$	C, H, Cl, N
l	4′-SCH_3	184–186	MeOH	82	$C_{15}H_{12}ClNO_4S$	C, H, Cl, N
m	4′-SCF_3	163–164	EtOAc–C_6H_6	79	$C_{15}H_9ClF_3NO_4S$	C, H, Cl, N
n	4′-OCF_3	124–125	HCO_2H–H_2O	100	$C_{15}H_9ClF_3NO_5$	C, H, Cl, N
o	4′-C_6H_5	205–206	EtOAc–C_6H_6	88	$C_{20}H_{14}ClNO_4$	C, H, Cl, N
p	4′-$COCH_3$	193–194	EtOAc	71	$C_{16}H_{12}ClNO_5$	C, H, Cl, N
q	4′-COC_6H_5	178–180	EtOAc–petr ether	81	$C_{21}H_{14}ClNO_5 \cdot 0.5H_2O$	C, H, Cl, N
r	4′-CN	246–248	MeOH	76	$C_{15}H_9ClN_2O_4$	C, H, Cl, N
s	4′-SO_2CH_3	219–221	Me_2CO–hexane	89	$C_{15}H_{12}ClNO_6S$	C, H, Cl, N
t	4′-SO_2CF_3	170–171	EtOAc–C_6H_6	95	$C_{15}H_9ClF_3NO_6S$	C, H, Cl, N
u	4′,5′-Cl_2	233–234	EtOAc	94	$C_{14}H_8Cl_3NO_4$	C, H, Cl, N
v	4′-SO_2NHCH_3				$C_{15}H_{13}ClN_2O_6S$	*b*, *c*
w	4′-$SO_2N(CH_3)_2$	141–143		81	$C_{16}H_{15}ClN_2O_6S$	*b*
x	4′-CO_2H	243–245	Me_2CO–hexane	76	$C_{15}H_{10}ClNO_6$	C, H, Cl, N
y	4′-$CONH_2$	263–265	HCO_2H–H_2O	86	$C_{15}H_{11}ClN_2O_5$	C, H, Cl, N
z	4′-SO_2NH_2				$C_{14}H_{11}ClN_2O_6S$	*c*

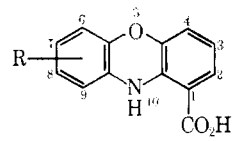
[a] Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected. [b] Material was contaminated with small amounts of the amine and was used without further purifications. [c] Material was a gum which could not be induced to solidify.

Moore[4] reported that metalation and carbonation of phenoxazine led to a monocarboxylic acid to which they assigned the structure phenoxazine-4-carboxylic acid. The melting point of their product corresponded to that of **6a**. However, the melting point of the methyl ester of **6a** (127–128°) was 15° higher than that of the methyl ester reported by Gilman and Moore (112.5–114°).[4] Repeating the metalation and carbonation using the reported procedures[4] gave a monocarboxylic acid in poor yield. This acid and its methyl ester were identical with **6a** and its methyl ester according to the following criteria: melting point, mixture melting point, ir and nmr spectra, and tlc. Therefore, we concluded that the product from the metalation and carbonation of phenoxazine was phenoxazine-1-carboxylic acid. In addition to fixing the structure of the metalation product this study indicated that metalation and carbonation of the lithio salts of phenoxazines was a less attractive route to phenoxazine-1-carboxylic acids than the four-step cyclization sequence for the

(4) H. Gilman and L. O. Moore, *J. Am. Chem. Soc.*, **80**, 2195 (1958).

TABLE IV

PHENOXAZINE-1-CARBOXYLIC ACIDS



Compd 6	R	Method	Mp, °C[a]	Recrystn solvent	% yield	Formula	Analyses
a	H	A	247–248	$CHCl_3$	72	$C_{13}H_9NO_3$	C, H, N
b	6-CF_3	A	305[b]	EtOAc	65	$C_{14}H_8F_3NO_3$	C, H, N
c	7-CF_3	A	238–239	C_6H_6	88		C, H, N
d	8-CF_3	A	264–265	CCl_4	70		C, H, N
e	9-CF_3	A	260–261	EtOAc	46		C, H, N
f	6-Cl	A	283–285	EtOAc–C_6H_6	79	$C_{13}H_8ClNO_3$	C, H, Cl, N
g	7-Cl	A	290–291	EtOAc	27		C, H, Cl, N
h	8-Cl	A	276–277	C_6H_6	42		C, H, Cl, N
i	7-F	A	248–250	EtOAc	30		C, H, N
j	8-F	A	264–265	EtOAc	40		C, H, N
k	8-CH_3	A	264–266	C_6H_5Me	53	$C_{14}H_{11}NO_3$	C, H, N
l	8-SCH_3	A	253–254	C_6H_5Me	59	$C_{14}H_{11}NO_3S$	C, H, N, S
m	8-SCF_3	A	278–279	EtOH	32	$C_{14}H_8F_3NO_3S$	C, H, N, S
n	8-OCF_3	B	245–246	EtOAc–C_6H_6	43	$C_{14}H_8F_3NO_4$	C, H, N
o	8-C_6H_5	A	294–295	EtOAc–C_6H_6	62	$C_{19}H_{13}NO_3$	C, H, N
p	8-$COCH_3$	A	289–291	EtOH	22	$C_{15}H_{11}NO_4$	C, H, N
q	8-COC_6H_5	A	293–294	*n*-BuOH	59	$C_{20}H_{13}NO_4$	C, H, N
r	8-CN	A	299–300	EtOH–H_2O	35	$C_{14}H_8N_2O_3$	C, H, N
s	8-SO_2CH_3	A	273–274	MeOH	75	$C_{14}H_{11}NO_5S$	C, H, N, S
t	8-SO_2CF_3	B	295–296	EtOAc	40	$C_{14}H_8F_3NO_5S$	C, H, N, S
u	7,8-Cl_2	A	331–333	AcOH	44	$C_{13}H_7Cl_2NO_3$	C, H, Cl, N
v	8-SO_2NHCH_3	A	310[b]	Dioxane		$C_{14}H_{12}N_2O_5S$	C, H, N, S
w	8-$SO_2N(CH_3)_2$	A	281–283	MeCN	45	$C_{15}H_{14}N_2O_5S$	C, H, N, S
x	8-CO_2H	A	333–335[b]	*n*-BuOH	26	$C_{14}H_9NO_5$	C, H, N

[a] Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected unless otherwise specified. [b] Melts with decomposition. Melting point was taken in a metal block and is uncorrected.

following reasons: (1) the substituted phenoxazines required in these syntheses were relatively inaccessible, (2) the yields were poor, and (3) the position of the carboxyl group was uncertain.

Of the compounds listed in Table IV, **6b** and **v** were not tested because insufficient material was available. Three compounds, **6d**, **h**, and **p** were active in the uv erythema assay.[5] In the granuloma assay[6] **6d**, **h**, **n**, **p**, and **u** were active after subcutaneous administration. Of these five compounds, **6d** alone had noteworthy activity: it was active at 40 mg/kg in the uv erythema assay and at 10, 20, and 80 mg/kg in the granuloma assay after subcutaneous administration. However, **6d** was inactive in the granuloma assay after oral doses of 20 and 80 mg/kg. Phenylbutazone served as a positive control in all assays and was consistently active at 20 mg/kg in the erythema assay and at 40 mg/kg in the granuloma assay.

Little can be said about structure–activity relationships except that in the series of chloro- and trifluoromethylphenoxazine-1-carboxylic acids (**6b–h**) the preferred position for substitution was C-8, and that 8-trifluoromethylphenothiazine-1-carboxylic acid (with an ED_{50} of 4.3 mg/kg in the uv erythema assay and of 5–10 mg/kg in the granuloma assay)[1] was more potent than **6d**.

(5) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *Arch. Intern. Pharmacodyn.*, **116**, 261 (1958).

(6) Modification of the methods reported by R. Meier, W. Schuler, and P. Desaulles, *Experientia*, **6**, 469 (1950), and A. Tanaka, F. Kobayashi, and T. Miyake, *Endocrinol. Japon.*, **7**, 357 (1960).

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

2-Chloro-3-(2-nitrophenoxy)benzoic Acid (3a).—A mixture of 30 g (0.165 mole) of **2**[7] and 20.1 g (0.36 mole) of KOH was heated for 10 min at 180° in a metal bath. The gummy liquid was allowed to cool by removing the metal bath; 14.1 g (0.1 mole) of 1-fluoro-2-nitrobenzene was added, and the mixture was kept at 200° for 30 min. The mixture was cooled to room temperature and dissolved in H_2O. The aqueous solution was acidified and a gum precipitated. The gum was dissolved in ether and the ether was washed with H_2O and 0.5% NaOH. The basic washes were acidified to give 27.8 g (95%) of **3a**.

Replacing 1-fluoro-2-nitrobenzene with 1-bromo-2-nitrobenzene in the above reaction resulted in the isolation of **3a** in only 20% yield.

***Substituted 2-Chloro-3-(2-nitrophenoxy)benzoic Acids (3b–z)* (Table I).** **A.**—KOH (2 equiv) was added to a stirred solution of equimolar amounts of **1** and **2** in absolute EtOH. The reaction was usually slightly exothermic and accompanied by the precipitation of KX. The mixture was refluxed until a sample of the reaction mixture indicated the disappearance of the reactants on tlc (silica gel G plates developed in a system of $CHCl_3$–EtOAc–AcOH, 80:20:1) (usually overnight). After cooling, the mixture was diluted (H_2O), stirred for several minutes, and acidified with dilute HCl. The resulting solid was filtered, dissolved in dilute aqueous NH_3, and reprecipitated with dilute HCl. This solid was usually pure enough for subsequent reactions.

B.—A mixture of 0.085 mole of **1**, 0.085 mole of **2**, and 0.25 mole of dry K_2CO_3 in 200 ml of DMF, dried over molecular sieves, was stirred under reflux for 2 hr. The mixture was cooled, diluted with H_2O, and acidified. The solid was filtered, washed with H_2O, and recrystallized.

(7) C. A. Buehler, J. O. Harris, C. Smackgell, and B. P. Block, *J. Am. Chem. Soc.*, **68**, 574 (1946).

C.—Same as method A except a solution of equal volumes of EtOH and diglyme was used as solvent.

D.—To a solution of 0.4 mole of NaOH in 75 ml of H_2O was added 0.2 mole of **2** and 500 ml of diglyme. To this mixture was added 0.2 mole of 1 and the mixture was stirred under reflux for 60 hr. The mixture was cooled, diluted with H_2O, and acidified. The precipitate was filtered, washed (H_2O), dried, and recrystallized.

Substituted 3-(2-Aminophenoxy)-2-chlorobenzoic Acids (4a–z) (Table II).—A solution of **3** in aqueous EtOH was prepared by dissolving **3** in EtOH and adding H_2O until the solution became cloudy (usually 1:1). A 4 g-atom excess of Fe powder was added and the mixture was stirred and heated to reflux. A 9 *M* excess of AcOH was added dropwise and the mixture was heated an additional 1 hr after the addition had been completed. The mixture was cooled to room temperature and made basic with aqueous NH_3. Air was drawn through the stirred mixture for 3–5 hr to ensure complete conversion of the dissolved Fe^{2+} to the more easily filtered $Fe(OH)_3$. The mixture of unreacted Fe and $Fe(OH)_3$ was filtered through a mat of Supercel, and the filter cake was washed thoroughly with dilute aqueous NH_3. The combined filtrates were concentrated to remove EtOH and excess NH_3. The concentrate was acidified carefully with dilute HCl until a drop of acid produced no further precipitation. The solid amino acid was filtered, washed with H_2O, and dried. This material was usually pure enough for the preparation of the N-formyl derivative **5**.

Substituted 2-Chloro-3-(2-formamidophenoxy)benzoic Acids (5a–z) (Table III).—A mixture of **4** and 97–100% formic acid (10 ml/g of **4**) was stirred and refluxed for 2–18 hr (the reaction was followed by tlc using the same system that was used in the preparation of **3**). The solution was cooled and poured into several volumes of H_2O with vigorous stirring. The solid was filtered and washed well with H_2O. The crude product was usually contaminated with trace amounts of unreacted **4** but was sufficiently pure for the next reaction.

Substituted Phenoxazine-1-carboxylic Acids (6a–x) (Table IV). **A.**—A mixture of 0.01 mole of **5**, 0.02 mole of K_2CO_3, 0.1 g of Cu bronze, and 100 ml of dry DMF was stirred and refluxed under N_2 for 30–60 min. The hot mixture was filtered into several volumes of warm H_2O. The filter cake was washed with a small volume of H_2O and the combined filtrates were acidified with dilute HCl. The resulting yellowish green precipitate was cooled, filtered, and redissolved in dilute NH_4OH. The solution was filtered and acidified again. The precipitate was filtered, washed, dried, and recrystallized.

B.—The reaction was carried out as described in A except dry diglyme was used in place of DMF and refluxing was continued for 3 hr.

Methyl Phenoxazine-1-carboxylate.—A mixture of 350 mg of **6a**[4] in 90 ml of MeOH was cooled and saturated with dry HCl. The mixture was stirred under reflux for 4 hr and the resulting solution was cooled and diluted with H_2O. The MeOH was distilled and the aqueous residue was extracted (Et_2O). The ether was washed (5% $NaHCO_3$, H_2O), dried ($MgSO_4$), and distilled. The residue was sublimed and recrystallized from EtOH–H_2O to give 200 mg of ester, mp 128–129°. *Anal.* ($C_{14}H_{11}NO_3$) C, H, N.

The methyl ester prepared from **6a** obtained from the cyclization route melted at 127–128° (EtOH). *Anal.* ($C_{14}H_{11}NO_3$) C, H, N.

3-(2-Amino-3-carboxyphenoxy)-2-chlorobenzoic Acid.—A mixture of **5b** and 5 *N* KOH was heated 2 hr on a steam bath. The solution was filtered, cooled, and neturalized. The solid was filtered, washed with H_2O, dried, and recrystallized from EtOAc, mp 273° dec. *Anal.* ($C_{14}H_{10}ClNO_5$) C, H, Cl, N.

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Hypotensive Activity of Some Cyanoguanidines

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A series of substituted cyanoguanidines was synthesized and screened for hypotensive activity. One of these, 1-*t*-amyl-3-cyanoguanidine (**2**), was selected for further animal studies.

Several years ago 1-*t*-butyl-3-cyanoguanidine[1] (**1**) was found to have appreciable hypotensive activity in a random screening test carried out in normotensive rats.[2] Since the simple unbranched homologs were devoid of activity, and we were not aware of any reported hypotensive activity for cyanoguanidines, we set out to prepare a number of analogous compounds. There are, of course, many examples in the literature of guanidine derivatives possessing hypotensive activities.[3] This report deals with the synthesis and hypotensive activity of the series of substituted cyanoguanidines listed in Table I.

Chemistry.—The synthesis of monosubstituted cyanoguanidines was accomplished by a well-established procedure[4] consisting of the condensation of the hydrochloride of the appropriate amine with sodium (or lithium) dicyanamide. The reactions were carried out in either 1-butanol or in H_2O. In a few cases the choice of solvent was critical.

$$RNH_2 \cdot HCl + NaN(CN)_2 \longrightarrow RNHC(=NCN)NH_2 + NaCl$$

To prepare compounds with substituents on both nitrogens, two additional methods were employed. In the first case, heating a mixture of 1-cyano-2,3-dimethyl-2-thiopseudourea, *t*-butylamine, and ethanol in an autoclave yielded 1-*t*-butyl-2-cyano-3-methylguanidine (**17**). This procedure has been used by Curd to prepare substituted dicyandiamides.[4]

(1) R. M. Acheson, G. A. Taylor, and M. L. Tomlinson, *J. Chem. Soc.*, 3750 (1958).

(2) J. R. Cummings, J. L. Grace, and C. N. Latimer, *J. Pharmacol. Exp. Ther.*, **141**, 349 (1963). The test compounds (100 mg/kg) were suspended in 2% starch and administered to conscious rats by gavage. Mean arterial blood pressure was measured 2 hr later.

(3) (a) E. Schlittler, J. Druey, and A. Marxer, *Progr. Drug Res.*, **4**, 341 (1962); (b) H. Najer, R. Giudicelli, and J. Sette, *Bull. Soc. Chim. France*, 1593 (1962); (c) J. H. Short, U. Biermacher, D. A. Dunnigan, and T. D. Leth, *J. Med. Chem.*, **6**, 275 (1963); (d) J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Worthing, and T. I. Wrigley, *ibid.*, **8**, 446 (1965); (e) R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *ibid.*, **5**, 944 (1962).

(4) F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murry, and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).