amine in refluxing ethanol, or in higher yield (77%) by catalytic hydrogenation over palladium–charcoal of N-methyl-2-benzylaminomethyl-1,4-benzodioxan in acetic acid. The secondary amine had b.p. 82–84° (0.4 mm.), $n^{25}D$ 1.5396 [lit.[47a] b.p. 124° (4 mm.), $n^{23}D$ 1.5390].

N-Methyl-2-benzylaminomethyl-1,4-benzodioxan.—2-Benzylaminomethyl-1,4-benzodioxan[48] (14.5 g.) was added to formic acid (6.45 g.) at 0°, followed by slow addition of formaldehyde (5.4 g., 35% solution). When the effervescence had ceased, the mixture was heated under reflux for 4 hr., and allowed to cool. Concentrated HCl (5.7 ml.) was added, and the volatile material was removed *in vacuo*. The residue was treated with 5 *N* NaOH and extracted into benzene. The benzene solution was extracted with dilute HCl, and this acid extract, along with an oil which had separated, was basified and extracted with ether. Distillation of the dried ethereal extract gave the product in 90% yield, b.p. 144–147° (0.4 mm.), $n^{25}D$ 1.5658.

Anal. Calcd. for $C_{17}H_{19}NO_2$: N, 5.20. Found: N, 5.11.

2-(1,4-Benzodioxanyl)methylbiguanide tosylate was synthesized according to the method of Oxley and Short.[49] An intimate mixture of equimolar quantities of the tosylate salt (m.p. 176–178°) of 2-aminomethyl-1,4-benzodioxan and dicyandiamide was maintained at 150–160° (internal temperature) for 30 min. After cooling, the glassy solid crystallized on trituration with 2-propanol. It was recrystallized from water to give the product as the tosylate salt (68%), m.p. 169°.

S-2-(1,4-benzodioxanyl)methylisothiourea Hydrobromide.—Equimolar quantities of 2-bromomethyl-1,4-benzodioxan and thiourea in ethanol were heated under reflux for 8 hr. After removal of some of the solvent, the reaction was cooled, and the product was collected and recrystallized from ethanol. It had m.p. 191–193°, yield 52%.

2-(1,4-Benzodioxanyl)acetamidine Hydrochloride.—2-Cyanomethyl-1,4-benzodioxan[50] (20 g., 0.114 mole) and dry ethanol (7 ml., 0.12 mole) in dry ether (200 ml.) were protected from atmospheric moisture, cooled to −10°, and a slow stream of dry HCl was passed through the mixture for 14 hr. After 2 days at 0°, the imino ether hydrochloride, m.p. 134°, was filtered off and washed with dry ether. The salt was then stirred with NH_3 (10% solution in ethanol, 200 ml.) at room temperature for 18 hr. Concentration of the mixture to *ca.* 50 ml. caused the product to crystallize. It was filtered off and recrystallized from ethanol–ether. It had m.p. 225–227° dec.

2-(1,4-Benzodioxanyl)acetamidoxime.—2-Cyanomethyl-1,4-benzodioxan[50] (3.0 g.) in ethanol (20 ml.) was added to hydroxylamine hydrochloride (1.2 g.) and anhydrous Na_2CO_3 (0.9 g.) in water (10 ml.), and the mixture was heated under reflux for 24 hr. The ethanol was evaporated and the residue was extracted with ether. The extract was washed with dilute HCl, and the washings were combined with the original ether-insoluble residue. Treatment with solid $NaHCO_3$ yielded a brown tar, which after being washed with water, was dissolved in warm ethanol. After treatment with charcoal, concentration of the solution gave the amidoxime, 0.5 g. (14%), m.p. 123–124°.

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Hydroxylamine Chemistry. V. Aralkoxyguanidines[1]

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A series of aralkoxyguanidines was prepared including several possessing interesting anorexigenic activity.

Conversion of some previously prepared O-aralkylhydroxylamines[1] into the corresponding aralkoxyguanidines was desired as a means of increasing their basicity and thereby varying their pharmacological actions. Accordingly, seven representative aralkoxyamines were allowed to react with 2-methyl-2-thiopseudourea sulfate[2] to form the corresponding aralkoxyguanidine sulfates which were converted into crystalline nitrate salts for isolation and purification.

$$2(RONH_2) + [CH_3SC(=NH)NH_2]_2H_2SO_4 \rightarrow [RONHC(=NH)NH_2]_2H_2SO_4 + 2CH_3SH$$

In the course of this work an improved procedure for the preparation of alkoxyguanidines was developed based on the reaction of cyanamide[3] with an alkoxyamine hydrochloride suspended in an inert solvent.

$$RONH_2 \cdot HCl + H_2N \cdot CN \rightarrow RONHC(=NH)NH_2 \cdot HCl$$

This cyanamide procedure was mild enough to permit the conversion of 2-phenethyloxyamine hydrochloride, which is unstable on standing at room temperature, into 2-phenethyloxyguanidine in 69% yield.

One N-alkylated alkoxyamine derivative, N-methylbenzyloxyamine hydrochloride,[4] was included in the series of alkoxyamines converted into guanidines with cyanamide. Another alkylated guanidine, 1-benzyloxy-2,3-diisopropylguanidine, was prepared by the reaction of benzyloxyamine with diisopropylcarbodiimide.[5] Fusion of benzyloxyamine hydrochloride with dimethylcyanamide afforded 1-benzyloxy-3,3-dimethylguanidine.

(1) Part IV: E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964).

(2) (a) *Cf.* D. D. Nyberg and B. E. Christensen, *J. Am. Chem. Soc.*, **78**, 781 (1956), and references cited. (b) Since the completion of this work, the preparation of aralkoxyguanidine sulfates by this procedure has been described: *cf.* J. G. Robert and G. M. Tartary, Rhone-Poulenc, Irish Patent 1140/63 (Nov. 24, 1963) (Derwent Basic No. 10296). Included in this patent were the sulfates corresponding to aralkoxyguanidines **1**–**3** and **6**–**8** of Table I.

(3) (a) *Cf.* A. T. Fuller and H. King, *J. Chem. Soc.*, 963 (1947). (b) Dr. J. J. Ursprung of these laboratories has prepared alkylguanidines by fusion of amine salts with cyanamide (private communication). In the present work with alkoxyamine hydrochlorides, attempted fusions often led to vigorous decomposition.

(4) B. J. R. Nicolaus, G. Pagani, and E. Testa, *Helv. Chim. Acta*, **45**, 1381 (1962).

(5) J. G. Moffatt and H. G. Khorana, *J. Am. Chem. Soc.*, **83**, 649 (1961), isolated the adduct of morpholine and dicyclohexylcarbodiimide in high yields.

TABLE I

ARALKOXYGUANIDINES

$$RONH-\overset{\overset{NH}{\|}}{C}-NH_2\cdot HX$$

No.	R	HX	Formula	M.p., °C.	Recrystn. solvent[a]	Yield, %	Procedure[b]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1a	$C_6H_5CH_2$	O	$C_8H_{11}N_3O$	104–107[c]	A	72	A	58.16	6.71	25.44	58.46	6.56	25.57
1b	$C_6H_5CH_2$	HNO_3	$C_8H_{11}N_3O\cdot HNO_3$	105 dec.	B	37	B	42.10	5.30	24.55	42.20	5.09	24.38
1c	$C_6H_5CH_2$	*c*-$C_6H_{11}NHSO_3H$	$C_8H_{11}N_3O\cdot C_6H_{13}NO_3S$	107–108	C			48.82	7.02	16.27	48.95	7.16	16.16
2	*p*-CH_3-$C_6H_4CH_2$	HNO_3	$C_9H_{13}N_3O\cdot HNO_3$	105 dec.	B	10	B	44.62	5.83	23.13	44.53	5.89	22.82
3	*p*-Cl-$C_6H_4CH_2$	HNO_3	$C_8H_{10}ClN_3O\cdot HNO_3$	138 dec.	D	23	B	36.58	4.22	21.33	36.68	4.17	21.01
				144 dec.	E	76	A						
4	2,6-$Cl_2C_6H_3CH_2$	HCl	$C_8H_9Cl_2N_3O\cdot HCl$	131.5–132.5	C	70	A[d]	35.51	3.72	15.53	35.69	3.76	15.34
5	*p*-C_6H_5-$C_6H_4CH_2$	O	$C_{14}H_{15}N_3O$	176–177	A	41	A[e]	69.69	6.27	17.42	69.73	6.40	17.69
6	$C_6H_5\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$	*c*-$C_6H_{11}NHSO_3H$	$C_9H_{13}N_3O\cdot C_6H_{13}NO_3S$	107–110	F	30	A[f]	50.26	7.31	15.63	50.40	7.14	15.57
7	$(C_6H_5)_2CH$	HNO_3	$C_{14}H_{15}N_3O\cdot HNO_3$	117 dec.	G	39	B	55.26	5.30	18.41	55.24	5.77	18.21
8a	$C_6H_5CH_2CH_2$	O	$C_9H_{13}N_3O$	77–78	H	69	A[g]	60.31	7.31	23.45	60.45	7.33	23.67
8b	$C_6H_5CH_2CH_2$	*c*-$C_6H_{11}NHSO_3H$	$C_9H_{13}N_3O\cdot C_6H_{13}NO_3S$	91.5–93.5	I			50.26	7.31	15.63	50.28	7.25	15.56
9	$C_6H_5CH_2CH(CH_3)$	*c*-$C_6H_{11}NHSO_3H$	$C_{10}H_{15}N_3O\cdot C_6H_{13}NO_3S$	128.5–130.5	F	59	A[h]	51.59	7.58	15.04	52.06	7.62	15.08
10a	$C_6H_5OCH_2CH_2$	O	$C_9H_{13}N_3O_2$	122–124	J	85	A	55.37	6.71	21.53	55.45	6.66	21.72
10b	$C_6H_5OCH_2CH_2$	HNO_3	$C_9H_{13}N_3O_2\cdot HNO_3$	104 dec.	B	37	B	41.86	5.46	21.70	41.66	5.73	21.58
10c	$C_6H_5OCH_2CH_2$	*c*-$C_6H_{11}NHSO_3H$	$C_9H_{13}N_3O_2\cdot C_6H_{13}NO_3S$	95.5–96.5[i]	F			48.11	7.00	14.96	48.22	7.10	15.11
11	*p*-C_6H_5-$C_6H_4OCH_2CH_2$	O	$C_{15}H_{17}N_3O_2$	186–188[j]	K	58	A	66.40	6.32	15.49	66.09	6.55	15.72
12a	$C_6H_5(CH_2)_3$	HCl	$C_{10}H_{15}N_3O\cdot HCl$	96–98	L	76	A[k]	52.28	7.02	18.29	52.40	7.02	18.07
12b	$C_6H_5(CH_2)_3$	HNO_3	$C_{10}H_{15}N_3O\cdot HNO_3$	111 dec.	M	51	B	46.87	6.29	21.86	46.67	6.31	22.07
13	$(C_6H_5)_2CHCH_2CH_2$	HNO_3	$C_{16}H_{19}N_3O\cdot HNO_3$	116 dec.	N	42	B	57.82	6.07	16.86	57.73	6.00	17.09

$$C_6H_5CH_2O\underset{\displaystyle R_1}{\underset{|}{N}}-\overset{\overset{NR_2}{\|}}{C}-N<\begin{matrix}R_3\\R_4\end{matrix}\cdot HX$$

	R_1	R_2	R_3	R_4									
14	H	H	CH_3	CH_3	*c*-$C_6H_{11}NHSO_3H$	$C_{10}H_{15}N_3O\cdot C_6H_{13}NO_3S$	120–123	F	65	C	51.59	7.58	15.04	51.50	7.61	15.05
15	CH_3	H	H	H	HCl	$C_9H_{13}N_3O\cdot HCl$	183–183.5[l]	J	38	B	50.12	6.54	19.48	50.22	6.04	19.93
16	H	*i*-Pr	*i*-Pr	H	HCl	$C_{14}H_{23}N_3O\cdot HCl$	125.5–126.5	G	29	D	58.83	8.46	14.70	58.66	8.48	14.61

[a] A, ethanol; B, ethanol–ether; C, methanol–ethyl acetate; D, methanol; E, aqueous methanol; F, ethyl acetate solution of aralkoxyguanidine treated with acetone solution of 1 equiv. of cyclohexane–sulfamic acid affording pure material without recrystallization; G, isopropyl alcohol–ethyl acetate; H, aqueous ethanol; I, ethanol–cyclohexane; J, isopropyl alcohol; K, ethanol–isopropyl alcohol; L, ethyl acetate–methylene chloride; M, methyl ethyl ketone–ethyl acetate; N, ethyl acetate. [b] A, cyanamide plus suspended aralkoxyamine hydrochloride in refluxing toluene; B, 2-methyl-2-thiopseudourea sulfate plus aralkoxyamine; C, dimethylcyanamide fusion with aralkoxyamine hydrochloride; D, diisopropylcarbodiimide plus the aralkoxyamine. [c] Dr. J. J. Ursprung of these laboratories first isolated crystalline benzyloxyguanidine using the 2-methyl-2-thiopseudourea procedure. J. G. Robert and G. M. Tartary[2b] reported m.p. 106–107° after recrystallization from water. [d] Purification was facilitated by conversion of the crude hydrochloride into the free base, m.p. 146–149°, and regeneration of the hydrochloride salt. [e] The usual work-up (Experimental section) was modified. The crude guanidine hydrochloride was extracted with ethanol and the extracts were evaporated to dryness. The residue was dissolved in methanol and basified with sodium methoxide, and the resulting suspension was diluted with water. The crude solid was dissolved in ethyl acetate, clarified with Celite, and crystallized. [f] The reaction was carried out in refluxing benzene instead of toluene. The oily guanidine hydrochloride on basification afforded an oily base which was isolated by ether extraction. [g] The reaction was carried out in benzene at 70–75° because of the reported instability of the starting amine hydrochloride (see ref. 1 and references cited therein). Basification of the oily guanidine hydrochloride afforded an oil; however, isolation by ether extraction left a crystalline free base after evaporation of the ether. [h] The reaction was carried out at 83–84° in toluene. Basification of the oily guanidine hydrochloride afforded an oil which was isolated by ether extraction. [i] Double melting point. Initial melting at 85.5–87.5°, then resolidification and melting at 95.5–96.5°. [j] The crude guanidine hydrochloride was a solid, m.p. 175–177°, but was converted into the free base with methanolic sodium methoxide and purified. [k] Purification was facilitated by conversion of the crude hydrochloride into the free base, m.p. 68–69°, and regeneration of the hydrochloride salt. [l] The N-methyl group has a marked effect on the physical properties. The hydrochloride was a high-melting solid and the free base an oil, whereas the free base of benzyloxyguanidine (**1**) was crystalline and its hydrochloride an oil. The N-methyl guanidine hydrochloride was recovered in a purified state by dissolving the crude hydrochloride in water, adding NaOH and NaCl, and chilling the solution.

The starting aralkoxyamines[6] for the preparation of aralkoxyguanidines **4, 5,** and **11** (Table I) were new compounds and were prepared by the alkylation of N-hydroxyphthalimide followed by hydrazinolysis.[7] Table I summarizes the properties and syntheses of the aralkoxyguanidines prepared.

Pharmacological Methods. A. Toxicity and Gross Observations in Mice.—Groups of four mice (albino Upjohn strain, 18–22 g.) were injected intraperitoneally with test compound dissolved or suspended in 0.25% aqueous methylcellulose. Observations of gross behavioral changes were carried out. The dose was decreased in 0.5 log units from 1000 mg./kg. until completely killing, and living doses were obtained. The LD_{50} was estimated by the method of Spearman and Karber.[8] The values are approximations with an accuracy of about +100 to −50%.

B. Reserpine Antagonism.—Groups of six mice were pretreated with the test compound and 30 min. later received 2.5 mg./kg. of reserpine i.p. Ninety minutes later the mice were observed and the degree of ptosis was scored on a four-point scale.

C. Anorexigenic Test in Dogs.—Dogs, on a once-a-day 30-min. feeding schedule, were given the compounds orally 1 hr. prior to presentation of food. The amount of food consumed during the 30-min. feeding period was recorded and compared to control values.

D. Potentiation of Tryptamine.—Treated mice were injected with tryptamine hydrochloride, 25 mg./kg. i.v. The mice were evaluated for the presence of the typical symptoms: head weave, arch back, hind limb spread, and pawing induced by large doses of tryptamine. The 25 mg./kg. i.v. dose of tryptamine alone did not produce symptoms.

Pharmacological Results.—The results of these test procedures are shown in Table II. Except for **11,** all compounds were in the same range of toxicity, LD_{50} values between 56 and 316 mg./kg. Compound **11,** tested twice, caused no deaths in mice at 1000 mg./kg. All of the compounds caused convulsions at the higher doses and most of them produced motor stimulation at or below the convulsive dose (exceptions were **2, 5, 7,** and **9**).

Only 4 of the 17 compounds at doses of 50 mg./kg. or less had any effect against the ptosis produced by i.p. reserpine. Compounds **3, 6, 13,** and **15** had ED_{50} values from 33 to 50 mg./kg. Tranylcypromine sulfate and *d*-amphetamine were run in parallel with all the compounds in the table and had ED_{50} values of 2.2 and 12.5 mg./kg., respectively.

The compounds exhibiting the greatest anorexigenic activity in the dogs were compounds **1, 6, 10, 12,** and **16.** Compared with *d*-amphetamine in the anorexigenic test, compounds **1** and **6** were approximately 1/5 and 1/15 as active, respectively, and compounds **10, 12,** and **16** were about 1/10 as active. While the potency of these aralkoxyguanidines as anorexigenic agents is less than that of *d*-amphetamine, they appear to lack some of the undesirable effects of this amine. The pharmacology of one or more of these guanidines will be reported in greater detail in a subsequent publication.

TABLE II

PHARMACOLOGICAL ACTIVITY OF ARALKOXYGUANIDINES

Compd.	LD_{50}, mg./kg., i.p., mice	Convulsions, mg./kg.	Stimulation, mg./kg.	Reserpine ED_{50}, i.p.	Anorexigenic % inhibition at 5 mg./kg. p.o. (dogs)
1a	75	30	30	...[a]	100
2	75	100	...	...	11[b]
3	167	100	10	50	10
4	100	100	30	...	0
5	56	100	...	...	0
6	316	300	100	40	65
7	65	100	...	...	26
8b	133	100	100	...	19
9	133	100	...	...	6
10a	56	100	100	...	86
11	>1000	1000	300	...	21
12b	65	100	100	...	83
13	65	100	100	50	0
14	237	300	100	...	7
15	178	300	100	33	0
16	56	100	30	...	82

[a] Indicates no activity at doses tested. [b] Tested only at 1 mg./kg.

When tested for tryptamine potentiating activity, none of this series of compounds was active at doses up to 50 mg./kg. Tranylcypromine sulfate and *d*-amphetamine sulfate were run in parallel with these compounds and had tryptamine potentiating ED_{50} values of 2.5 and >2.5 mg./kg., respectively.

The failure of these materials to block reserpine-induced ptosis or potentiate tryptamine would suggest that the anorexigenic effects are not due to the usual involvement of sympathomimetic amine actions.

When compared to the previously published data on O-aralkylhydroxylamines,[1] the aralkoxyguanidines, as a group, tended to be more toxic when administered i.p. to mice and had greater anorexigenic activity *p.o.* in dogs.

Experimental[9]

Starting Materials.—Eleven of the starting aralkoxyamines (for **1–3, 6–10, 12–14,** and **16**) were described in ref. 1 and references cited therein. In addition, N-methylbenzyloxyamine[1] was known. The remaining three aralkoxyamines were prepared from the corresponding aralkyl halides with the triethylamine salt of N-hydroxyphthalimide[10] followed by hydrazinolysis as described below.

N-(2,6-Dichlorobenzyloxy)phthalimide.—A solution of 2,6-dichlorobenzyl chloride[10] (39.1 g., 0.2 mole), 32.6 g. of N-hydroxyphthalimide, and 61 ml. of triethylamine in 300 ml. of dimethylformamide (DMF) was stirred and warmed on a steam bath for 1 hr. and 10 min., cooled, and diluted with 500 ml. of water affording 60.5 g. of the aralkoxyphthalimide, m.p. 168.5–169.5°. Recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{15}H_9Cl_2NO_3$: C, 55.92; H, 2.82; Cl, 22.01; N, 4.35. Found: C, 55.67; H, 3.03; Cl, 22.25; N, 4.26.

2,6-Dichlorobenzyloxyamine Hydrochloride.—A suspension of N-(2,6-dichlorobenzyloxy)phthalimide (55 g., 0.17 mole) in 500 ml. of methylene chloride was treated with 8.6 g. of hydrazine hydrate in a small volume of methanol and stirred for 23 hr.

(6) A recent review includes a summary of methods for the preparation of O-substituted hydroxylamine derivatives. See A. O. Ilvespää and A. Marxer, *Chimia* (Aarau), **18,** 1 (1964).

(7) A. F. McKay, D. L. Garmaise, G. Y. Paris, and S. Gelblum, *Can. J. Chem.*, **38,** 343 (1960).

(8) "Statistical Method in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952, p. 524.

(9) Melting points were taken on a Unimelt apparatus (A. H. Thomas Co., Philadelphia, Pa.) and are corrected.

(10) Obtained from the Aldrich Chemical Co., Inc., Milwaukee, Wis.

at room temperature. Solid was removed by filtration and washed with CH_2Cl_2. The filtrate was evaporated to dryness under reduced pressure and the residue was extracted with ether. The ethereal extracts were acidified with HCl in isopropyl alcohol affording 38.2 g. of crude aralkoxyamine hydrochloride, m.p. 199–201° dec. Recrystallization (methanol–ethyl acetate) afforded 27.2 g. of analytically pure material, m.p. 206° dec.

Anal. Calcd. for $C_7H_7Cl_2NO \cdot HCl$: C, 36.79; H, 3.53; Cl, 46.55; N, 6.13. Found: C, 37.21; H, 3.51; Cl, 46.50; N, 6.31.

N-(4-Phenylbenzyloxy)phthalimide.—4-Biphenylmethanol[10] (16.5 g., 0.09 mole) was converted into 4-phenylbenzyl chloride with thionyl chloride and the crude halide was stirred and warmed on the steam bath with 14.7 g. of N-hydroxyphthalimide, 28 ml. of triethylamine, and 100 ml. of DMF for 1 hr. The solution was cooled and diluted with water (500 ml.). The solid was collected, washed with water and methanol, and dried affording 23.6 g. of the product, m.p. 191–193°. A sample recrystallized from benzene–ethanol for analysis had m.p. 192–194°.

Anal. Calcd. for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59. Found: C, 76.04; H, 4.55.

4-Phenylbenzyloxyamine Hydrochloride.—A methylene chloride suspension of N-(4-phenylbenzyloxy)phthalimide (23 g., 0.07 mole) was stirred with 3.6 g. of hydrazine hydrate and 10 ml. of methanol for 16 hr. The solid was removed by filtration and washed with CH_2Cl_2. The filtrate was evaporated, and the residue extracted with warm ether. The extracts were washed with water, diluted with methanol, and concentrated on a steam bath to remove the ether. Dilution with water afforded 12.4 g., m.p. 61–63°, of the free base. Recrystallization from isopropyl alcohol afforded 9.3 g. of the aralkoxyamine having m.p. 63–64°, which was dissolved in isopropyl alcohol and treated with HCl. The crude solid was collected and recrystallized from 95% ethanol affording 8.0 g. of the **hydrochloride**, m.p. 255–256° dec.

Anal. Calcd. for $C_{13}H_{13}NO \cdot HCl$: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.46; H, 5.92; N, 5.74.

2-(4-Biphenylyloxy)ethyl Chloride.—To a chilled suspension of 26 g. (0.12 mole) of 2-(4-biphenylyloxy)ethanol[11] in 200 ml. of benzene containing 9.75 ml. of pyridine was slowly added 9.0 ml. of $SOCl_2$ with vigorous stirring. The mixture was stirred briefly at room temperature, refluxed for 3 hr., washed with water and then brine, and dried ($MgSO_4$). The solution was concentrated and the benzene was displaced with methanol. On cooling, 22.85 g., m.p. 101–103°, of the chloro compound was obtained. Recrystallization from methanol afforded an analytical sample, m.p. 102–104°.

Anal. Calcd. for $C_{14}H_{13}ClO$: C, 72.26; H, 5.63; Cl, 15.24. Found: C, 72.60; H, 5.42; Cl, 14.87.

N-[2-(4-Biphenylyloxy)ethoxy]phthalimide.—A solution of 28.2 g. (0.12 mole) of 2-(4-biphenylyloxy)ethyl chloride, 19.8 g. of N-hydroxyphthalimide, and 37 ml. of triethylamine in 185 ml. of DMF was stirred and heated on the steam bath for 28 hr. (after 1 hr. on the steam bath 90% of the biphenylyloxyethyl chloride was still present). The solution was cooled and diluted with 250 ml. of water with stirring. The solid was collected, washed with water, taken up in CH_2Cl_2, and dried (Na_2SO_4). The methylene chloride was displaced with ethanol, and the solution was allowed to cool affording 11.1 g. of crude aralkoxyphthalimide, m.p. 169–171°. A sample recrystallized from methylene chloride–ethanol for analysis had m.p. 171–172°.

Anal. Calcd. for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77. Found: C, 73.73; H, 5.10.

2-(4-Biphenylyloxy)ethoxyamine Hydrochloride.—A stirred solution of N-[2-(4-biphenylyloxy)ethoxy]phthalimide (9.1 g., 0.025 mole) in 200 ml. of CH_2Cl_2 was treated with 1.27 g. of hydrazine hydrate in 5 ml. of methanol. After 5 hr. the precipitate was removed by filtration and washed with methylene chloride. The filtrate was evaporated to dryness under reduced pressure. The residue was extracted with ethyl acetate and the extracts were washed with water, dried (K_2CO_3 and $MgSO_4$), and acidified with isopropanolic HCl, affording 5.60 g., m.p. 227° dec., of product. The salt was converted into its free base, m.p. 129–130.5° after recrystallization, and the purified base was reconverted into the hydrochloride, m.p. 225–227°. A sample recrystallized from ethanol–isopropyl alcohol for analysis had m.p. 225–226°.

Anal. Calcd. for $C_{14}H_{15}NO_2 \cdot HCl$: C, 63.27; H, 6.07; N, 5.27. Found: C, 63.23; H, 6.06; N, 5.59.

2-Phenoxyethoxyguanidine. A.[12]—To a stirred suspension of 20 g. (0.105 mole) of 2-phenoxyethoxyamine hydrochloride in 150 ml. of toluene was added 4.44 g. (0.105 mole) of cyanamide,[13] and the mixture was refluxed under nitrogen for 2 hr.[14] During this time the solid present liquified to an insoluble oil. The toluene was evaporated under reduced pressure, and the oily residue was suspended in water with stirring and basified with aqueous NaOH. The resulting suspension was chilled and stirred briefly, and the solid was collected, washed with water, and dried affording 17.45 g. (85%), m.p. 120–122°. Recrystallization from isopropyl alcohol afforded analytically pure material, m.p. 122–124°.

3-Phenylpropoxyguanidine Nitrate. B.[12]—The free base, prepared from 18.8 g. (0.1 mole) of 3-phenylpropoxyamine hydrochloride by treatment with alkali, was dissolved in 100 ml. of 50% aqueous methanol. To this solution 13.9 g. (0.1 mole) of 2-methyl-2-thiopseudourea sulfate was added, and the mixture was heated under reflux for 6 hr., then evaporated to dryness under reduced pressure. The residue was dissolved in 500 ml. of 50% aqueous methanol and the solution was saturated with ammonium nitrate. Methanol was evaporated on the steam bath under an air stream, and the remaining aqueous solution was refrigerated. The solid that precipitated was separated by filtration and recrystallized twice from a mixture of methyl ethyl ketone and ethyl acetate to give 13 g. (51% yield) of product as white needles which decomposed sharply at 111°.

1-Benzyloxy-3,3-dimethylguanidine Cyclohexanesulfamate. C.[12]—Benzyloxyamine hydrochloride (16 g., 0.1 mole) and dimethyl cyanamide[15] (7 g.) were stirred under nitrogen and heated in an oil bath at 150–160° for 1.5 hr. The resulting gum was suspended in water and basified; the oil which separated was extracted with ether, and the extracts washed with water, dried, and evaporated to dryness under reduced pressure leaving 15.5 g. of mobile oil. This oil was dissolved in 155 ml. of ethyl acetate and treated with a solution of 14.4 g. of cyclohexylsulfamic acid in acetone (150 ml.) affording 24.2 g. of the hexamate salt, m.p. 120–123°.

1-Benzyloxy-2,3-diisopropylguanidine Hydrochloride. D.[12]—Benzyloxyamine (12.3 g., 0.10 mole), diisopropylcarbodiimide[10] (6.3 g., 0.05 mole), and 10 ml. of *t*-butyl alcohol were heated on a steam bath for 14.5 hr. Volatile materials were removed by heating under reduced pressure (100° at 10 mm.) leaving a blue oil. The oil was dissolved in acetone, briefly refluxed, and evaporated to dryness leaving 10.8 g. of pale green oil. This was redissolved in acetone and treated with a solution of 8.95 g. of cyclohexylsulfamic acid in acetone. On chilling overnight only a trace of insoluble material separated and was removed by filtration. The filtrate was evaporated to dryness leaving an oil which was distributed between ether and water. The aqueous layer was separated, basified, and extracted with ether. This extract was dried (K_2CO_3 and $MgSO_4$) and evaporated to dryness leaving 5.95 g. of a yellow oil. Dissolution in ethyl acetate–ether and acidification with 2-propanolic HCl afforded 5.80 g. of crude aralkoxyguanidine hydrochloride, m.p. 113–122°. Recrystallization from isopropyl alcohol–ethyl acetate afforded 4.10 g. of the pure material, m.p. 125.5–126.5°.

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(11) C. C. Vernon, E. F. Struss, M. A. O'Neil, and M. A. Ford, *J. Am. Chem. Soc.*, **57**, 527 (1935).

(12) Procedures A–D are listed in Table II.

(13) Practical grade cyanamide from Eastman Kodak Co., Rochester, N. Y., was employed. The material used was almost completely soluble in ether.

(14) In other runs, reflux periods of 1–6 hr. were employed.

(15) Practical grade from Matheson Coleman and Bell, East Rutherford, N. J.