Synthesis and Hypoglycemic Activity of Substituted Alkyl- and Alkoxyguanidines

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A series of ω-guanidino- and ω-guanidinooxyalkanols and a number of their ester and carbamate derivatives have been prepared for pharmacological evaluation as hypoglycemic agents. Also included were a variety of ω-guanidinooxyalkanoic acids. A number of the compounds exhibited significant blood glucose lowering activity when administered to rats and rabbits.

In the 50 years that have elapsed since the pioneering work of Watanabe[1] on the hypoglycemic activity of guanidine, a large number of substituted guanidines have been synthesized and evaluated for their effectiveness in lowering blood sugar concentration.

While the lower alkyl derivatives, 1-methylguanidine and 1,1-dimethylguanidine, are completely devoid of activity, isoamylguanidine and isoamyleneguanidine (Galegine) are more active than guanidine itself. When the alkylguanidines are substituted by a terminal basic moiety as in 4-aminobutylguanidine (Agmatin) and decamethylenediguanidine (Synthalin), potent hypoglycemic agents are obtained. On the other hand, the terminal carboxy-substituted compounds, exemplified by ω-guanidinoalkanoic acids, are inactive.[2]

The report that ω-guanidinoalkanoic esters (Ia) and amides (Ib) are useful therapeutic agents for the treatment of diabetes[3] and that γ-guanidinobutyramide possesses potent hypoglycemic activity in animals[4] prompted us to explore the hypoglycemic activity of a series of ω-guanidinoalkanols (Ic), their esters (Id), and their carbamates (Ie). Certain members of these series were found to possess marked hypoglycemic activity when administered to rats and rabbits. Our interest in substituted hydroxylamines led us to extend this study to include a variety of ω-guanidinooxyalkanols and ω-guanidinooxyalkanoic acids and their derivatives (II).

In this manuscript we report the synthesis and blood sugar lowering activity of these guanidino and guanidinooxy compounds.

I II

a, X = COOR
b, X = $CONH_2$
c, X = OH
d, X = OCOR
e, X = $OCONR^1R^2$

The guanidinoalkanols (Ic) were obtained by treating the corresponding aminoalkanols with 2-methyl-2-thiopseudourea. Conversion of the guanidinoalkanol salts to their esters (Id) and carbamate derivatives (Ie) was accomplished using standard procedures, and no interaction between the acylating agent and the guanidino group was encountered. Phosgenation of guanidinoethanol in the form of its sulfate salt surprisingly yielded, in addition to the chlorocarbonate derivative, a substantial quantity of guanidinoethyl sulfate. The latter compound was also obtained by heating the guanidinoethanol hydrochloride in concentrated H_2SO_4.

The aminooxyalkanols used in the preparation of the guanidinooxyalkanols (IIc) were obtained by appropriate alkylation of N-hydroxyphthalimide followed by hydrazinolysis of the resulting phthalimide. Because of the tendency for 4-bromobutanol to cyclize under the basic conditions required in the alkylation of N-hydroxyphthalimide, 4-bromobutyl benzoate was employed instead. Debenzoylation to obtain 4-aminooxybutanol was carried out subsequent to hydrazinolysis of the phthalimide.

Since attempts to prepare 3-guanidinooxypropyl acetate (IId, $n = 3$, R = CH_3) and 3-guanidinooxypropyl carbamate (IIe, $n = 3$, $R^1 = R^2 = H$) by direct acylation of 3-guanidinooxypropanol salts were unsuccessful, introduction of the acetyl and carbamoyl groups was carried out at an earlier stage in the synthesis. Acetylation of phthalimidooxypropanol prior to hydrazinolysis and carbamoylation of the haloalkanol prior to phthalimidation permitted the introduction of these groups, and their presence in no way interfered in the sequence of reactions used to obtain the desired guanidinooxy compounds.

The aminooxyalkanoic acids, precursors of the guanidinooxyalkanoic acids, were obtained by hydrolysis of their phthalimide or isopropylidine adducts. Attempts to prepare 4-guanidinooxybutyramide (IIb, $n = 3$) through 4-phthalimidooxybutyramide by ammonolysis of ethyl 4-phthalimidooxybutyrate in MeOH yielded instead phthalamide and ethyl 4-aminooxybutyrate. The desired 4-guanidinooxybutyramide was obtained by ammonolysis of methyl 4-guanidinooxybutyrate (IIa, $n = 3$, R = CH_3).

Most of the compounds prepared in this study were obtained as stable, relatively low-melting, water-soluble crystalline hydrochloride, sulfate, or cyclohexanesulfamate salts. A few of the N-substituted carbamoyloxyalkylguanidine salts resisted all efforts to obtain them in crystalline form, and attempted purification by short-path vacuum distillation of the free bases resulted in excessive decomposition. The physical constants and analytical data for these compounds are summarized in Tables I and II.

Pharmacology.—The guanidino compounds prepared in this study were evaluated for their hypoglycemic activity in male Charles River CD rats and in male albino rabbits. Groups of six animals, fasted overnight, were used in each experiment. The com-

(1) C. K. Watanabe, *J. Biol. Chem.*, **33**, 253 (1918).

(2) For a comprehensive review of the literature on hypoglycemic guanidines, see W. Creutzfeldt and H. Söling, *Ergeb. Inn. Med. Kinderheilk.*, **15**, 1 (1960).

(3) Horlicks Ltd., French Patent 5,924M (1968).

(4) W. J. H. Butterfield, B. D. Cox, M. J. Whichelow, paper presented at the European Association for the Study of Diabetes, Louvain, July 22–24, 1968.

TABLE I
GUANIDINOALKANOLS AND DERIVATIVES

$$H_2NC(=NH)NH(CH_2)_nX$$

No.	n	X	Salt	Mp, °C	Recrystn solvent	Formula	Analyses
1[a]	2	OH	H_2SO_4	132–135	AcOH	$C_6H_{20}N_6O_6S$	C, H, N, S
2	2	$OCONH_2$	HCl	125–128	*i*-PrOH	$C_4H_{11}ClN_4O_2$	C, H, Cl, N
3	2	OSO_3H		201–204	EtOH–H_2O	$C_3H_9N_3O_4S$	C, H, N, S
4[b]	3	OH	HCl	80–82	*i*-PrOH–Me_2CO	$C_4H_{12}ClN_3O$	C, H, Cl, N
5	3	$OCOCH_3$	HCl	78–80	EtOH–Et_2O	$C_6H_{14}ClN_3O_2$	C, H, Cl, N
6	3	$OCOC_6H_5$	HCl	143–145	*i*-PrOH	$C_{11}H_{16}ClN_3O_2$	C, H, Cl, N
7	3	$OCONH_2$	HCl	122–124	*i*-PrOH	$C_5H_{13}ClN_4O_2$	C, H, Cl, N
8	3	$OCON(C_2H_5)_2$	HCl	*c*		$C_9H_{21}ClN_4O_2$	C, H, Cl, N
9	3	$OCON(CH_2)_4$	HCl	*c*		$C_9H_{19}ClN_4O_2$	C, H, Cl, N
10	3	OSO_3H		179–181	EtOH–H_2O	$C_4H_{11}N_3O_4S$	C, H, N, S
11[b]	4	OH	HCl	107–109	*i*-PrOH	$C_5H_{14}ClN_3O$	C, H, Cl, N
12	4	$OCOCH_3$	HCl	*c*		$C_7H_{16}ClN_3O_2$	C, H, Cl, N
13	4	$OCOC_6H_5$	HCl	111–113	*i*-PrOH	$C_{12}H_{18}ClN_3O_2$	C, H, Cl, N
14	4	$OCONH_2$	HCl	180–183	*i*-PrOH	$C_6H_{15}ClN_4O_2$	C, H, Cl, N
15	4	$OCONHCH_3$	HCl	*c*		$C_7H_{17}ClN_4O_2$	C, H, Cl, N
16	4	$OCONHCH_3$	CHS[d]	125–126	*i*-PrOH	$C_{13}H_{29}N_5O_5S$	C, H, N, S

[a] Reported by Schering-Kahlbaum A-G, German Patent 462,995 (1928). [b] The corresponding nitrate and picrate salts are described.[7] [c] Noncrystallizable liquid. [d] Cyclohexanesulfamate salt.

TABLE II
GUANIDINOOXY ALKANOLS, ALKANOIC ACIDS, AND DERIVATIVES

$$H_2NC(=NH)NHO(CH_2)_nX$$

No.	n	X	Salt	Mp, °C	Recrystn solvent	Formula	Analyses
17	1	COOH		195–196[a]	Me_2CO–H_2O		
18	2	OH	CHS[b]	102–103	*i*-PrOH–Me_2CO	$C_9H_{22}N_4O_5S$	C, H, N, S
19	3	COOH		207–208.5[c]	H_2O	$C_5H_{11}N_3O_3$	C, H, N
20	3	$COOCH_3$	HCl	77–79	*i*-PrOH–Et_2O	$C_6H_{14}ClN_3O_3$	C, H, Cl, N, OCH_3
21	3	$CONH_2$	CHS[b]	109.5–111	*i*-PrOH	$C_{11}H_{25}N_5O_5S$	C, N, S; H[d]
22	3	OH	CHS[b]	108–109	*i*-PrOH–Me_2CO	$C_{10}H_{24}N_4O_5S$	C, H, N, S
23	3	OH	H_2SO_4	109–111	*i*-PrOH–MeOH	$C_8H_{24}N_6O_8S$	C, H, N, S
24	3	$OCOCH_3$	H_2SO_4	108.5–110	EtOH	$C_{12}H_{28}N_6O_{10}S$	C, H, N, S
25	3	$OCONH_2$	H_2SO_4	152–153	MeOH–EtOH	$C_{10}H_{26}N_8O_{10}S$	C, H, N, S
26	3	$OCONHCH_3$	H_2SO_4	138–138.5	MeOH–EtOAc	$C_{12}H_{30}N_8O_{10}S$	C, H, N, S
27	3	$OCON(CH_3)_2$	H_2SO_4	151.5–152	MeOH–EtOAc	$C_{14}H_{34}N_8O_{10}S$	C, S; H, N[e]
28	3	$OCONC_4H_8O$[f]	CHS[b]	97–98	*i*-PrOH–*i*-Pr_2O	$C_{15}H_{31}N_5O_7S$	C, H, N, S
29	4	COOH		192–195	H_2O	$C_6H_{13}N_3O_3$	C, H, N
30	4	OH	CHS[b]	80.5–81.5	*i*-PrOH–*i*-Pr_2O–EtOAc	$C_{11}H_{26}N_4O_5S$	C, H, N, S

[a] Lit.[8] mp 195°. [b] Cyclohexanesulfamate salt. [c] Lit.[8] mp 205°. [d] H: calcd, 7.42; found, 6.95. [e] H: calcd, 6.77; found, 6.31. N: calcd, 22.12; found, 22.45. [f] NC_4H_8O = morpholino.

pound was dissolved in saline and injections were made subcutaneously. Blood samples were obtained before administration of the compound and 2.5 and 5 hr after drug injection. Phenformin was used as positive control. Blood glucose was measured by the Hoffman procedure as modified for the Technicon Auto-Analyzer[5] Graded doses of compound were employed, and the concentration producing a significant lowering of blood glucose at 2.5 or 5 hr was determined.

Of the 30 compounds evaluated, six were equal or superior to γ-guanidinobutyramide when evaluated in the rat and five in the rabbit (see Table III). The remaining compounds failed to produce a significant lowering of blood sugar in rats at 300 mg/kg and in rabbits at 400 mg/kg after subcutaneous administration.

(5) W. S. Hoffman, *J. Biol. Chem.*, **120**, 51 (1937). We thank Drs. J. F. Douglas and H. Singer for these determinations.

3-Guanidinooxypropanol sulfate (**23**) was the most potent compound when evaluated in the rat and approximated phenformin in its activity. In the rabbit, 4-guanidinobutyl methylcarbamate hydrochloride (**15**) exhibited the greatest activity.

Experimental Section[6]

ω-Guanidinoalkanols.—2-Guanidinoethanol sulfate (**1**) was obtained in 67% yield from 2-aminoethanol and 2-methyl-2-thiopseudourea sulfate. 3-Guanidinopropanol hydrochloride (**4**) and 4-guanidinobutanol hydrochloride (**11**) were prepared in 79 and 84% yields, respectively, essentially by the method of Fishbein and Gallaghan.[7]

(6) Melting points were determined using a Thomas–Hoover melting point apparatus and are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.3% of the theoretical values.

(7) L. Fishbein and J. A. Gallaghan, *J. Am. Chem. Soc.*, **76**, 3217 (1954).

TABLE III

Compd	Hypoglycemic act., mg/kg sc[a]	
	Rat	Rabbit
4	600	300
7	300	150
14	300	150
15	300	125
16	600	300
22	300	>275
23	75	>600
30	300	>600
3-Guanidinobutyramide	300	400
Phenformin	90	125

[a] Concentration of drug required to produce a significant lowering of blood sugar.

3-Guanidinopropyl Acetate Hydrochloride (5).—A mixture of 21 g of **4** and 30 g of Ac_2O was heated to reflux. When the exothermic reaction subsided, the mixture was heated for several minutes, cooled, and treated with Et_2O. The precipitate was removed, washed with Et_2O, and dried *in vacuo* at 40°. The crude product weighed 15.3 g (57%), mp 75–78°.

Guanidinoalkyl ester hydrochlorides **6**, **12**, and **13** were prepared in 75–80% yield in a similar manner from the appropriate ω-guanidinoalkanols. Attempts to induce crystallization of **12** were unsuccessful.

3-Guanidinopropyl Carbamate Hydrochloride (7).—A stirred suspension of 25 g of **4** in 200 ml of Me_2CO–THF (1:1) was treated with excess $COCl_2$ at room temperature until a clear solution was obtained. The solvent was removed *in vacuo*, and the residual oil was dissolved in 200 ml of Me_2CO. Excess NH_3 gas was added, the Me_2CO was decanted, and the mixture of oil and solid was washed with Me_2CO. Warm HOAc (75 ml) was added, and the mixture was filtered. Et_2O was added to the chilled HOAc solution producing an oil which crystallized on standing. After two recrystallizations, the purified product weighed 16 g (51%).

2-Guanidinoethyl carbamate hydrochloride (2) and 4-guanidinobutyl carbamate hydrochloride (14) were prepared in a similar manner from **1** and **11**. They were obtained as crystalline solids in yields of 35 and 60%, respectively.

3-Guanidinopropyl diethylcarbamate hydrochloride (8), 3-guanidinopropyl tetramethylenecarbamate hydrochloride (9), and 4-guanidinobutyl methylcarbamate hydrochloride (15) were prepared as described for **7** with the following modification. When the reaction with the amine was completed, the Me_2CO was removed *in vacuo*, H_2O was added, and the resulting solution was adjusted to pH 13.5 with aqueous NaOH. It was washed ($CHCl_3$), neutralized (dilute HCl), charcoaled, and evaporated to dryness. The residue was extracted with *i*-PrOH, and the solution was treated with charcoal, filtered, and concentrated to dryness under N_2. The oil residue was analyzed without further purification.

4-Guanidinobutyl Methylcarbamate Cyclohexanesulfamate (16).—Compound **15** was converted to its free base with excess 50% NaOH. A solution of the base in *i*-PrOH was treated with an equimolar quantity of cyclohexanesulfamic acid in *i*-PrOH. The mixture was warmed, clarified, and cooled, yielding **16** in the form of a white crystalline solid (65%).

2-Guanidinoethyl Sulfate (3) and 3-Guanidinopropyl Sulfate (10).—A solution of 0.01 mole of guanidinoalkanol hydrochloride in 3 ml of H_2SO_4 was heated on a steam bath for 5 min and allowed to stand at room temperature for 2 hr. EtOH (30 ml) was added, and the precipitate which formed was removed by filtration, washed with EtOH, and dried. The crude product was recrystallized from aqueous EtOH, yield 35%.

Reaction of 2-Guanidinoethanol Sulfate (1) with $COCl_2$.—Gaseous $COCl_2$ was added to a stirred mixture of 14.1 g of **1** in 250 ml of 1:1 THF–Me_2CO for 5 hr. The solid was separated, washed with Me_2CO, and dried, yielding 6.5 g of crude product, mp 180–190° dec. Two recrystallizations from aqueous EtOH gave 4.7 g of a substance, mp 201–204° and identical (ir spectra and mmp) with **3** obtained in the reaction of 2-guanidinoethanol hydrochloride with H_2SO_4.

The THF–Me_2CO filtrate was concentrated *in vacuo* at 30° and treated with 75 ml of concentrated NH_4OH. The solution was stirred at room temperature for 10 min, evaporated to dryness *in vacuo* on a steam bath, extracted with 100 ml of hot *i*-PrOH, filtered, concentrated to 50 ml, and chilled. The solid was removed by filtration and washed with Me_2CO. Recrystallization (*i*-PrOH) yielded 1.5 g of pure carbamate hydrochloride **2**.

Table I summarizes the physical constants, crystallizing solvents, and analyses for these compounds.

Guanidinooxyacetic Acid (17).[8] Aminooxyacetic acid was prepared by a modification of the "Organic Syntheses" procedure.[9] H_2SO_4 (50%, w/w aqueous) was used instead of concentrated HCl, and it was removed by addition of $Ba(OH)_2$ to pH 3.5. After filtration and evaporation of the filtrate *in vacuo*, the residue of crude aminooxyacetic acid (23.8 g), 36.2 g of 2-methyl-2-thiopseudourea sulfate, and 41.3 g of $Ba(OH)_2 \cdot 8H_2O$ were heated in 150 ml of H_2O for 3 hr. Filtration of the $BaSO_4$ and evaporation of the filtrate *in vacuo* yielded 10.1 g of **17** which was purified by recrystallization (Table II).

4-(Guanidinooxy)butyric Acid (19).[10] Ethyl 4-(phthalimidooxy)butyrate was prepared by treating a solution of 130.5 g of N-hydroxyphthalimide in 800 ml of DMF with 43.2 g of MeONa followed by 156 g of ethyl 4-bromobutyrate, and heating on a steam bath for 6 hr. The residue after filtration of the mixture and evaporation of the solvent *in vacuo* was poured into H_2O and taken up in Et_2O. Washing the organic layer with 5% aqueous Na_2CO_3 and with H_2O, drying (Na_2SO_4), and evaporation of the Et_2O yielded 196 g of ethyl 4-(phthalimidooxy)butyrate, mp 40–44°. *Anal.* ($C_{14}H_{15}NO_5$) C, H, N.

The ester (108.6 g) was hydrolyzed by refluxing with 500 ml of 3 *N* HCl for 2 hr, then chilling and filtering off the phthalic acid. Evaporation of the solution *in vacuo*, azeotropic drying of the residue with C_6H_6, and crystallization from MeOH–*i*-PrOH–Et_2O yielded 44.5 g of crude 4-(aminooxy)butyric acid hydrochloride.

The hydrochloride in 600 ml of *i*-PrOH was treated with 15.5 g of MeONa. After 2 hr, the NaCl was filtered off and the filtrate was concentrated *in vacuo*, yielding crude 4-(aminooxy)butyric acid. This was converted to 4-(guanidinooxy)butyric acid by the route described for **17**. The crude acid was crystallized as described by Borek and Clarke[8] to give 29.7 g of product which was purified by recrystallization. The cyclohexanesulfamate salt had mp 105–107° from *i*-PrOH–Et_2O. *Anal.* ($C_{19}H_{34}N_4O_6S$) C, H, N, S.

5-(Guanidinooxy)valeric acid (29) was prepared by the procedure used for **19**. Ethyl 5-(phthalimidooxy)valerate had mp 59–60° from *i*-Pr_2O. *Anal.* ($C_{15}H_{17}NO_5$) C, H, N.

Methyl 4-(Guanidinooxy)butyrate Hydrochloride (20).—A mixture of 20.2 g of **19**, 41 ml of MeOH, 12.5 ml of concentrated HCl, and 160 ml of acetone dimethyl keral was allowed to stand at room temperature for 17 hr. Evaporation of the solvent *in vacuo* and crystallization of the solid residue from (*i*-PrOH–Et_2O) yielded 92% of purified **20**.

4-(Guanidinooxy)butyramide Cyclohexanesulfamate (21). Methyl 4-(guanidinooxy)butyrate, liberated from 19.0 g of its hydrochloride (**20**) as described in the procedure for preparing **19**, was dissolved in 200 ml of concentrated NH_4OH[10] and a slow stream of NH_3 was bubbled into the solution at room temperature for 4 hr.[10] H_2O and NH_3 were removed by evaporation *in vacuo* and an aqueous solution of the residue was adjusted to pH 5.5 by addition of cyclohexanesulfamic acid. Concentration *in vacuo* and crystallization of the residue yielded 50% of purified **21**.

2-(Guanidinooxy)ethanol Cyclohexanesulfamate (18).—2-(Phthalimidooxy)ethanol was prepared from N-hydroxyphthalimide and 2-bromoethanol by the method described for the preparation of **19** except that the crude product, after removal of DMF, was dissolved in $CHCl_3$ and filtered free of NaBr, and the solvent was evaporated *in vacuo*. The residue, when poured into *i*-Pr_2O, solidified and was filtered off and recrystallized from hexane–EtOAc, mp 83–84°. *Anal.* ($C_{10}H_9NO_4$) C, H, N.

The phthalimidooxy compound (104 g), 29.4 g of 85% $N_2H_4 \cdot H_2O$, and 500 ml of MeOH were refluxed for 1.5 hr and the mixture was chilled. Phthalhydrazide was separated and the filtrate

(8) E. Borek and H. T. Clarke, *J. Biol. Chem.*, **125**, 479 (1938).

(9) H. S. Aaron and H. T. Clarke, in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, pp 172–174.

(10) Attempts to convert the ester into the amide with 15% (w/w) NH_3 in MeOH at room temperature for 7 days and at 80 and 125° for 6.5 hr under pressure were unsuccessful.

(11) Modification of the method of N. Von Than and A. Olomucki, *Biochim. Biophys. Acta*, **59**, 545 (1962).

was concentrated *in vacuo*. The residue was taken up in $CHCl_3$, and the solution was filtered and concentrated *in vacuo*, leaving crude 2-(aminooxy)ethanol as an oil.

The aminooxy compound (39 g), 135 g of 2-methyl-2-thiopseudourea cyclohexanesulfamate (preparation follows), and 1 l. of EtOH were refluxed for 13 hr. The cooled mixture was filtered and the filtrate was evaporated *in vacuo*. Compound **18** was crystallized by addition of 350 ml of *i*-PrOH. Filtration and addition of *i*-Pr_2O to the filtrate provided a second crop, bringing the crude yield to 30%. The product was purified by recrystallization.

3-(Guanidinooxy)propanol cyclohexanesulfamate (22) was prepared in the same manner as described for **19**, except that the crude 3-(phthalimidooxy)propanol, after removal of the NaBr and DMF, was poured into H_2O and solidified. It was separated from an oily contaminant by extraction into hot CCl_4 from which it crystallized on cooling. 3-(Phthalimidooxy)propanol, recrystallized from *i*-Pr_2O, melted at 85.5–86.5°. *Anal.* ($C_{11}H_{11}NO_4$) C, H, N.

3-(Guanidinooxy)propanol Sulfate (23).—3-(Phthalimidooxy)propanol was converted to 3-(aminooxy)propanol as described above for 2-(aminooxy)ethanol. The aminooxypropanol (57 g), 89 g of 2-methyl-2-thiopseudourea sulfate, and 400 ml of H_2O were heated on a steam bath for 2 hr. Unchanged thiouronium salt was removed by concentrating the reaction mixture *in vacuo*, dissolving the residue in 100 ml of MeOH, and filtering. The MeOH was removed *in vacuo* and the residue was extracted with hot C_6H_6, Et_2O, and *i*-PrOH. The product was crystallized from MeOH–*i*-PrOH.

3-(Guanidinooxy)propyl Acetate Sulfate (24).—3-(Phthalimidooxy)propanol (38 g), 38 ml of Ac_2O, and 228 ml of pyridine were refluxed for 5 min, cooled, and poured onto 760 g of ice. Concentrated HCl (235 ml) was added to precipitate the acetate. It was filtered off, washed (H_2O), and converted, without purification, to 3-(aminooxy)propyl acetate as described for the preparation of **18**. This was converted to 3-(guanidinooxy)propyl acetate sulfate by the method described for **23**.

A portion of 3-(phthalimidooxy)propyl acetate, recrystallized from CCl_4–hexane, had mp 61.5–63.5°. *Anal.* ($C_{13}H_{13}NO_5$) C, H, N.

A portion of 3-(aminooxy)propyl acetate was converted to its HCl salt, mp 79–82° (*i*-PrOH–Et_2O). *Anal.* ($C_5H_{12}ClNO_3$) C, H, Cl, N.

4-(Guanidinooxy)butanol Cyclohexanesulfamate (30).—4-(Phthalimidooxy)butyl benzoate was prepared from N-hydroxyphthalimide and 4-bromobutyl benzoate[12] by the procedure described for the preparation of **19** except that the crude product, after removal of DMF, was poured into H_2O and allowed to solidify. Recrystallized (*i*-PrOH) 4-(phthalimidooxy)butyl benzoate had mp 84–85.5°. *Anal.* ($C_{19}H_{17}NO_5$) H, N; C: calcd, 67.25; found, 67.94. This was converted to 4-(aminooxy)butyl benzoate by the procedure described for the preparation of **18**.

A solution of the crude 4-(aminooxy)butyl benzoate (from 0.2 mole of phthalimidooxy compound) in 400 ml of MeOH, to which 160 mg of MeONa had been added, was refluxed for 9 hr and concentrated *in vacuo*, and the residue was dissolved in $CHCl_3$. The solution was freed of MeONa by filtration and the solvent was removed *in vacuo*. The crude residual 4-(aminooxy)butanol was separated from methyl benzoate by extraction into H_2O, evaporation *in vacuo*, and drying by azeotropic distillation with C_6H_6. The 4-(aminooxy)butanol was converted to **30** by the method described for **18**.

3-(Guanidinooxy)propyl Carbamate Sulfate (25).—3-(Phthalimidooxy)propyl carbamate was prepared from N-hydroxyphthalimide and 3-chloropropyl carbamate[13] by the procedure described for the preparation of **30**, mp 134–135° (*i*-PrOH, C_6H_6). *Anal.* ($C_{12}H_{12}N_2O_5$) C, H, N.

The phthalimidooxy compound yielded 3-(aminooxy)propyl carbamate by the hydrazinolysis procedure described for the preparation of **18**. The aminooxy compound was purified by conversion to its hydrochloride with ethanolic HCl, mp 127–128° (*i*-PrOH, BuOH). *Anal.* ($C_{14}H_{11}ClN_2O_3$) C, H, Cl, N.

The aminooxy compound, liberated from the hydrochloride as described in the preparation of **19**, was converted to **25** by the method described for **23**.

3-(Guanidinooxy)propyl Methylcarbamate Sulfate (26).—A THF solution of 3-bromopropyl chloroformate was treated with 2 equiv of $MeNH_2$ in THF and the amine salt was filtered off. The filtrate was concentrated *in vacuo* and the crude 3-bromopropyl methylcarbamate was used to alkylate N-hydroxyphthalimide as described for the preparation of **19**. 3-(Phthalimidooxy)propyl methylcarbamate, recrystallized from EtOAc–*i*-Pr_2O, melted at 99–100.5°. *Anal.* ($C_{13}H_{14}N_2O_5$) C, H, N.

Crude 3-(aminooxy)propyl methylcarbamate, obtained from the phthalimidooxy compound by the procedure described for **18**, was converted to 3-(guanidinooxy)propyl methylcarbamate cyclohexanesulfamate by the procedure described for **23**, using 2-methyl-2-thiopseudourea cyclohexanesulfamate instead of the sulfate. When all attempts to crystallize the cyclohexanesulfamate failed, the free guanidinooxy base was liberated with MeONa in *i*-PrOH as described for the preparation of **19**, dissolved in H_2O, and adjusted to pH 5.0 by addition of aqueous H_2SO_4. The solution was concentrated *in vacuo* and **26** was crystallized in 16% yield.

3-(Guanidinooxy)propyl Dimethylcarbamate Sulfate (27).—A THF solution of 78.3 g of 3-chloropropyl chloroformate was treated with 124 g of 40% (w/w) aqueous Me_2NH with cooling, the solution was concentrated *in vacuo*, and the residual carbamate was taken up in EtOAc, washed (2% HCl, aqueous $NaHCO_3$, H_2O), and dried (Na_2SO_4). The crude 3-chloropropyl dimethylcarbamate after removal of the solvent was used to alkylate N-hydroxyphthalimide as described for the preparation of **19**. The crude 3-(phthalimidooxy)propyl dimethylcarbamate was extracted three times with *i*-Pr_2O, the extracts were discarded, and the insoluble oil was treated with $N_2H_4 \cdot H_2O$ as described for the preparation of **18**. The crude 3-(aminooxy)-propyl dimethylcarbamate was purified by conversion to the sulfate, mp 148–149° from EtOH–*i*-PrOH. *Anal.* ($C_{12}H_{30}N_4O_{10}S$) C, H, N, S.

An aqueous solution of the sulfate was treated with 1 equiv of $Ba(OH)_2 \cdot 8H_2O$ and then converted to **27** *via* the cyclohexanesulfamate as described for the preparation of **26**.

3-(Guanidinooxy)propyl 4-Morpholinecarboxylate Cyclohexanesulfamate (28).—3-Bromopropyl 4-morpholinecarboxylate was prepared from 3-bromopropyl chloroformate and 2.5 equiv of 40% aqueous morpholine as described for the preparation of **27**. The solvent was removed *in vacuo* and replaced by *i*-Pr_2O. Ethanolic HCl was added and the mixture was filtered. The filtrate was washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo*. The residual crude bromocarbamate was converted by the procedure described for **30** to 3-(phthalimidooxy)propyl 4-morpholinecarboxylate, mp 96–97° (hexane–CCl_4). *Anal.* ($C_{16}H_{18}N_2O_6$) C, H, N.

The phthalimidooxy compound was converted to **28** by the procedure described for **18**.

2-Methyl-2-thiopseudourea Cyclohexanesulfamate.—A solution of 27.3 g of $Ba(OH)_2 \cdot 8H_2O$ in 70 ml of hot H_2O was mixed with a solution of 27.8 g of 2-methyl-2-thiopseudourea sulfate in 150 ml of H_2O and the mixture was stirred for 45 min, then filtered with the aid of Celite. The filtrate was concentrated *in vacuo*, MeOH was added to the residue, and the evaporation was repeated. A hot solution of the residue in 50 ml of MeOH was treated with a hot solution of 35.8 g of cyclohexanesulfamic acid in 60 ml of MeOH and chilled, and the cyclohexanesulfamate salt was filtered off, mp 172.5–175° from EtOH. *Anal.* ($C_8H_{19}N_3O_3S_2$) C, H, N, S.

Reaction of Ethyl 4-(Phthalimidooxy)butyrate with NH_3 in MeOH.—Ethyl 4-(phthalimidooxy)butyrate (13.9 g) was dissolved in 30 ml of MeOH and 50 ml of 6.5 *N* NH_3 in MeOH was added. The mixture was filtered free of phthalamide (identified by mp and ir) after 1.5 hr at room temperature. The filtrate was concentrated *in vacuo* and the residue was treated with 50 ml of C_6H_6. More phthalamide was filtered from this solution and the filtrate was once again concentrated *in vacuo*, yielding 4.5 g (61%) of crude ethyl 4-(aminooxy)butyrate, which was converted to its hydrochloride, mp 105–108°, lit.[14] mp 106–107°.

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