35 (23–52) mg./kg., respectively. Subsequent doses depressed the polysynaptic pathway to a greater degree than the monosynaptic reflex. The duration of the effect was from 40 to 60 min.

Potentiation of the loss of righting reflex induced by hexobarbital (100 mg./kg.) was observed in the mouse while ether-induced loss of righting reflex was much more influenced in the rat. When administered to mice just recovering from hexobarbital hypnosis[15] recurrence of the loss of righting reflex resulted in 100% of the animals tested.

Discussion

The exact mode of action of these substituted biurets on inhibition of gastric secretion and incidence of ulcer formation is not clear. Various classes of compounds will inhibit these gastric parameters in the ligated rat (*i.e.*, anticholinergics, antispasmodics, carbonic anhydrase inhibitors, CNS depressants). While no data are available on possible inhibition of carbonic anhydrase, no evidence of diuresis (qualitative observed with acetazolamide) was noted at near-lethal doses. Phenethylbiuret did not demonstrate properties of anticholinergic or antispasmodic agents as tested by the antichromodacryorrhea and charcoal meal test in animals. It possesses some action at the level of the central nervous system as evidenced by anticonvulsant activity, inhibition of poly- and monosynaptic reflexes, and conditioned avoidance response. The potentiation and recurrence of hexobarbital-induced loss of righting reflex is further evidence of a central effect, according to the interpretation of Brodie, *et al.*[15] However, by comparison with other central nervous system agents, such as phenobarbital and meprobamate, these effects are relatively weak. Doses of phenobarbital and meprobamate required to produce comparable protection against ulcer formation produced signs of neurological depression not observed with phenethylbiuret.

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(15) B. Brodie, P. A. Shore, S. L. Silver, and R. Pulver, *Nature*, **175**, 1133 (1955).

Bacteriostats. VI.[1a] Bacteriostatic Activities of Some Substituted Guanidines[1b]

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A number of guanidine derivatives were prepared for screening for antibacterial activity. Some of these derivatives were quite active against both Gram-positive and Gram-negative bacteria. The bacteriostatic activity of 1,10-di(3,4-dichlorobenzylguanidino)decane dihydrochloride was comparable with Hibitane.

The performance of 1,6-di(4-chlorophenyldiguanido)-hexane (Hibitane)[2] as a bacteriostat prompted the synthesis of a number of guanidines for screening as antibacterial agents. Although it was reported[2] that 1,6-di(4-chlorophenylguanidino)hexane possessed $^1/_{30}$ the antibacterial activity of Hibitane, the benzylguanidine derivatives were expected[3] to exhibit higher bacteriostatic activities than the corresponding phenylguanidines.

The guanidine derivatives generally were prepared by condensing amines with the corresponding S-methylisothiuronium iodides. New thioureas and isothiuronium salts prepared during this investigation are listed in Tables I and II, respectivly. Tables III to VII, inclusive, describe the properties of the substituted guanidines.

TABLE I

THIOUREAS, $(RNH)_2CS$

R	M.p., °C.	Yield, %	Empirical formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	S Calcd.	S Found
4-Methylbenzyl	135–136[a]	100	$C_{17}H_{20}N_2S$	71.80	72.02	7.09	7.33	9.85	9.81	11.28	11.26
3,4-Dimethylbenzyl	98–99[b]	99	$C_{19}H_{24}N_2S$	73.03	72.87	7.74	7.66	8.97	8.78	10.26	10.36
3,4-Dichlorophenethyl	124–125[c]	82	$C_{17}H_{16}Cl_4N_2S$[d]	48.36	48.54	3.82	3.96	6.64	6.82	7.59	7.58
α-Naphthylmethyl	168–169[e]	70	$C_{23}H_{20}N_2S$	77.48	77.34	5.65	5.62	7.86	7.35	8.99	8.60
3,4-Dimethoxyphenethyl	135–136[a]	93	$C_{21}H_{28}N_2O_4S$	62.35	62.20	6.98	6.90	6.93	7.22	7.93	7.98
2,5-Dichlorobenzyl	169–170[f]	76	$C_{15}H_{12}Cl_4N_2S$	45.71	46.08	3.07	3.13	7.11	7.39	8.13	8.05
Furfuryl	83–85[b]	88	$C_{11}H_{12}N_2O_2S$	55.90	55.51	5.12	5.33	11.86	11.60	13.57	13.35

[a] Crystallized from ethanol. [b] From aqueous ethanol. [c] From ether–hexane. [d] Calcd.: Cl, 33.86. Found: Cl, 33.60. [e] Crystallized from aqueous dimethylformamide. [f] From acetone. [g] Calcd.: Cl, 35.98. Found: Cl, 36.06.

In the disubstituted guanidine series, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl derivatives of 4-chlorobenzyl- and 3,4-dichlorobenzylguanidines displayed the highest bacteriostatic activities while in the benzylguanidine series, the undecyl and dodecyl derivatives were the most active (see Table VIII). N-Nonyl-N′-3,4-dichlorobenzylguanidine hydrochloride exhibited

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(1) (a) Paper V: D. L. Garmaise, R. W. Kay, R. Gaudry, H. A. Baker, and A. F. McKay, *Can. J. Chem.*, **39**, 1493 (1961); (b) Contribution No. 39, Monsanto Canada Limited.

(2) G. E. Davies, J. Francis, A. R. Martin, F. L. Rose, and G. Swain, *Brit. J. Pharmacol.*, **9**, 192 (1954).

(3) A. F. McKay, *Soap and Chemical Specialties*, **36**, No. 11, 99 (1960).

Table II

S-Methylisothiourea Hydriodides, $RNHC(SCH_3)=NR'\cdot HI$

					Analyses, %									
					C		H		X		N		S	
R	R′	M.p., °C.	Yield, %	Empirical formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Benzyl	H	99–100[a]	91	$C_9H_{13}IN_2S$	35.08	35.32	4.25	4.32	41.17	41.38	9.09	8.99	10.40	10.46
4-Chlorobenzyl	H	92–95	90	$C_9H_{12}ClIN_2S$	31.54	31.10	3.53	3.81	47.38	47.64	8.18	8.09	9.36	9.44
2,5-Dichlorobenzyl	H	169–170	84	$C_9H_{11}Cl_2IN_2S$	28.66	28.49	2.94	3.05	52.46	52.49	7.43	7.58	8.50	8.66
3,4-Dichlorobenzyl	H	117–118	95	$C_9H_{11}Cl_2IN_2S$	28.66	28.96	2.94	3.21	52.46	52.16	7.43	7.49	8.50	8.37
4-Chlorobenzyl	4-Chlorobenzyl	141–142	73	$C_{16}H_{17}Cl_2IN_2S$	41.13	41.31	3.67	3.75	41.33	41.54	6.00	6.16	6.86	6.85
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	175–176[b]	85	$C_{16}H_{15}Cl_5N_2S$	43.22	43.28	3.46	3.49	39.87	39.59	6.30	6.55	7.21	7.19
3,4-Dichlorobenzyl	2-Tetrahydropyranomethyl	115–117	86	$C_{15}H_{21}Cl_2IN_2OS$	37.91	37.92	4.45	4.39	41.36	41.35	5.90	5.92	6.75	6.86
4-Methylbenzyl	4-Methylbenzyl	129–130	100	$C_{18}H_{23}IN_2S$	50.70	50.81	5.41	5.39	29.76	29.74	6.57	6.58	7.52	7.57
3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	120–120.5	100	$C_{20}H_{27}IN_2S$	52.86	52.64	5.99	6.06	27.93	27.95	6.17	6.00	7.06	6.99
3,4-Dichlorophenethyl	3,4-Dichlorophenethyl	125–126	97	$C_{18}H_{19}Cl_4IN_2S$	38.33	38.65	3.40	3.44	47.64	47.54	4.97	4.86	5.68	5.76
α-Naphthylmethyl	α-Naphthylmethyl	113–115	99	$C_{26}H_{29}IN_2S\cdot C_2H_5OH$	57.36	57.04	5.37	5.36	23.30	23.03	5.15	4.94	5.89	6.78
2,5-Dichlorobenzyl	2,5-Dichlorobenzyl	204–206	77	$C_{16}H_{15}Cl_4IN_2S$	35.85	35.44	2.82	2.80	50.14	50.18	5.23	5.37	5.98	6.10
n-Dodecyl	*n*-Dodecyl	61–62	83	$C_{26}H_{55}IN_2S$	56.29	56.03	9.93	9.74	22.88	23.26	5.05	5.34	5.78	6.05
Furfuryl	Furfuryl	123–125	79	$C_{12}H_{15}IN_2O_2S$	38.44	38.05	4.00	4.08	33.56	33.21	7.40	7.63	8.48	8.58

[a] All of the compounds were recrystallized from ethanol–ether. [b] Hydrochloride salt.

outstanding activity against both Gram-positive and Gram-negative bacteria.

Among the trisubstituted guanidines listed in Table IX, N,N′-di(3,4-dichlorobenzyl)-N″-benzyl-, N,N′-di(3,4-dichlorobenzyl)-N″-(α-naphthylmethyl)-, N,N′,-N″-tri(3,4-dichlorobenzyl)guanidines were most active against Gram-positive microorganisms. These trisubstituted guanidines were comparable in antibacterial activity with Hibitane but their performance in the presence of 10% serum was much lower (*cf.* values in Tables IX and X). Serum drastically lowered the bacteriostatic activities of all di- and trisubstituted guanidines evaluated.

The α,ω-di(3,4-dichlorobenzyl)alkanes (Table X) exhibited quite similar bacteriostatic activities against both Gram-negative and Gram-positive bacteria. 1,10-Di(3,4-dichlorobenzylguanidino)decane exhibited antibacterial activity comparable with Hibitane both in the absence and presence of 10% serum. The α,ω-di(substituted-benzylguanidino)alkanes in general performed better in the presence of serum than the simple di- and trisubstituted guanidines.

The aminoguanidine moiety required a longer-chain aliphatic substituent to reach optimum bacteriostatic activity compared with the benzyl- and substituted benzylguanidines. Tetradecylaminoguanidine displayed the highest activity in this series (*cf.* Table XI).

Some of the guanidine derivatives listed in Tables III to VII were evaluated for fungistatic activities. A few of the more active compounds are listed in Table XII. N-*n*-Nonyl-N′-3,4-dichlorobenzylguanidine hydrochloride possessed oustanding activity against both *Microsporum gypseum* and *Trichophyton granulosum*.

Experimental(4)

Symmetrically Substituted Thioureas.—4-Methylbenzylamine (121 g., 1.0 mole) was added to a solution of carbon disulfide (38 g., 0.50 mole) in ethanol (500 ml.) at 0–30° over a 30 min. period, and the suspension was heated under reflux for 22 hr. The solution on concentration and cooling gave 1,3-di(4-methylbenzyl)-thiourea, m.p. 130–135°, yield 142 g. (100%). Recrystallization from ethanol raised the m.p. to 135–136°.

The thioureas listed in Table I were prepared in the same general way. In some cases the reagents were refluxed in butanol rather than ethanol.

2,5-Dichlorobenzyl Isothiocyanate.—2,5-Dichlorobenzyl isothiocyanate, b.p. 150–151° (1 mm.), was prepared in 76% yield by the method previously(5) described for the preparation of isothiocyanates.

Anal. Calcd. for $C_8H_5Cl_2NS$: C, 44.10; H, 2.31; Cl, 32.50; N, 6.42; S, 14.67. Found: C, 44.22; H, 2.30; Cl, 32.52; N, 6.82; S, 14.64.

2,5-Dichlorobenzylthiourea.—Aqueous ammonium hydroxide (10 ml. of 28% solution) was added to 2,5-dichlorobenzyl isothiocyanate (10.0 g., 0.05 mole) in ethanol (50 ml.) and the solution was allowed to stand for 1 hr. After evaporation of the solution, the residue was crystallized from dilute ethanol to give material of m.p. 176–177°, yield 8.8 g. (82%).

Anal. Calcd. for $C_8H_8Cl_2N_2S$: C, 40.53; H, 5.31; halogen, 41.65; N, 6.51. Found: C, 40.56; H, 5.36; halogen, 41.19; N, 6.85.

N-(2-Tetrahydropyranomethyl)-N′-(3,4-dichlorobenzyl)thiourea.—A solution of 3,4-dichlorobenzyl isothiocyanate (10.9 g., 0.05 mole) and 2-aminomethyltetrahydropyran (5.8 g., 0.05 mole) in ethanol (20 ml.) was allowed to stand overnight. The

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(4) All meeting points are uncorrected. This work was completed before the requirement for corrected melting points was introduced by American Chemical Society journals. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Illinois, and by Dr. C. Daessle, Montreal, Quebec.

(5) A. F. McKay, D. L. Garmaise, R. Gaudry, H. A. Baker, G. Y. Paris, R. W. Kay, G. E. Just, and R. Schwartz, *J. Am. Chem. Soc.*, **81**, 4328 (1959).

TABLE III

N,N′-DISUBSTITUTED GUANIDINES RNHC(=NH)NHR′

R	R′	M.p., °C.	Yield, %	Empirical formula	Analyses, %							
					C		H		X		N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4-Chlorobenzyl	4-Chlorobenzyl	150–151[a,b]	70	$C_{15}H_{16}Cl_2IN_3$	41.27	41.37	3.70	4.05	45.35	45.10	9.64	9.70
4-Chlorobenzyl	4-Chlorobenzyl	150–151.5[c,d]	86	$C_{15}H_{16}Cl_3N_3$	52.14	52.09	4.68	4.55	30.86	30.96	12.19	12.21
3,4-Dichlorobenzyl	4-Chlorobenzyl	166.5–168[a,b]	79	$C_{15}H_{15}Cl_3IN_3$	38.27	38.41	3.21	3.40	49.56	49.78	8.93	8.44
3,4-Dichlorobenzyl	2,4-Dichlorobenzyl	189–190[a,e]	42	$C_{15}H_{14}Cl_4IN_3$	35.67	35.52	2.79	3.04	53.20	52.94	8.32	8.32
3,4-Dichlorobenzyl	2,4-Dichlorobenzyl	160–161[c,d]	93	$C_{16}H_{14}Cl_5N_3$	43.46	43.40	3.41	3.50	42.77	43.16	10.16	10.16
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	148–150[a,f]	69	$C_{15}H_{14}Cl_4IN_3$	35.67	35.21	2.79	3.08	53.20	53.32	8.32	8.62
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	153–154[c,d]	93	$C_{15}H_{14}Cl_5N_3$	43.46	43.43	3.41	3.62	42.77	42.96	10.16	9.84
3,4-Dichlorobenzyl	*n*-Propyl	117.5–118.5[a,g]	95	$C_{11}H_{16}Cl_2IN_3$	34.04	34.13	4.16	4.13	50.97	50.85	10.83	10.57
3,4-Dichlorobenzyl	*n*-Butyl	110–111[a,g]	66	$C_{12}H_{18}Cl_2IN_3$	35.84	35.90	4.51	4.51	49.19	49.20	10.45	10.44
3,4-Dichlorobenzyl	*n*-Amyl	124–126[a,g]	88	$C_{13}H_{20}Cl_2IN_3$	37.52	37.72	4.84	4.82	47.54	47.25	10.10	9.96
3,4-Dichlorobenzyl	*n*-Hexyl	107–108[a,g]	88	$C_{14}H_{22}Cl_2IN_3$	39.09	39.28	5.16	5.23	45.98	45.85	9.77	9.83
3,4-Dichlorobenzyl	*n*-Heptyl	109.5–111[a,f]	81	$C_{15}H_{24}Cl_2IN_3$	40.56	40.59	5.45	5.60	44.53	44.54	9.46	9.31
3,4-Dichlorobenzyl	*n*-Octyl	109–110[a,f]	67	$C_{16}H_{26}Cl_2IN_3$	41.94	42.12	5.72	5.91	43.17	43.34	9.17	8.98
3,4-Dichlorobenzyl	*n*-Nonyl	95–96[a,f]	99	$C_{17}H_{28}Cl_2IN_3$	43.23	43.16	5.98	6.01	41.90	41.50	8.90	9.18
3,4-Dichlorobenzyl	*n*-Nonyl	65–67[c,f]	95	$C_{17}H_{28}Cl_3N_3$	53.62	53.42	7.41	7.13	27.93	28.00	11.04	11.35
3,4-Dichlorobenzyl	*n*-Decyl	98–100[a,h]	84	$C_{18}H_{30}Cl_2IN_3$	44.46	44.62	6.22	6.21	40.68	40.67	8.64	8.64
3,4-Dichlorobenzyl	*n*-Decyl	69–71[c,f]	99	$C_{18}H_{30}Cl_3N_3$	54.75	54.49	7.66	7.65	26.94	27.15	10.64	10.43
3,4-Dichlorobenzyl	*n*-Undecyl	94.5–95[a,h]	85	$C_{19}H_{32}Cl_2IN_3$	45.61	45.53	6.45	6.40	39.44	39.83	8.40	8.50
3,4-Dichlorobenzyl	*n*-Undecyl	67–69[c,f]	95	$C_{19}H_{32}Cl_3N_3$	55.81	55.89	7.89	7.90	26.02	26.39	10.28	10.40
3,4-Dichlorobenzyl	*n*-Dodecyl	96–97[a,g]	67	$C_{20}H_{34}Cl_2IN_3$	46.70	46.65	6.66	6.46	38.47	38.90	8.17	8.39
3,4-Dichlorobenzyl	*n*-Dodecyl	69–70[c,i]	98	$C_{20}H_{34}Cl_3N_3$	56.80	56.40	8.10	8.16	25.15	24.96	9.94	9.74
4-Chlorobenzyl	*n*-Nonyl	85–86[a,g]	96	$C_{17}H_{29}ClIN_3$	46.63	46.92	6.68	6.71	37.09	36.98	9.60	9.55
4-Chlorobenzyl	*n*-Nonyl	67–68[c,g]	99	$C_{17}H_{29}Cl_2N_3$	58.95	58.79	8.44	8.35	20.47	20.23	12.13	11.95
4-Chlorobenzyl	*n*-Decyl	85.5–86.5[a,g]	69	$C_{18}H_{31}ClIN_3$	47.84	47.92	6.92	6.92	35.94	36.31	9.30	9.08
4-Chlorobenzyl	*n*-Decyl	62–63[c,g]	100	$C_{18}H_{31}Cl_2N_3$	59.99	59.70	8.67	8.69	19.68	19.55	11.66	11.34
4-Chlorobenzyl	*n*-Undecyl	94–94.5[a,g]	95	$C_{19}H_{33}ClIN_3$	48.98	49.27	7.14	7.33	34.85	34.75	9.02	8.97
4-Chlorobenzyl	*n*-Undecyl	65–67[c,g]	98	$C_{19}H_{33}Cl_2N_3$	60.95	61.05	8.88	8.85	18.94	19.04	11.22	11.35
4-Chlorobenzyl	*n*-Dodecyl	92–93[a,g]	93	$C_{20}H_{35}ClIN_3$	50.05	50.12	7.35	7.40	33.84	34.03	8.76	8.65
4-Chlorobenzyl	*n*-Dodecyl	65–67[c,g]	99	$C_{20}H_{35}Cl_2N_3$	61.84	61.53	9.08	9.15	18.26	18.32	10.82	10.84
4-Chlorobenzyl	*n*-Hexadecyl	85–86[a,f]	67	$C_{24}H_{43}ClIN_3$	53.78	53.66	8.09	8.23	30.29	30.48	7.84	7.74
Benzyl	*n*-Heptyl	92–93[c,f]	56	$C_{15}H_{26}ClN_3$	63.48	63.21	9.24	9.23	12.49	12.57	14.81	14.59
Benzyl	*n*-Octyl	70–72[a,f]	90	$C_{16}H_{28}IN_3$	49.36	49.47	7.25	7.09	32.60	32.60	10.79	10.71
Benzyl	*n*-Octyl	85–86[c,f]	74	$C_{16}H_{28}ClN_3$	64.51	64.34	9.47	9.29	11.90	12.11	14.11	14.56
Benzyl	*n*-Nonyl	84–85[a,f]	98	$C_{17}H_{30}IN_3$	50.62	50.43	7.50	7.56	31.47	31.60	10.42	10.50
Benzyl	*n*-Nonyl	102–103[c,f]	91	$C_{17}H_{30}ClN_3$	65.46	65.18	9.70	9.53	11.37	11.18	13.47	13.59
Benzyl	*n*-Decyl	90–91[a,f]	96	$C_{18}H_{32}IN_3$	51.79	51.72	7.74	7.72	30.41	30.42	10.07	10.26
Benzyl	*n*-Decyl	106–107[c,f]	99	$C_{18}H_{32}ClN_3$	66.33	66.31	9.90	9.76	10.88	11.16	12.89	12.82
Benzyl	*n*-Undecyl	87–89[a,f]	90	$C_{19}H_{34}IN_3$	52.89	52.88	7.94	8.00	29.42	29.24	9.74	9.62
Benzyl	*n*-Undecyl	110–111[c,f]	90	$C_{19}H_{34}ClN_3$	67.13	67.14	10.08	9.97	10.43	10.68	12.36	12.25
Benzyl	*n*-Dodecyl	85.5–86.5[a,f]	98	$C_{20}H_{36}IN_3$	53.92	54.25	8.15	8.00	28.49	28.70	9.43	9.22
Benzyl	*n*-Dodecyl	113–114[c,f]	100	$C_{20}H_{36}ClN_3$	67.86	68.19	10.25	10.27	10.02	10.07	11.87	11.89

[a] Hydriodide. [b] Crystallized from acetone-ether. [c] Hydrochloride. [d] Crystallized from ethanol-chloroform. [e] From ethanol. [f] From ethanol-ether. [g] From ethyl acetate-ether. [h] From aqueous ethanol. [i] From water.

Table IV

N,N′,N″-Trisubstituted Guanidines, RNHC(=NR′)NHR″

R	R′	R″	M.p., °C.	Yield, %	Empirical formula	C		H		X		N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Methyl	198–200^{a,b}	73	$C_{16}H_{16}Cl_4IN_3$	37.02	37.22	3.11	3.48	51.76	51.59	8.10	8.05
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Methyl	98–100^{c,b}	90	$C_{16}H_{16}Cl_5N_3 \cdot C_2H_5OH$	45.64	45.73	4.68	4.70	37.43	37.70	8.87	9.21
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Ethyl	124–125^{a,d}	76	$C_{17}H_{18}Cl_4IN_3$	38.30	37.91	3.40	3.64	50.42	50.61	7.88	7.94
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2-Hydroxyethyl	158–159^{a,b}	47	$C_{17}H_{18}Cl_4IN_3O$	37.18	37.43	3.30	3.53	48.93	48.69	7.65	7.49
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2-Hydroxyethyl	118–119^{c,b}	99	$C_{17}H_{18}Cl_5N_3O \cdot H_2O$	42.93	43.15	4.24	4.10	37.27	37.35	8.83	8.62
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Propyl	149–150^{a,b}	79	$C_{18}H_{20}Cl_4IN_3$	39.52	39.58	3.69	3.92	49.12	49.04	7.68	7.76
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Propyl	104–105^{c,e}	98	$C_{18}H_{20}Cl_5N_3$	47.46	47.03	4.43	4.65	38.92	38.88	9.23	9.15
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Allyl	139–140^{a,b}	40	$C_{18}H_{18}Cl_4IN_3$	39.66	39.78	3.33	3.21	49.31	48.96	7.71	7.45
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3-Hydroxypropyl	139–140^{c,b}	55	$C_{18}H_{20}Cl_5N_3O$	45.84	45.56	4.28	4.37	37.59	37.74	8.91	8.99
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Butyl	112–114^{a,c}	92	$C_{19}H_{22}Cl_4IN_3$	40.67	40.82	3.95	4.14	47.88	48.11	7.49	7.53
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Butyl	94–96^{c,e}	94	$C_{19}H_{22}Cl_5N_3$	48.58	48.13	4.72	4.73	37.75	38.10	8.95	8.92
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Octyl	131–132^{a,b}	44	$C_{23}H_{30}Cl_4IN_3$	44.80	44.85	4.90	5.03	43.58	43.34	6.82	7.13
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Octyl	129–130^{c,b}	48	$C_{23}H_{30}Cl_5N_3$	52.54	52.54	5.75	5.94	33.72	33.24	7.99	8.08
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Hexadecyl	138–139^{a,d}	32	$C_{31}H_{46}Cl_4IN_3$	51.04	50.98	6.36	6.62	36.84	36.62	5.76	5.71
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	β-(Dimethylaminoethyl)	124–125^{a,b}	94	$C_{19}H_{23}Cl_4IN_4$	39.61	39.61	4.02	4.17	46.64	46.39	9.72	9.92
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Benzyl	175–176^{a,f}	67	$C_{22}H_{20}Cl_4IN_3$	44.39	44.63	3.39	3.47	45.16	44.93	7.06	7.09
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Benzyl	179–181^{c,g}	85	$C_{22}H_{20}Cl_5N_3$	52.46	52.37	4.00	4.01	35.20	35.07	8.34	8.41
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	94–95^{a,c,h}	87	$C_{22}H_{17}Cl_6N_3$	49.28	49.45	3.20	3.30	39.67	39.65	7.84	7.95
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	229–230^{a,c}	83	$C_{22}H_{18}Cl_6IN_3$	39.79	40.05	2.73	3.00	51.14	50.98	6.33	6.45
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	217–219^{c,e}	83	$C_{22}H_{18}Cl_7N_3$	46.14	46.11	3.17	2.90	43.35	43.60	7.34	7.32
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2,4,5-Trimethylbenzyl	208–210^{a,i}	74	$C_{25}H_{26}Cl_4IN_3$	47.12	47.25	4.11	4.23	42.17	42.29	6.59	6.50
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2,4,5-Trimethylbenzyl	232–233^{c,i}	96	$C_{25}H_{26}Cl_5N_3$	55.01	55.26	4.80	4.98	32.49	32.30	7.70	7.59
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	4-Isopropylbenzyl	178–179^{a,b}	72	$C_{25}H_{26}Cl_4IN_3$	47.12	46.97	4.11	4.10	42.17	42.07	6.59	6.53
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	4-Isopropylbenzyl	178–180^{c,d}	74	$C_{25}H_{26}Cl_5N_3$	55.01	54.82	4.80	4.81	32.49	32.51	7.70	7.59
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3,4-Dimethoxyphenethyl	152–153^{a,j}	83	$C_{25}H_{26}Cl_4IN_3O_2$	44.87	45.15	3.92	4.04	40.15	39.95	6.28	6.42
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3,4-Dimethoxyphenethyl	136–138^{c,b}	84	$C_{25}H_{26}Cl_5N_3O_2$	51.95	51.67	4.54	4.48	30.67	30.40	7.27	7.15
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	α-Naphthylmethyl	226–227^{a,k}	73	$C_{26}H_{22}Cl_4IN_3$	48.41	48.45	3.44	3.68	41.65	41.36	6.51	6.38
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	α-Naphthylmethyl	209–210^{c,k}	99	$C_{26}H_{22}Cl_5N_3 \cdot H_2O$	54.62	54.69	4.23	3.97	31.01	31.40	7.35	7.43
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Furfuryl	135–136^{a,b}	53	$C_{20}H_{18}Cl_4IN_3O$	41.06	40.86	3.10	3.28	45.93	46.04	7.18	7.37
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Furfuryl	148–149^{c,b}		$C_{20}H_{18}Cl_5N_3O$	48.66	48.68	3.67	3.59	35.91	36.16	8.54	8.74
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2-Tetrahydropyranomethyl	92–94^{c,e}	96	$C_{21}H_{24}Cl_5N_3O$	49.28	48.90	4.73	4.77	34.66	34.92	8.21	8.15
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Phenethyl	129–130^{c,b}	44	$C_{23}H_{22}Cl_5N_3$	53.35	53.23	4.28	4.23	34.24	34.19	8.12	8.19
3,4-Dichlorobenzyl	Benzyl	Benzyl	183–184^{a,c}	99	$C_{22}H_{22}Cl_2IN_3$	50.21	50.52	4.21	4.38	37.58	37.57	7.99	7.85
3,4-Dichlorobenzyl	Benzyl	Benzyl	188–189^{b,c}	97	$C_{22}H_{22}Cl_3N_3$	60.77	60.54	5.10	5.02	24.47	24.60	9.66	9.47
3,4-Dichlorobenzyl	α-Naphthylmethyl	α-Naphthylmethyl	199–201^{a,b}	94	$C_{30}H_{26}Cl_2IN_3$	57.52	57.53	4.18	4.26	31.58	31.58	6.71	6.59
3,4-Dichlorobenzyl	α-Naphthylmethyl	α-Naphthylmethyl	240–241^{b,c}	98	$C_{30}H_{26}Cl_3N_3$	67.36	67.29	4.90	5.06	19.89	19.64	7.86	7.48
3,4-Dichlorobenzyl	2-Tetrahydropyranomethyl	2-Tetrahydropyranomethyl	120–122^{a,b}	80	$C_{20}H_{30}Cl_2IN_3O_2$	44.29	44.12	5.58	5.34	36.48	36.57	7.75	7.64
3,4-Dichlorophenethyl	β-(3,4-Dichlorophenylethyl)	3,4-Dichlorophenethyl	140–141^{a,b}	78	$C_{25}H_{24}Cl_6IN_3$	42.53	42.66	3.43	3.43	48.09	47.96	5.95	6.17
3,4-Dichlorophenethyl	β-(3,4-Dichlorophenylethyl)	3,4-Dichlorophenethyl	114–115^{b,c}	98	$C_{25}H_{24}Cl_7N_3$	48.85	48.88	3.94	4.27	40.37	39.87	6.84	6.92
2,5-Dichlorobenzyl	2,5-Dichlorobenzyl	*n*-Decyl	165–166^{c,d}	60	$C_{25}H_{34}Cl_4IN_3$	46.53	46.56	5.31	5.36	41.65	41.49	6.51	6.85
4-Methylbenzyl	4-Methylbenzyl	4-Methylbenzyl	88–88.5^{a,c,h}	95	$C_{25}H_{29}N_3$	80.82	80.64	7.87	7.97			11.31	11.33
4-Methylbenzyl	4-Methylbenzyl	4-Methylbenzyl	211–212^{a,j}	80	$C_{25}H_{30}IN_3$	60.12	60.16	6.05	6.03	25.41	25.49	8.42	8.60
4-Methylbenzyl	4-Methylbenzyl	4-Methylbenzyl	237–238^{b,c}	94	$C_{25}H_{30}ClN_3$	73.59	73.45	7.41	7.53	8.69	8.81	10.30	10.12
3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	182–184^{a,j}	78	$C_{28}H_{36}IN_3$	62.10	62.21	6.70	6.68	23.43	23.35	7.76	7.63
3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	215–216^{b,c}	86	$C_{28}H_{36}ClN_3$	74.73	74.34	8.06	7.97	7.88	7.98	9.34	9.25
3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	Ethyl	150–152^{a,b}	90	$C_{21}H_{30}IN_3$	55.87	55.37	6.70	6.65	28.11	28.24	9.31	9.07

3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	Ethyl	164–165^{c,e}	88	$C_{21}H_{30}ClN_3$	70.08	69.88	8.40	8.38	9.85	10.09	11.68	11.40
3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	*n*-Butyl	102–104^{a,d}	68	$C_{23}H_{34}IN_3$	57.61	57.60	7.15	7.27	26.47	26.46	8.77	8.96
Furfuryl	Furfuryl	Furfuryl	173–175^{a,b}	60	$C_{16}H_{18}IN_3O_3$	44.99	45.26	4.25	4.43	29.71	30.07	9.84	10.04
Furfuryl	Furfuryl	Furfuryl	138–139^{b,c}	93	$C_{16}H_{18}ClN_3O_3$	57.23	56.96	5.40	5.42	10.56	10.55	12.51	12.75

[a] Hydriodide. [b] Recrystallized from ethanol–ether. [c] Hydrochloride. [d] Crystallized from ethyl acetate–ether. [e] From aqueous ethanol. [f] From acetone–ether. [g] From ethanol–chloroform. [h] Free base. [i] Crystallized from dimethylformamide–ether. [j] From ethanol. [k] From aqueous dimethylformamide.

TABLE V: α,ω-DI(GUANIDINO)ALKANES, $RNHC(=NR')NH(CH_2)_nNHC(=NR')NHR$

				Yield,	Empirical	C		H		X		N	
n	R	R′	M.p., °C.	%	formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2	3,4-Dichlorobenzyl	H	248–249^{a,b}	56	$C_{18}H_{22}Cl_4I_2N_6$	30.10	30.16	3.09	3.21	55.10	54.95	11.70	11.53
2	3,4-Dichlorobenzyl	H	205–206^{b,c}	100	$C_{18}H_{22}Cl_6N_6$	40.40	40.53	4.14	4.34	39.75	39.57	15.71	15.59
2	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	276–277^{a,d}	56	$C_{32}H_{30}Cl_8I_2N_6$	37.10	37.32	2.92	3.04	51.88	51.60	8.11	8.23
2	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	253–254^{c,d}	46	$C_{32}H_{30}Cl_{10}N_6 \cdot C_2H_5OH$	45.41	45.86	4.04	4.31			9.35	9.35
2	Benzyl	H	212.5–213^{a,e}	12	$C_{18}H_{26}I_2N_6$	37.25	37.27	4.52	4.52	43.74	43.73	14.48	14.48
4	3,4-Dichlorobenzyl	H	200–201^{c,e}	92	$C_{20}H_{26}Cl_6N_6$	42.65	42.60	4.65	4.85			14.92	14.63
4	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	145–147^{b,c}	60	$C_{34}H_{34}Cl_{10}N_6$	46.34	46.08	3.89	4.10	40.24	40.14	9.54	9.48
6	3,4-Dichlorobenzyl	H	168–168.5^{a,b,f}	81	$C_{24}H_{34}Cl_4N_{12}O_{14}$	41.81	42.01	3.51	3.53	14.53	14.68	17.22	16.98
6	4-Chlorobenzyl	H	Amorphous^{a,e}		$C_{22}H_{32}Cl_2I_2N_6$	37.46	37.26	4.57	4.82	46.04	46.28	11.92	11.72
6	Benzyl	H	165–167^{a,b}	76	$C_{22}H_{34}I_2N_6$	41.52	41.62	5.39	5.45	39.89	40.07	13.21	13.04
10	3,4-Dichlorobenzyl	H	Amorphous^{a,e}	100	$C_{26}H_{38}Cl_4I_2N_6$	37.61	37.88	4.61	4.72	47.70	47.61	10.12	9.91
11	3,4-Dichlorobenzyl	H	Amorphous^{a,e}	90	$C_{27}H_{40}Cl_4I_2N_6$	38.41	38.86	4.77	4.86	46.87	46.55	9.95	9.83
12	3,4-Dichlorobenzyl	H	167.5–169.5^{a,b}	76.5	$C_{28}H_{42}Cl_4I_2N_6$	39.18	39.47	4.93	4.95	46.10	46.08	9.79	9.95

[a] Hydriodide. [b] Recrystallized from ethanol. [c] Hydrochloride. [d] Recrystallized from dimethylformamide–ethanol. [e] From ethanol–ether. [f] Picrate.

TABLE VI: MONO- AND DISUBSTITUTED AMINOGUANIDINES, $RNHC(=NR')NHNH_2$

			Yield,		C		H		X		N	
R	R′	M.p., °C.	%	Empirical formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
n-Decyl	H	83–85^{a,b}	50	$C_{11}H_{27}IN_4$	38.59	38.81	7.95	8.01	37.08	37.01	16.37	16.15
n-Decyl	H	118–120^{c,d}	83	$C_{11}H_{27}ClN_4$	52.68	52.73	10.85	10.91	14.14	14.17	22.34	22.04
n-Undecyl	H	123–124^{c,d}	66	$C_{12}H_{29}ClN_4$	54.42	54.40	11.04	11.01	13.39	13.43	21.16	21.16
n-Dodecyl	H	88–90^{a,b}	13	$C_{13}H_{31}IN_4$	42.17	42.13	8.44	8.28	34.28	34.18	15.13	14.96
n-Dodecyl	H	118–120^{c,d}	91	$C_{13}H_{31}ClN_4$	55.98	55.76	11.20	11.16	12.72	12.46	20.09	19.86
n-Tetradecyl	H	118–120^{c,d}	61	$C_{15}H_{35}ClN_4$	58.70	58.26	11.49	11.40	11.55	11.76	18.25	17.90
n-Hexadecyl	H	118–120^{c,d}	55	$C_{17}H_{39}ClN_4$	60.95	60.63	11.73	11.40	10.58	10.42	16.73	16.68
n-Octadecyl	H	115–117^{c,d}	25	$C_{19}H_{43}ClN_4$	62.86	62.94	11.94	11.90	9.77	9.48	15.44	15.67
4-Chlorobenzyl	H	147–148^{e,f}	64	$C_{14}H_{14}ClN_7O_7$	39.30	39.24	3.30	3.50	8.29	8.37	22.92	23.00
4-Chlorobenzyl	H	157–158^{c,d}	94	$C_8H_{12}Cl_2N_4$	40.86	41.29	5.15	5.48	30.16	29.96	23.85	23.87
3,4-Dichlorobenzyl	H	162–163^{e,f}	86	$C_{14}H_{13}Cl_2N_7O_7$	36.38	36.55	2.84	2.96	15.34	15.46	21.21	21.15
3,4-Dichlorobenzyl	H	167–168^{c,d}	34	$C_8H_{11}Cl_3N_4$	35.63	35.75	4.11	3.84	39.45	39.93	20.78	20.64
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	207–208^{a,d}	92	$C_{15}H_{15}Cl_4IN_4$	34.63	34.80	2.91	2.90	51.67	51.70	10.77	10.90
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	178.5–180^{c,d}	94	$C_{15}H_{15}Cl_5N_4$	42.03	42.30	3.53	3.49	41.37	41.67	13.07	13.44
4-Chlorobenzyl	4-Chlorobenzyl	170–170.5^{a,d}	94	$C_{15}H_{17}Cl_2IN_4$	39.93	39.83	3.80	3.63	43.85	43.85	12.42	12.41
n-Dodecyl	*n*-Dodecyl	61.5–62.5^{a,g}	46	$C_{25}H_{55}IN_4$	55.74	55.54	10.29	10.27	23.56	23.67	10.40	10.35
n-Dodecyl	*n*-Dodecyl	91.5–93.5^{c,d}	55	$C_{25}H_{55}ClN_4$	67.08	65.83	12.45	12.55	7.92	7.97	12.52	12.57
4-Chlorobenzyl	*n*-Dodecyl	107–108.5^{a,d}	89	$C_{20}H_{36}ClIN_4$	48.53	48.50	7.33	7.17	32.80	32.91	11.32	11.45
4-Chlorobenzyl	*n*-Dodecyl	89–91^{c,d}	94	$C_{20}H_{36}Cl_2N_4$	59.54	59.24	8.99	9.26	17.58	17.81	13.89	13.65

[a] Hydriodide. [b] Recrystallized from water. [c] Hydrochloride. [d] Recrystallized from ethanol–ether. [e] Picrate. [f] Recrystallized from ethanol. [g] From aqueous ethanol.

Table VII

α,ω-Di(aminoguanidino)alkanes, $NH_2NHC(=NH)NH(CH_2)_nNHC(=NH)NHNH_2$

				Analyses, %							
				C		H		X		N	
n	M.p., °C.	Yield, %	Empirical formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2	202–203^{a,b}	37	$C_4H_{16}I_2N_8$	11.17	11.27	3.75	3.80	59.02	58.83	26.06	26.25
2	240.5–241.5^{b,c}	100	$C_4H_{16}Cl_2N_8$	19.44	19.72	6.53	6.90	28.69	28.70	45.34	45.67
4	161–162^{a,d}	35	$C_6H_{20}I_2N_8$	15.73	15.84	4.40	4.82	55.41	55.17	24.46	24.63
6	201.5–203^{a,b}	87	$C_8H_{24}I_2N_8$	19.76	19.77	4.97	5.08	52.21	51.97	23.05	23.32

^{a} Hydriodide. ^{b} Recrystallized from methanol–ether. ^{c} Hydrochloride. ^{d} Recrystallized from butanol.

product (m.p. 89–90°) was isolated by the addition of petroleum ether, yield 14.2 g. (85%).

Anal. Calcd. for $C_{14}H_{18}Cl_2N_2OS$: C, 50.45; H, 5.44; Cl, 21.28; N, 8.41; S, 9.62. Found: C, 50.25; H, 5.11; Cl, 21.75; N, 8.61; S, 9.46.

S-Methylisothiuronium Iodides.—1,3-Di(4-methylbenzyl)thiourea (28.4 g., 0.1 mole) was added to methyl iodide (28.4 g., 0.2 mole) in ethanol (40 ml.) and the solution was allowed to stand overnight. Evaporation of the solution gave S-methyl-N,N′-di(4-methylbenzyl)isothiuronium iodide, m.p. 129–130°, yield 42.6 g. (100%). Recrystallization from ethanol-ether solution did not change the melting point.

The other isothiuronium salts listed in Table II were prepared by this general method.

S-Methyl-N,N′-di(3,4-dichlorobenzyl)isothiuronium chloride was prepared by passing the corresponding hydriodide through a column of Amberlite IRA 400 in the chloride form.

Preparation of Guanidines.—A solution of S-methyl-N,N′-di(4-methylbenzyl)isothiuronium iodide (42.6 g., 0.1 mole) and 4-methylbenzylamine (12.1 g., 0.1 mole) in ethanol (70 ml.) was heated under reflux for 1 hr. Addition of ether (70 ml.) precipitated N,N′,N″-tri(4-methylbenzyl)guanidine hydriodide, m.p. 208–209°, yield 41.2 g. (83%).

The hydriodide salt (39.6 g., 0.08 mole) in ethanol (500 ml.) was passed through a column of Amberlite IRA 400 in the chloride form (250 ml.), and the column was washed with ethanol (250 ml.). Evaporation of the eluate gave the hydrochloride salt, m.p. 236–238°, yield 30.5 g. (95%). Recrystallization from ethanol–ether raised the melting point to 237–238°.

The disubstituted guanidines (Table III), trisubstituted guanidines (Table IV), and α,ω-di(guanidino)alkanes (Table V) were all prepared by this general method. To obtain optimum yields individual preparations were varied with regard to time, temperature, and solvent. Butanol and isoamyl alcohol were used as well as ethanol, while in some cases the reagents were heated together without solvent.

3,4-Dichlorobenzylguanidine Hydrochloride.—A solution of 3,4-dichlorobenzylamine (35.2 g., 0.2 mole) and S-methylisothiuronium iodide (43.6 g., 0.2 mole) in ethanol (100 ml.) was heated under reflux for 3 hr. The solution was evaporated and the residue was crystallized from ethanol–ether to give 3,4-dichlorobenzylguanidine hydriodide, m.p. 167–168°, yield 52.1 g. (75%).

Anal. Calcd. for $C_8H_{10}Cl_2IN_3$: C, 27.77; H, 2.91; halogen, 57.17; N, 12.15. Found: C, 27.80; H, 2.91; halogen, 56.77; N, 11.66.

A solution of the hydriodide (10.5 g., 0.03 mole) in ethanol (50 ml.) was passed through a column of Amberlite IRA 400 in the chloride form, and the column was washed with ethanol (200 ml.). The eluate was evaporated and the residue was crystallized from ethanol–ether to give 3,4-dichlorobenzylguanidine hydrochloride, m.p. 165–166.5°, yield 5.9 g. (74%).

Anal. Calcd. for $C_8H_{10}Cl_3N_3$: C, 37.73; H, 3.96; Cl, 41.78; N, 16.50. Found: C, 37.70; H, 4.02; Cl, 42.00; N, 16.04.

N,N′-Di(3,4-dichlorobenzoyl)guanidine.—A solution of 3,4-dichlorobenzoyl chloride (4.2 g., 0.02 mole) in ether (50 ml.) was added to guanidine hydrochloride (3.82 g., 0.04 mole) in *N* sodium hydroxide (40 ml.), and the mixture was stirred at room temperature for 4 hr. The products was obtained by evaporation of the ether solution, m.p. 224–225°, yield 3.3 g. (81%). Recrystallization from aqueous dimethylformamide did not change the melting point.

Anal. Calcd. for $C_{15}H_9Cl_4N_3O_2$: C, 44.36; H, 2.24; Cl, 35.00; N, 10.37. Found: C, 44.31; H, 2.52; Cl, 35.01; N, 10.47.

N-(3,4-Dichlorobenzoyl)-N′-(3,4-dichlorobenzyl)guanidine Hydrochloride.—A solution of 3,4-dichlorobenzylguanidine hydriodide (3.46 g., 0.01 mole) in ethanol (20 ml.) was neutralized with sodium hydroxide (0.40 g., 0.01 mole) in water (40 ml.). The solution was extracted with ether (70 ml.), and the ether layer was washed with water and dried. 3,4-Dichlorobenzoyl chloride (2.10 g., 0.01 mole) was added and the solution was allowed to stand overnight. The precipitate was filtered and recrystallized from ethanol to give the product as the hydrochloride, m.p. 223–224°, yield 0.71 g. (16%).

Anal. Calcd. for $C_{15}H_{12}Cl_5N_3O$: C, 42.13; H, 2.83; Cl, 41.47; N, 9.83. Found: C, 41.92; H, 2.78; Cl, 41.40; N, 10.00.

11-Bromo-N,N-dimethylundecanoamide.—11-Bromoundecanoic acid (29.4 g., 0.11 mole) in thionyl chloride (30 g.) was heated under reflux for 1 hr. The solution was evaporated and the residue of crude 11-bromoundecanoyl chloride was distilled, b.p. 125–128° (0.1 mm.) [lit.[6] b.p. 174–175° (10 mm.)], yield 28.4 g. (91%).

A solution of dimethylamine (4.50 g., 0.10 mole) in ether (25 ml.) was added dropwise to 11-bromoundecanoyl chloride (10.0 g., 0.04 mole) in ether (25 ml.) at 0°. After being allowed to stand at room temperature for 1 hr., the solution was evaporated. Crystallization of the residue from aqueous ethanol gave 11-bromo-N,N-dimethylundecanoamide, m.p. 51–53°, yield 8.3 g. (81%).

Anal. Calcd. for $C_{13}H_{26}BrNO$: C, 53.42; H, 8.97; Br, 27.34; N, 4.79. Found: C, 53.47; H, 8.81; Br, 26.98; N, 4.58.

11-Amino-N,N-dimethylundecanoamide.—A solution of 11-bromo-N,N-dimethylundecanoamide (6.6 g., 0.02 mole) and concentrated ammonium hydroxide (200 ml.) in dimethylformamide (50 ml.) was stirred for 3 days at 25°. Evaporation of this solution *in vacuo* yielded a crystalline residue of 11-amino-N,N-dimethylundecanoamide hydrobromide (m.p. 110–112°, yield 5.6 g.). The salt on addition to *N* sodium hydroxide (20 ml.) gave the base, m.p. 38–40°, yield 4.2 g. (80%).

Anal. Calcd. for $C_{13}H_{28}N_2O$: C, 68.36; H, 12.36; N, 12.27. Found: C, 68.84; H, 12.21; N, 12.46.

11-Guanidino-N,N-dimethylundecanoamide.—A solution of 11-amino-N,N-dimethylundecanoamide (3.6 g., 0.02 mole) and S-methylisothiuronium iodide (3.44 g., 0.02 mole) in ethanol (20 ml.) was heated under reflux for 3 hr. The solution was evaporated and the residue was crystallized from ethanol–ether giving the product as the hydriodide, m.p. 100–102°, yield 2.95 g. (47%). A portion of the product was treated with aqueous picric acid to give 11-guanidino-N,N-dimethylundecanoamide picrate, m.p. 142–144°.

Anal. Calcd. for $C_{20}H_{23}N_7O_8$: C, 48.10; H, 6.66; N, 19.63. Found: C, 48.32; H, 6.65; N, 19.49.

N,N′-Disubstituted-N″-aminoguanidines.—A solution of N,-N′-di(4-chlorobenzyl)-S-methylisothiuronium iodide (10.0 g., 0.02 mole) and 85% hydrazine hydrate (1.23 g., 0.02 mole) in butanol (20 ml.) was stirred at 100–105° for 1 hr. The solution was cooled and diluted with ether (100 ml.) to yield N,N′-di(4-chlorobenzyl)-N″-aminoguanidine hydriodide, m.p. 169–170°, yield 9.0 g. (94%). Recrystallization from ethanol–ether raised the m.p. to 170–170.5°.

The other N,N′-disubstituted-N″-aminoguanidines listed in Table VI were prepared by the same procedure.

N-Substituted-N′-aminoguanidines.—A solution of dodecylamine (18.5 g., 0.1 mole) and S-methylisothiosemicarbazide hydriodide (23.3 g., 0.10 mole) in ethanol (100 ml.) was heated under reflux for 1 hr. The solution was cooled and diluted with ether, giving a gummy pink precipitate (12 g.). The crude product was extracted with hot ethanol (100 ml.) giving a small quantity (0.18 g.) of insoluble 3,6-diamino-1,2,4,5-tetrazine.

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(6) F. J. Buckle, F. L. M. Pattison, and B. C. Saunders, *J. Chem. Soc.*, 1471 (1949).

TABLE VIII

BACTERIOSTATIC ACTIVITIES (M.I.C., $1/X \times 10^{-3}$)[a] OF MONO- AND DISUBSTITUTED GUANIDINES, RNHC(=NH)NHC′·HCl

R	R″	*M. pyogenes*[b] var. *aureus* (S)	*M. pyogenes*[c] var. *aureus* (R)	*Sarcina lutea*	*Strept. faecalis*	*E. coli* No. 198	*A. aerogenes*	*S. pullorum*	*Pseudomonas aeruginosa*	*Proteus mirabilis*	*Proteus vulgaris*
n-Dodecyl	H	2560	2560	2560	1280	320	160	320	160	160	80
3,4-Dichlorobenzyl	H	80	80	40	20	40	20	80	20	20	20
3,4-Dichlorobenzyl	2,4-Dichlorobenzyl	320	320	640	320	160	80	80	40	40	40
3,4-Dichlorobenzyl	4-Chlorobenzyl	320	320	320	160	80	20	20	40	20	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	640	640	640	320	160	40	40	80	80	80
4-Chlorobenzyl	4-Chlorobenzyl	160	80	80	40	40	20	20	40	40	40
3,4-Dichlorobenzyl	*n*-Propyl	10	20	10	10	10	20	20	40	20	20
3,4-Dichlorobenzyl	*n*-Butyl	80	40	80	40	40	20	20	20	20	20
3,4-Dichlorobenzyl	*n*-Hexyl	20	20	20	20	20	80	80	320	160	160
3,4-Dichlorobenzyl	*n*-Heptyl	640	640	320	320	640	40	80	40	40	40
3,4-Dichlorobenzyl	*n*-Octyl	1280	1280	1280	640	640	80	320	80	80	80
3,4-Dichlorobenzyl	*n*-Nonyl	10240	2560	40960	40960	1280	640	1280	80	160	80
3,4-Dichlorobenzyl	*n*-Decyl	2560	2560	5120	2560	320	320	2560	160	80	80
3,4-Dichlorobenzyl	*n*-Undecyl	1280	1280	5120	2560	1280	320	5120	40	80	20
3,4-Dichlorobenzyl	*n*-Dodecyl	640	1280	2560	2560	320	160	160	20	80	20
4-Chlorobenzyl	*n*-Nonyl	640	640	1280	640	160	80	320	80	80	40
4-Chlorobenzyl	*n*-Decyl	1280	640	1280	1280	320	640	320	80	160	80
4-Chlorobenzyl	*n*-Undecyl	640	640	2560	640	320	160	320	20	40	40
4-Chlorobenzyl	*n*-Dodecyl	1280	1280	2560	2560	160	80	320	10	40	40
4-Chlorobenzyl	*n*-Hexadecyl	320	320	640	1280	10	10			10	10
Benzyl	*n*-Heptyl	40	40	80	40	10	10	160	10	10	10
Benzyl	*n*-Octyl	80	80	160	80	10	10	160	20	10	10
Benzyl	*n*-Nonyl	160	160	640	320	20	20		20	20	20
Benzyl	*n*-Decyl	320	320	640	640	80	80		40	40	20
Benzyl	*n*-Undecyl	1280	640	1280	1280	160	160		80	80	40
Benzyl	*n*-Dodecyl	640	640	2560	1280	160	160		80	40	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzoyl	640	1280	1280	640	160	20	10	10	40	40
3,4-Dichlorobenzoyl	3,4-Dichlorobenzoyl	20	10	80	10	10	10	10	10	10	10

[a] Minimal inhibitory concentration determined by serial dilution technique, *e.g.*, the value 80 is equivalent to a dilution of one part in 80,000. The serial dilution technique can give quite wide variations in results and the relative order of activities is more meaningful than the absolute values listed. [b] (S) indicates penicillin sensitive. [c] (R) indicates penicillin resistant.

TABLE IX: BACTERIOSTATIC ACTIVITIES (M.I.C.,[a] 1/X × 10⁻³) OF TRISUBSTITUTED GUANIDINES, RNHC(=NR′)NHR″·HCl

R	R′	R″	*M. pyogenes* var. *aureus* (S)[a]	*M. pyogenes* var. *aureus* (R)[a]	*Sarcina lutea*	*Strept. faecalis*	*E. coli* No. 198	*A. aerogenes*	*S. pullorum*	*Pseudomonas aeruginosa*	*Proteus mirabilis*	*Proteus vulgaris*
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Methyl	640	320	640	160	320	40	40	20	80	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Ethyl	160	320	320	160	80	20	20	20	20	20
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2-Hydroxyethyl	160	160	640	160	40	10	40	10	80	10
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Propyl	640	320	1280	320	320	80	160	40	80	20
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3-Hydroxypropyl	160	160	320	80	40	20	20	20	10	20
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Butyl	640	640	2560	640	320	160	160	40	40	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Octyl	640	640	1280	1280	80	80	40	20	20	20
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	*n*-Hexadecyl	80	40	160	40	80	80	10	10	10	10
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	β-(Dimethylaminoethyl)	320	640	2560	640	320	80	40	80	40	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Benzyl	5120	2560	5120	640	640	160	160	160	80	80
In presence of 10% serum			160	80	160	160	160	20	20	20	40	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2560	5120	20480	20480	640	160	160	80	160	160
In presence of 10% serum			80	80	80	80	20	20	20	10	10	10
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2,4,5-Trimethylbenzyl	640	320	2560	640	160	40	40	20	20	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	4-Isopropylbenzyl	640	640	1280	2560	320	40	80	40	40	40
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	3,4-Dimethoxyphenethyl	320	160	320	160	160	40	40	20	20	10
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	α-Naphthylmethyl	2560	2560	2560	320	320	60	40	20	40	20
In presence of 10% serum			160	160	160	40	10	10	10	10	10	10
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	2-Tetrahydropyranomethyl	10	10	10	10	10	10	10	10	10	10
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	Furfuryl	1280	640		2560	160	320			80	40
3,4-Dichlorobenzyl	Benzyl	Benzyl	640	640	2560	320	320	160	160	80	80	80
3,4-Dichlorophenethyl	3,4-Dichlorophenethyl	3,4-Dichlorophenethyl	640	640	>5120	>5120	160	80	40		80	80
3,4-Dichlorobenzyl	α-Naphthylmethyl	α-Naphthylmethyl	640	640	2560	1280	320	40	40	20	40	20
4-Methylbenzyl	4-Methylbenzyl	4-Methylbenzyl	640	1280	1280	320	80	20	40	40	20	20
3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	640	640	1280	2560	160	20	40	20	10	10
3,4-Dimethylbenzyl	3,4-Dimethylbenzyl	Ethyl	40	80	80	20	20	10	<10	10	10	10

[a] M.i.c., (S), and (R) mean the same as in Table VIII.

TABLE X: BACTERIOSTATIC ACTIVITIES (M.I.C.,[a] 1/X × 10⁻³) OF α,ω-DI(GUANIDINO)ALKANES, RNHC(=NR′)NH(CH$_2$)$_n$NHC(=NR′)NHR·2HCl

n	R	R′	See column headings in Table IX above									
2	3,4-Dichlorobenzyl	H	1280	1280	2560	640	320	160	160	160	80	80
	In presence of 10% serum		320	160	640	40	160	40	40	20	20	20
2	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	160	320	640	160	80	80	40	40	40	10
4	3,4-Dichlorobenzyl	H	1280	1280	2560	640	640	80	40	40	80	80
6	3,4-Dichlorobenzyl	H	1280	1280	2560	1280	320	80	40	80	80	80
	In presence of 10% serum		160	160	640	320	160	40	20	20	20	40
6	3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	640	640	640	2560	160	80	40	40	80	20
6	4-Chlorobenzyl	H	1280	640	2560	160	160	80		40	40	40
6	Benzyl	H	160	80	320	20	20	10	40	10	10	10
10	3,4-Dichlorobenzyl	H	2560	2560	20480	10240	640	320	1280	80	160	80
	In presence of 10% serum		640	640	1280	320	160	80	80	20	40	20
11	3,4-Dichlorobenzyl	H	1280	1280	1280	2560	640	320	160	160	160	80
12	3,4-Dichlorobenzyl	H	640	640	1280	2560	640	160	160	80	80	40
6	N-(4-Chlorophenyl)guanyl	N-(4-Chlorophenyl)guanyl[b]	5120	2560	5120	5120	320	320	320	320	160	160
	In presence of 10% serum		1000	1000	5120	160	640	80	160	40	80	40

[a] M.i.c., (S), and (R) mean the same as in Table VIII. [b] "Hibitane".

TABLE XI

BACTERIOSTATIC ACTIVITIES (M.I.C.,[a] $1/X \times 10^{-3}$) OF AMINOGUANIDINES, $RNHC(=NR')NHNH_2 \cdot HCl$

R	R′	*M. pyogenes* var. *aureus* (S)[a]	*M. pyogenes* var. *aureus* (R)[a]	*Sarcina lutea*	*Strept. faecalis*	*E. coli* No. 198	*A. aerogenes*	*S. pullorum*	*Pseudomonas aeruginosa*	*Proteus mirabilis*	*Proteus vulgaris*
n-Undecyl	H	160	160	320	320	40	40	160	40	40	20
n-Dodecyl	H	640	640	1280	640	160	80		40	40	40
n-Tetradecyl	H	1280	1280	>5120	>5120	320	160	160	40	80	40
n-Octadecyl	H	160	160	5120	2560	20	10	40	10	20	10
4-Chlorobenzyl	H	20	40	20	40	10	10	80	10	20	40
3,4-Dichlorobenzyl	H	160	160	40	20	20	10	320	10	10	10

[a] M.i.c., (S), and (R) mean the same as in Table VIII.

TABLE XII

FUNGISTATIC ACTIVITIES (M.I.C., $1/X \times 10^{-3}$) OF SOME GUANIDINE DERIVATIVES

Compound	*Candida albicans*	*M. gypseum*	*Tr. granulosum*
N-Nonyl-N′-3,4-dichlorobenzylguanidine	128	1024	1024
N-Dodecyl-N′-3,4-dichlorobenzylguanidine	256	256	128
N,N′,N′′-Tri(3,4-dichlorobenzyl)guanidine	320	320	640
N,N′-Di(3,4-dichlorobenzyl)-N′′-(4-isopropylbenzyl)guanidine	640	640	640
1,10-Decamethylenebis(3,4-dichlorobenzylguanidine)	256	256	128
1,11-Undecamethylenebis(3,4-dichlorobenzylguanidine)	1280	400	640
1,12-Dodecamethylenebis(3,4-dichlorobenzylguanidine)	256	256	128

This substance, which was isolated as a microcrystalline red solid, was sublimed for analysis at 180° (0.25 mm.).

Anal. Calcd. for $C_2H_4N_6$: C, 21.43; H, 3.59; N, 74.98. Found: C, 21.62; H, 3.61; N, 74.42.

The isolation of 3,6-diamino-1,2,4,5-tetrazine from this type of reaction has been previously described.[7,8]

On cooling, the ethanolic solution deposited crystals of the hemihydriodide salt of guanazine (3,4,5-triamino-1,2,4-triazole), m.p. 192–193°, yield 2.71 g.

Anal. Calcd. for $C_4H_{13}IN_{12}$: C, 13.49; H, 3.68; I, 35.63; N, 47.20. Found: C, 13.62; H, 3.76; I, 35.85; N, 47.19.

The ethanolic filtrate was evaporated to dryness and the residue was crystallized three times from water, giving N-dodecyl-N′-aminoguanidine hydriodide, m.p. 88–90°, yield 4.71 g. (13%).

The other monosubstituted aminoguanidines listed in Table VI and the α,ω-di(aminoguanidino)alkanes described in Table VII were prepared in the same manner.

Guanazine.—A solution of the hemihydroiodide salt of guanazine (1.20 g.) in ethanol (50 ml.) was passed through a column of Amberlite IRA 400 in the hydroxyl form (50 ml.), and the column was washed with ethanol (50 ml.). Evaporation of the eluate yielded guanazine, m.p. 254–257° dec. (lit.[9] m.p. 257°).

The conversion of S-methylisothiosemicarbazide to guanazine was demonstrated as follows: S-methylisothiosemicarbazide hydriodide (2.33 g., 0.01 mole) in water (50 ml.) was passed through a column of Amberlite IRA 400 in the hydroxyl form, and the column was washed with water (150 ml.). The eluate was concentrated to 10 ml., and the solution was heated on the steam bath for 1 hr. Evaporation of the solution and recrystallization of the pink residue from ethanol (10 ml.) gave guanazine, m.p. 253–255°, yield 0.16 g. (28%).

The product was characterized by its picrate, m.p. 284° (lit.[9] m.p. 276°) and its benzaldehyde condensation product, m.p. 199–201° (lit.[9] m.p. 196°).

An attempted preparation of the triacetyl derivative, m.p. 240°, described by Pellizarri and Repetto,[9] gave a product, m.p. 223–225°, which appears to arise from the dehydration of the triacetyl derivative.

Anal. Calcd. for $C_8H_{10}N_6O_2$: C, 43.23; H, 4.54; N, 37.82. Found: C, 43.13; H, 4.62; N, 37.97.

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(7) F. L. Scott and J. Reilly, *Chem. Ind.* (London), 908 (1952).

(8) C. H. Lin, E. Lieber, and J. P. Horwitz, *J. Am. Chem. Soc.*, **76**, 427 (1954).

(9) G. Pellizarri and A. Repetto, *Gazz. Chim. Ital.*, [2] **37**, 317 (1907).