Preparation of the reference compounds followed literature directions. *O*-ethylcaprolactim[12] (infrared: 3.4, 5.95, 6.90, 7.26, 7.45, 7.98, 8.37, 9.17, 9.52 μ), *N*-ethylcaprolactam[12] (infrared: 3.42, 6.12, 6.74, 6.96, 7.25, 8.34 μ), *N*-methylvalerolactam[22] [infrared: 2.9 (hygroscopic), 3.4, 6.14, 6.64, 7.38 μ]. *O-Methylvalerolactim* was prepared using the method described for *O*-methylcaprolactim.[23] The fraction b.p. 56°/32 mm. was collected, yield 48%, n_D^{25} 1.4538. Infrared: 3.4, 5.96, 6.96, 7.35, 7.45, 8.22, 9.83 μ.

Anal. Calcd. for $C_6H_{11}ON$ (113.15): C, 63.68; H, 9.80; N, 12.38. Found: C, 63.4; H, 9.65; N, 12.3.

Attempted *O*-alkylation[23] of 2-pyrrolidone (butyrolactam) gave, as the only product, *N*-ethylbutyrolactam,[24] b.p. 90–92°/15 mm., n_D^{25} 1.4624 in 38% yield.

Treatment of ethyl D,L-5-pyrrolidone-2-carboxylate under the same conditions[23] with ethyl sulfate resulted in a partial reaction (ethyl sulfate recovered) and a poor yield of ethyl 1-ethyl 5-pyrrolidone-2-carboxylate.

The following method for preparation of the known[25] ethyl D,L-5-pyrrolidone-2-carboxylate was used: A suspension of 15 g. of D,L-5-pyrrolidone-2-carboxylic acid[26] in 150 ml. of ethanol was mixed with 1.5 g. of *p*-toluenesulfonic acid monohydrate and heated under reflux. The solution was treated with 50 ml. of benzene and slowly distilled using a Vigreux column over a period of 0.5 hr. During another 4.5 hr., addition of a mixture of 75 ml. of benzene and 19 ml. of ethanol was made to keep the volume of the reaction mixture essentially constant. The cooled reaction mixture was treated with 0.42 g. of anhydrous sodium carbonate, filtered, and the ethanol and benzene removed at reduced pressure. The residue was distilled. The fraction boiling at 136–138°/0.5 mm. was collected. The liquid product (15.9 g., 87% yield) solidified after long standing, m.p. 49–51°; infrared: 3.05, 3.32, 5.75, 5.85, 8.28 μ.

Anal. Calcd. for $C_7H_{11}O_3N$ (157.17): C, 53.49; H, 7.06; N, 8.91. Found: C, 53.4; H, 6.99; N, 8.80.

Ethyl 1-ethyl-5-pyrrolidone-2-carboxylate. The reaction of 3 g. of D,L-5-pyrrolidone-2-carboxylic acid with two equivalents of diazoethane[18] gave a liquid product. Distillation produced 0.8 g. of liquid, b.p. 83–85°/2 mm., n_D^{25} 1.4496, and 1.8 g. of ethyl 5-pyrrolidone-2-carboxylate. The first fraction was not homogenous as shown by gas chromatography. The purified sample was isolated from the effluent helium stream of the gas chromatography unit, n_D^{25} 1.4596, infrared: 3.36, 5.74, 5.88, 6.85, 7.03, 7.80, 8.34 μ.

Anal. Calcd. for $C_9H_{15}O_3N$ (185.22): C, 58.36; H, 8.16; N, 7.56. Found: C, 57.6; H, 8.15; N, 7.45.

The product was stable at 180–220° and also was recovered after heating in boiling water for 5 hr.[12,27]

Acknowledgments. The author is indebted to H. G. Walker, J. W. Corse, and L. A. Goldblatt for gifts of reagents and for discussions of the problem. The analyses were made by L. M. White and G. E. Secor. The 2-pyrrolidone was a gift from Antara Chemicals, New York.

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[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN & PHARMACEUTICAL CORP.]

Guanamines. V. Chloromethylguanamines

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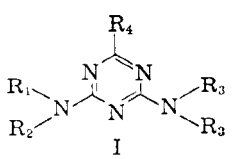
A series of chloromethylguanamines (I) have been prepared. The reduction of I, R_4 = —CH_2Cl to I, R_4 = —CH_3 with acetone-sodium iodide-acetic acid has been effected in a wide variety of I, and a mechanism for this reaction proposed.

As intermediate reactants for preparation of aminomethylguanamines[1] and allied derivatives, halomethylguanimines of the type I were required.



I

R_1 = alkyl, aralkyl, aryl
R_2 = hydrogen, alkyl
R_1R_2N = heterocyclic rings
R_3 = hydrogen, methyl
R_4 = —CH_2Cl, —$CHCH_3Cl$

The compounds were obtained from the R_1-R_2—N^1—, R_3R_3—N^5— substituted biguanide upon reaction with the appropriate ester, $R_4COOC_2H_5$, or acid chloride, R_4COCl, as previously described[2] (Table I).

As reactions of the halogen in chloromethylguanamines have been only briefly evaluated,[3–5] it was of interest to study this in further detail.

Heating typical compounds wherein I, R_4 = —CH_2Cl (or even —CH_2I), —$CHCH_3Cl$ in alcoholic silver nitrate gave no precipitate of silver halide. Treatment of such compounds with sodium iodide in acetone, with warming, yielded rapid precipitation of sodium chloride. Employment of acetone–sodium iodide–acetic acid reagent[3] (ASA reagent) resulted in rapid oxidation of iodide to iodine. Upon treatment of the reaction mixture with aqueous sodium bisulfite, a variety of I,

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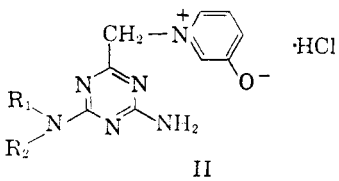
R = —CH_2Cl, were converted to I, R = —CH_3 including compounds in which R_1, R_2, and R_3 afforded mono-tetra substitution on the amino nitrogens.

The conversion was confirmed by identity of the dehalogenated compounds with authentic I, R_4 = CH_3 prepared from the biguanide and ethyl acetate or acetyl chloride, or through the corresponding picrates. In the preparation of compound 47, using acetyl chloride, 67% of *N*-carbamidoindoline was isolated, presumably from hydrolysis of the reactant biguanide.[6]

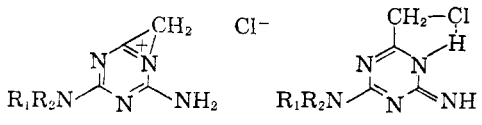
When the acetic acid was not incorporated in the ASA reagent, the reduction of the I, R_4 = —CH_2Cl to I, R_4 = CH_3 was effected, with compound 9 giving compound 39.

The chloromethylguanamines reacted readily with 3-hydroxypyridine to give betaines[7] (II).



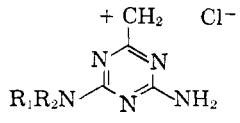
II

Consideration of the structural formula of the chloromethylguanamines in terms of such reactions indicates that forms such as Ia–Ic may be proposed in addition to the conventional formula, I.



Ia

Ib



Ic

The ionic character of the halogen in formulas Ia and Ic is not consistent with the noted inactivity of the compounds with the alcoholic silver nitrate. Elimination of formula Ia, a modification of the ethyleneimonium ion, excluded consideration of these compounds as typical of adrenergic blocking agents.[8]

Form Ib, requires that at least one of the amino nitrogen substituents, R_1—R_3 be hydrogen and conversion to I, R_4 = CH_3 of the tetra-substituted compound 23 with the ASA reagent eliminates form Ib in this reaction.

In the attempt to elucidate, in particular, the "positive halogen"[9] reaction with the ASA reagent, other types of halomethyl compounds were evaluated. Benzyl halides were not reduced to toluene with the ASA reagent. However, selected benzotrichlorides[9] give this reaction in acetic acid medium on prolonged heating, with enhancement of positive halogen activity as the number of chlorine atoms on the reactant group increases. By contrast, in this work the reaction proceeded in less than one hour at 20°, and in the absence of acetic acid. It was observed as well, that as additional halogen was introduced to give I, R_4 = —$CHCl_2$,[3] —$CHBr_2$, —CCl_2F, —CF_3[2] the reaction failed. Additionally, compound 25, where I, R_4 = —$CHCH_3Cl$ was recovered unchanged suggesting a steric influence, although the excellent yield with I, R_4 = —$CHCH_3Br$ to I, R_4 = —C_2H_5[3] argues for greater reactivity of bromine in this reaction.[10] The mechanism proposed by the Spanish workers[9] does not therefore, apply in the ASA reaction.

The phenacyl halides were reduced to the acetophenones[11,12] under conditions more vigorous than herein employed. In this work phenacyl halides were found to react promptly in the ASA reaction to give the acetophenones.

Significant distinctions are found, however, between the phenacyl halides and I, R_4 = —CH_2Cl, in that the former react rapidly with alcoholic silver nitrate, whereas the latter do not react at all. Additionally, I, R_4 = —CH_2Cl is readily reduced to I, R_4 = —CH_3 with palladium on calcium carbonate,[3] whereas 2,4′-dibromoacetophenone is reduced to phenacyl bromide by palladium on charcoal.[13]

Paralleling some of the properties of I, R_4 = —CH_2Cl, is 1-phenyl-5-chloromethyl tetrazole[14] which is highly reactive in second order nucleophilic substitution reactions, but unreactive under first order conditions. This compound also reacts rapidly with amines.[15]

In keeping with concepts embodying the —C = N— group of the triazine ring as a carbonyl type function,[2,16] and with analogies similarly applied by Herbst[17] to the tetrazoles, the halomethylguan-

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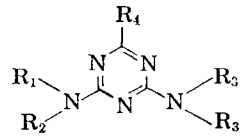
TABLE I

GUANAMINES[a]



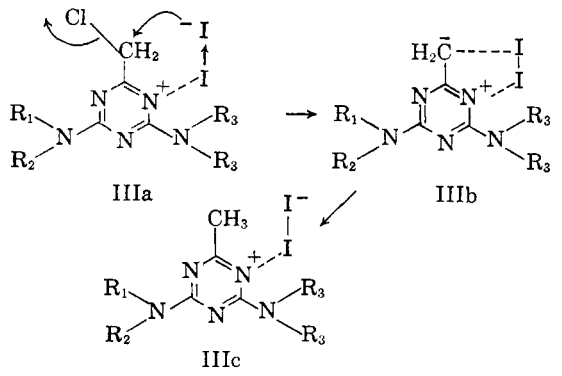
No.	R_1	R_2	M.P.[b]	S[c]	Yield,[d] %	Formula	Analyses,[e] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R_4 = CH_2Cl							
1	CH_3—	CH_3—	176–179	A	57	$C_6H_{10}ClN_5$	38.4	38.5	5.4	5.5	37.2	37.4
2	C_3H_5—[f]	H	125–126	A	52	$C_7H_{10}ClN_5$	42.1	41.7	5.1	4.9	35.1	35.2
3	n-C_4H_9—	H	118–120	A	32	$C_8H_{14}ClN_5$					32.5	32.4
4	n-C_5H_{11}—	H	118–119	A	39	$C_9H_{16}ClN_5$					30.5	30.2
5	HPic[g]		135–136	B		$C_{15}H_{19}ClN_8O_7$	39.3	38.8	4.2	4.2	24.4	24.4
6	i-C_5H_{11}—	H	103–105	A	37	$C_9H_{16}ClN_5$	47.7	48.1	7.0	7.3		
7	HPic[g]		142–143	B		$C_{15}H_9ClN_8O_7$	39.3	39.4	4.2	4.1	24.4	24.5
8	—$(CH_2)_5$—		160–162	A	59	$C_9H_{14}ClN_5$	47.5	48.0	6.2	6.5		
9	$C_6H_5CH_2CH_2$—	H	145–147	A	85	$C_{12}H_{14}ClN_5$	54.7	54.8	5.4	5.3	26.6	26.8
10	$C_6H_5CH_2$—	CH_3—	115–117	A	60	$C_{12}H_{14}ClN_5$	54.7	55.1	5.4	5.3	26.6	26.4
11	p-$CH_3C_6H_4$—	H	162–163	A	61	$C_{11}H_{12}ClN_5$					28.1	27.9
12	p-$CH_3OC_6H_4$—	H	185–187	A	35	$C_{11}H_{12}ClN_5O$	49.7	49.3	4.6	5.0		
13	m-ClC_6H_4—	H	129–134	C	23	$C_{10}H_9Cl_2N_5$					25.9	25.5
14	p-ClC_6H_4—	H	185–187	A	73	$C_{10}H_9Cl_2N_5$					25.9	26.2
15	3,4-di$CH_3C_6H_3$—	H	218	F	13	$C_{12}H_{14}ClN_5$					26.6	26.6
16	—$C_6H_4CH_2CH_2$—		>300	i	57	$C_{12}H_{12}ClN_5$	55.1	54.8	4.6	4.6	26.8	26.9
17	—$C_6H_4CH_2CH_2CH_2$—[k]		135–147	C	53	$C_{13}H_{14}ClN_5$[l]	56.6	56.8	5.1	5.3		
18	—$CH_2C_6H_4CH_2CH_2$—[m]		178–180	F	62	$C_{13}H_{14}ClN_5$	56.6	57.0	5.1	5.2		
19[a1]	CH_3—	CH_3—	65–67	C	30	$C_8H_{14}ClN_5$	44.5	45.0	6.5	6.4	32.5	32.2
20[a1]	C_6H_5—	H	105	D	57	$C_{12}H_{14}ClN_5$					26.6	26.1
21[a1]	2,6-di$CH_3C_6H_3$—	H	140–141	A	16	$C_{14}H_{18}ClN_5$					24.0	23.5
22[a1]	HPic[g]		165–167	E		$C_{20}H_{21}ClN_8O_7$	46.1	46.3	4.1	4.5		
23[a1]	—$C_6H_4CH_2CH_2$—[h]		135–136	C	58	$C_{14}H_{16}ClN_5$	58.0	57.8	5.6	5.6		
					R_4 = —$CHCH_3Cl$							
24	CH_3—	CH_3—	159–160	C	49	$C_7H_{12}ClN_5$	41.7	42.0	6.0	5.9	34.7	35.1
25	$C_6H_5CH_2CH_2$—	H	128–129	C	66	$C_{13}H_{16}ClN_5$	56.2	56.1	5.8	6.1	25.2	25.4
26	C_6H_5—	H	140–141	C	62	$C_{11}H_{12}ClN_5$	52.9	52.8	4.9	5.1	28.1	28.2
27	o-$CH_3C_6H_4$	H	155–157	C	49	$C_{12}H_{14}ClN_5$	54.7	54.6	5.4	5.3	26.6	26.9
28	2,6-di$CH_3C_6H_3$—	H	198–200	C	28	$C_{13}H_{16}ClN_5$	56.2	56.2	5.8	6.0	25.2	25.5
29	o-ClC_6H_4—	H	127–128	C	30	$C_{11}H_{11}Cl_2N_5$	46.5	46.2	3.9	4.0		
30	m-ClC_6H_4—	H	51–54	C	18	$C_{11}H_{11}Cl_2N_5$	46.5	46.6	3.9	4.3	24.7	24.8
31	2-CH_3-5-ClC_6H_3—	H	148–149	C	40	$C_{12}H_{13}Cl_2N_5$	48.3	48.4	4.4	4.1		
32	o-BrC_6H_4—	H	131–133	C	40	$C_{11}H_{11}BrClN_5$	40.2	40.3	3.4	3.2	21.3	20.9
33	m-X-C_6H_4—[n]	H	141–143	C	18	$C_{13}H_{16}ClN_5O$	53.2	52.9	5.5	5.7	23.8	24.0

TABLE I (*Continued*)

No.	R_1	R_2	M.P.[b]	S[c]	Yield,[d] %	Formula	Analyses,[e] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					R_4 = CH_3—[o]							
34	CH_3—	CH_3—	192–193	A	39[o1]	$C_6H_{11}N_5$	47.0	47.0	7.2	6.9		
35	C_3H_5—[f]	H	117–119	A	44	$C_7H_{11}N_5$					42.4	42.7
36	*n*-C_5H_{11}—	H	138–141	A	69	$C_9H_{17}N_5$	55.4	55.8	8.8	8.7	35.9	35.8
37	*i*-C_5H_{11}—	H	134–135	A	40	$C_9H_{17}N_5$	55.4	55.3	8.8	8.8	35.9	36.2
38	—$(CH_2)_5$—		192–193	A	73	$C_9H_{15}N_5$	55.9	55.9	7.8	7.9	36.2	36.4
39	$C_6H_5CH_2CH_2$—	H	145–147	A	67	$C_{12}H_{15}N_5$	62.9	62.6	6.6	6.6	30.6	30.6
40	HPic[g]		240–241	E		$C_{18}H_{18}N_8O_7$	47.2	47.2	4.0	3.7	24.5	24.3
41	$C_6H_5CH_2$—	CH_3—	134–136	A	56	$C_{12}H_{15}N_5$	62.9	63.0	6.6	6.6	30.6	30.5
42	HPic[g]		169–171	G		$C_{18}H_{18}N_8O_7$	47.2	47.3	4.0	3.4	24.5	24.6
43	*p*-$CH_3C_6H_4$—	H	211–213	A	21	$C_{11}H_{13}N_5$	61.4	61.1	6.1	5.9	32.5	32.9
44	*p*-$CH_3OC_6H_4$—	H	213–214	A	14	$C_{11}H_{13}N_5O$					30.3	30.3
45	*p*-ClC_6H_4—	H	194–196	A	15	$C_{10}H_{10}ClN_5$	51.0	51.1	4.3	4.4	29.7	30.0
46	HPic[g]		215–219	E		$C_{16}H_{13}ClN_8O_7$					24.1	23.9
47	—$C_6H_4CH_2CH_2$—		229–233	A	12[o1]	$C_{12}H_{13}N_5$	63.4	62.8	5.8	5.8	30.8	31.3
48[a1]	C_6H_5—	H	119–120	A	37[o1]	$C_{12}H_{15}N_5$	62.9	62.5	6.6	6.7		
49[a1]	2,6-di$CH_3C_6H_3$—	H	196–199	A	22[o1]	$C_{14}H_{19}N_5$	65.3	65.4	7.4	7.0		
50[a1]	—$C_6H_4CH_2CH_2$—		108–109	A	63[o1]	$C_{14}H_{17}N_5$	65.9	65.7	6.7	6.5	27.4	27.4

[a] R_3 = hydrogen, unless otherwise specified; [a1] R_4 = methyl. [b] Melting points are uncorrected. [c] S = recrystallizing solvent; A = isopropyl alcohol; B = acetone-water; C = acetonitrile; D = methanol; E = water; F = propanol; G = ethanol. [d] Yields are reported as recrystallized product. [e] Analyses by Weiler and Strauss, Oxford, England. [f] C_3H_5— = allyl. [g] HPic = picrate of compound listed immediately above. [h] With attached nitrogen, is derived from indoline. [i] Not recrystallized. [j] Chlorine, Calcd./Found: 13.6/13.6. [k] With attached nitrogen is derived from tetrahydroquinoline. [l] Chlorine, Calcd./Found: 12.9/13.0. [m] With attached nitrogen is derived from tetrahydroisoquinoline. [n] X = *m*-CH_3CHOH—. [o] The compounds were prepared from the biguanide and ethyl acetate; [o1] prepared from acetyl chloride.

amines might be considered as analogs of the phenacyl halides. Sufficient distinction has been demonstrated to question this parallelism, and consideration of the mechanism of the ASA reaction with these chloromethyltriazines has suggested that molecular iodine may participate,[18] in a form similar to that described for pyridine,[19] as shown for IIIa followed by IIIb,[20,21] which is protonated, IIIc followed by deiodination through



IIIa IIIb IIIc

the sodium bisulfite to I, $R_4 = CH_3$. This mechanism is being explored further.

EXPERIMENTAL[22]

Biguanides not previously reported are given in Table II and were prepared as described elsewhere.[2,23]

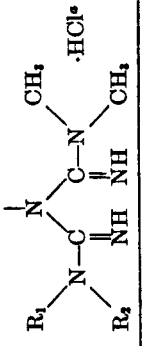
2-Amino-4-indolino-6-chloromethyl-s-triazine (Table I, Compound 16). A solution of 13.8 g. (0.6 g.-atom) of sodium in 480 ml. of methanol was chilled to −40° and 37.2 g. (0.31 mole) of ethyl chloroacetate added, followed by 70 g. (0.3 mole) of the biguanide. The reaction mixture was stirred as it warmed to 20° over a period of 6 hr. A solution of 48 ml. of hydrochloric acid in 108 ml. of methanol was added, and the reaction mixture stored at 10° for 20 hr. The formed precipitate was separated by filtration, rinsed with 500 ml. of acetone, and then suspended in 500 ml. of water which was adjusted to *p*H 6.0. The insoluble suspension of product was separated, 44.5 g. (57%), m.p. >300°.

2-Dimethylamino-4-indolino-6-chloromethyl-s-triazine (Table I, Compound 23). A mixture of 5.5 g. (0.0206 mole) of the biguanide (Table II, compound 8) was suspended in a mixture of 8 ml. of water and 12 ml. of acetonitrile. With continued stirring and cooling (10°) 7.5 ml. of 40% sodium hydroxide solution was added, followed by addition over 20 min. of 3.4 g. (0.03 mole) of chloroacetyl chloride in 10 ml. of acetonitrile. After the addition was complete, stirring was continued at 20° for 1 hr., and the product separated and recrystallized.

2-Amino-6-chloromethyl-4-(β-phenethyl)amino-s-triazine (Table I, Compound 9). A solution of 24.1 g. (0.1 mole) of β-phenethylbiguanide hydrochloride in 50 ml. of water and 75 ml. of acetonitrile was maintained at 10° during the addi-

TABLE II

N^1,N^5-BIGUANIDES



No.	R_1	R_2	M.P.	S[b]	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
1	CH_3—	CH_3—	227–230	A	40	$C_8H_{16}ClN_5$	37.2	36.8	8.3	8.1	36.2	36.3
2	C_6H_5—	H	257–258	B	44	$C_{10}H_{12}ClN_5$	49.7	49.8	6.7	6.9	29.0	28.6
3	*m*-ClC_6H_4	H	>250	B	56	$C_{10}H_{11}Cl_2N_5$	43.5	43.6	5.5	5.6	25.3	25.3
4	*p*-ClC_6H_4—	H	239–241	B	67	$C_{10}H_{11}Cl_2N_5$					25.4	25.5
5	*p*-$NH_2SO_2C_6H_4$—	H	162–164	B	52	$C_{10}H_{17}ClN_6O_2S$	37.4	37.1	5.3	5.4		
6	$HSO_3C_6H_4$—	H	243–245	B		$C_{10}H_{18}ClN_5O_4S_1$	36.1	36.6	5.9	5.7		
7	2,6-di$CH_3C_6H_3$—	H	197–199	C		$C_{12}H_{19}N_5$[c]	61.8	61.7	8.2	8.1	30.0	29.9
8	—$C_6H_5CH_2CH_2$—		243–245	D	83	$C_{12}H_{15}ClN_5$	53.8	54.0	6.8	6.9	26.2	26.1

[a] The salt is hydrochloride unless otherwise specified; [c] hydrochloride hydrate; [c] free base. [b] S = recrystallizing solvent: A = acetonitrile; B = water; C = isopropyl alcohol; D = ethanol-hexane.

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(19) R. A. Zingaro and W. E. Tolberg, *J. Am. Chem. Soc.*, 81, 1353 (1959).

(20) J. G. Carey and I. T. Millar, *Chem. & Ind.*, 97 (1960).

(21) J. G. Carey, G. Jones, and I. T. Millar, *Chem. & Ind.*, 1018 (1959).

(22) Descriptive data shown in the tables are not reproduced in the Experimental.

(23) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, 81, 3725 (1959).

tion of 30 ml. (0.3 mole) of 10*N* sodium hydroxide. Stirring and cooling were continued during the addition of a solution of 16.9 g. (0.15 mole) of chloroacetyl chloride in 40 ml. of acetonitrile over 30 min. Stirring was continued over 2 hr. as the temperature was allowed to rise to 20°. The product, 24.4 g. (92%), was separated, m.p. 145–147°.

2-Amino-4-(o-bromo)anilino-6-α-chloroethyl-s-triazine (Table I, Compound 32). A suspension of 10.2 g. (0.035 mole) of *o*-bromophenylbiguanide hydrochloride in 30 ml. of methanol was treated with 11.0 ml. (0.05 mole) of 25% sodium methoxide in methanol, followed by 5.5 g. (0.04 mole) of ethyl α-chloropropionate. After 48 hr. the reaction mixture was decanted into 150 ml. of water and the product separated, 6.33 g. (55%), m.p. 120–126°.

2-Amino-4-(n-amyl)amino-6-methyl-s-triazine (Table I, Compound 36). Following the procedure described above using *n*-amylbiguanide hydrochloride, and ethyl acetate, as the reactant ester, the product was obtained in 75% crude yield, m.p. 133–136°.

2-Amino-6-ethyl-4-(β-phenethyl)amino-s-triazine. Following the procedure above and using β-phenethylbiguanide hydrochloride and ethyl propionate as the reactant ester, the product was obtained in 66% yield, m.p. 135–137°.

Anal. Calcd. for $C_{12}H_{17}N_5$: C, 64.2; H, 7.0; N, 28.8. Found: C, 64.4; H, 7.0; N, 29.0.

N-[(2-Anilino-4-dimethylamino-triazin-6-yl)methyl]-3-oxypyridyl betaine hydrochloride. A mixture of 2.6 g. (0.01 mole) of 2-anilino-4-dimethylamino-6-chloromethyl-s-triazine and 1.0 g. (0.01 mole) of 3-hydroxypyridine in 15 ml. of isopropyl alcohol was heated under reflux with stirring for 6 hr. When cool, the product was separated and recrystallized (ethanol), m.p. over 250°.

Anal. Calcd. for $C_{17}H_{19}ClN_6O$: C, 56.9; H, 5.3; N, 23.4. Found: C, 56.5; H, 5.3; N, 23.8.

In a similar manner, using compound 10 (Table I) the corresponding betaine was prepared, m.p. 206–208° (acetonitrile).

Anal. Calcd. for $C_{17}H_{19}ClN_6O$: C, 56.9; H, 5.3; N, 23.4. Found: C, 56.9; H, 5.6; N, 23.5.

In a similar manner, using compound 4 (Table I) the corresponding betaine was prepared, m.p. 244–245° (isopropyl alcohol).

Anal. Calcd. for $C_{12}H_{19}ClN_6O$: C, 50.2; H, 6.2; N, 27.1. Found: C, 50.2; H, 6.4; N, 27.4.

2-Amino-4-indolino-6-methyl-s-triazine (Table I, Compound 47). A slurry of 5.0 g. (0.02 mole) of indolinylbiguanide hydrochloride and 40 ml. of acetonitrile was treated (cooling to 10°) with a solution of 1.6 g. (0.04 mole) of sodium hydroxide in 10.0 ml. of water, followed by 2.4 g. (0.03 mole) of acetyl chloride in 15 ml. of acetonitrile added dropwise over 0.5 hr. After standing at 20° for 20 hr., the reaction mixture was decanted into 150 ml. of water, and the product, 0.53 g. (12%), m.p. 229–233°, separated.

The filtrate, treated with 6 ml. of 10*N* sodium hydroxide, yielded a solid (3.84 g.) which after solution in 100 ml. of boiling water gave, after cooling, 2.17 g. (67%) of *N*-carbamidoindoline, m.p. 159–161°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.9; H, 6.3; N, 17.1.

The melting point was not depressed on admixture with authentic *N*-carbamidoindoline, mixed m.p. 162–165°.

N-Carbamidoindoline. To a stirred warmed (30°) mixture of 17.3 g. (0.145 mole) of indoline in 30 ml. (0.177 mole) of 6*N* hydrochloric acid, was added portionwise, over 20 min., 12.5 g. (0.155 mole) of finely powdered potassium cyanate, forming a dense white precipitate of product. After dilution with 100 ml. of water, the product was separated, 21.3 g. (91%), m.p. 162–165°; recrystallized (water), m.p. 163–165°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.7; H, 6.2. Found: C, 66.6; H, 6.3.

Reduction of I, $R_3 = CH_2Cl$. In a typical procedure, compound 1 (Table I) 0.375 g. (0.002 mole) in 5 ml. of acetone was added to a solution of 3.0 g. of sodium iodide in 10 ml. of acetone and 1 ml. of acetic acid. Within 10 min. the rapidly browning (iodine) solution had reached maximum color intensity. A solution of 0.25 g. of sodium bisulfite in 10 ml. of water was added, and the reaction mixture made basic with sodium hydroxide. After standing, the precipitate was separated and recrystallized (isopropyl alcohol) 0.13 g. (40%), m.p. 192–193°, not depressing the melting point of compound 34 (Table I).

In a similar manner, the following I, $R_4 = —CH_2Cl$, compounds 4, 6, 8, 11, 12, 16, and 20 (Table I), were reduced to I, $R_3 = —CH_3$, compounds 36, 37, 38, 43, 44, 47, and 48 (Table I), as established by mixed melting point and analysis. In the following group the reduction of compounds 9, 10, and 14 produced I, $R_4 = —CH_3$ confirmed as the picrates, compounds 40, 42, and 46.

The reaction proceeded in a similar manner in the absence of acetic acid; compound 9, Table I, yielded compound 39.

Although a substantial liberation of iodine occurred, the following compounds were not reduced to the corresponding alkyl derivatives, and the reactant halo compound was isolated unchanged: Compound 25, Table I; and I, $R_1R_2N— = C_6H_5CH_2NH—$ (or $(CH_3)_2N—$), $R_5R_6N— = NH_2$, $R_4 = CHBr_2$, $—CFCl_2$, $—CF_3$.

Reduction of compound 23, Table I. This compound, reduced as described above, yielded a compound with an unsatisfactory analysis, but showed ultraviolet absorption spectra identical with compound 50.

2-Amino-6-iodomethyl-4-(β-phenethyl)amino-s-triazine. A solution of 2.64 g. (0.01 mole) of compound 9 (Table I) in 30 ml. of acetone was treated with a solution of 15 g. of sodium iodide in 50 ml. of acetone. After 2 hr., the sodium chloride was separated, rinsed with acetone, and dried, 0.52 g. (92%). The filtrate, on standing, formed a dense precipitate which on exposure to air and light colored in sequence from orange to red-brown to violet to white. (See forms III above.) The precipitate was separated and triturated with water (this immediately decolorized any colored portions of the precipitate). There was obtained 2.15 g. (61%) m.p. 138–139°, recrystallized (acetonitrile), m.p. 149–153°, not obtained analytically pure.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA

No.[a]	λ_{max}, mμ	$\epsilon \times 10^{-3}$
1	273	3.8
17	260	14.5
18	271	4.5
23	234	18.6
	266	22.2
	298	15.6
50	230	18.3
	268	20.7
	294	17.8
[b]	276	3.9

[a] Compound number in Table I. [b] Iodo analog of compound 9.

Anal. Calcd. for $C_{12}H_{14}IN_5$: C, 40.6; H, 4.0; N, 19.7. Found: C, 41.4; H, 4.4; N, 21.2.

Reduction of phenacyl halides. Employing the ASA reagent, the following were reduced: *p*-Chlorophenacyl chloride gave *p*-chloroacetophenone (64%), b.p. 46° (0.6 mm.), confirmed by its 2,4-dinitrophenylhydrazone, m.p. 231–232° (ethanol).

Anal. Calcd. for $C_{14}H_{11}ClN_4O_4$: C, 50.2; H, 3.3. Found: C, 50.3; H, 3.4.

In a similar manner, *m*-nitrophenacyl chloride gave *m*-

nitroacetophenone (55%), m.p. 79–80° (ethanol), confirmed by its 2,4-dinitrophenylhydrazone, m.p. 218–221° (ethanol).

Anal. Calcd. for $C_{14}H_{11}N_5O_6$: C, 48.7; H, 3.2; N, 20.3. Found: C, 48.4; H, 3.1; N, 20.5.

Ultraviolet absorption data. Selected spectra were established in methanol and are reported in Table III.

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[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN & PHARMACEUTICAL CORP.]

Guanamines. VI. Aminomethylguanamines

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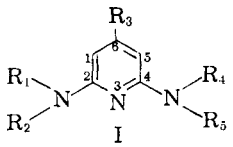
A series of guanamines of the class I, R_3 = $-CH_2NR_6R_7$ has been synthesized and examined for antiinflammatory, analgesic, and tranquilizing activity.

In continuation of our explorations of guanamines with pharmacological activity,[1] compounds of type I, R_3 = $-CH_2NR_6R_7$ have been examined for pharmacological activity. These compounds have



I

R_1R_2N- = substituted amino and anilino
R_4R_5N- = $-NH_2$ and $-N(CH_3)_2$

been envisioned as chlorpromazine analogs wherein the R_1R_2N-, as indolino, tetrahydroquinolino, and tetrahydroisoquinolino, replaces the phenothiazine ring and the trimethylene chain of chlorpromazine has been substituted by a four atom unit extending from the 2-position of the triazine ring to the amino methyl nitrogen.[2] Treatment of the halomethylguanamine[3] with an excess of the required amines under mild heat gave the aminomethylguanamine (see Table I) in good yield.

There was no evidence of *trans*-amination of the 2- and 4-amino substituents of I.[4] Further, when the reactant was a primary amine, there were no indications of formation of the tertiary amines involving reaction of two equivalents of I, R_3 = $-CH_2Cl$.[5] Monoethanolamine reacted readily[6] to give I, R_3 = $-CH_2NHCH_2CH_2OH$.

Although I, R_3 = $-CHCH_3Cl$ was not as active in other systems,[8] it reacted readily with *N*-methylpiperazine to give the required aminomethylguanamine.

The compounds were inspected, in particular, for tranquilizing,[7] antiinflammatory,[8] and analgesic[9] properties with effective compounds being found in each category. Other interesting effects were the antihistamine activity of compound 2 and the marked potentiation of adrenalin by compound 25.

EXPERIMENTAL[10]

The biguanides[1b,4,11] and halomethylguanamines[3] required as intermediates have been described.

2-Amino-4-indolino-6-[(N-ethyl)ethanolaminomethyl]-s-triazine (Compound 7). A mixture of 2.6 g. of 2-amino-4-indolino-6-chloromethyl-*s*-triazine and 6 ml. of *N*-ethylethanolamine was warmed to effect complete solution and then heated in an oil bath maintained at 100° for 5 min. When cool, the reaction mixture was decanted into 100 ml. of water, and 3.4 g. of the product separated.

Unless otherwise stated the compounds were prepared by this general procedure.

2-Dimethylamino-4-indolino-6-dimethylaminomethyl-s-triazine (Compound 16). A mixture of 2.9 g. of 2-dimethylamino-4-indolino-6-chloromethyl-*s*-triazine and 10 g. of dimethylamine in a pressure bomb was heated at 100° for 30

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(2) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc. (Sci. Ed.)*, **46**, 333 (1957).

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(5) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959).

(6) C. B. Kremer, M. Meltsner, and H. Hindin, *J. Am. Chem. Soc.*, **64**, 1010 (1942).

(7) The procedure in S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958) gave the following: compound no./LD_{min} mg./kg. s.c. (mice)/% reduction in motor activity at a test dose of 100 mg./kg. s.c.: 4/450/53; 16/300/48; 17/400/31; 19/150/31; 20/400/52; and at 50 mg./kg. s.c.: 5/200/47; 11/200/31; 13/300/39; 24/350/47.

(8) The procedure of E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957) gave the following: compound no./LD_{min}/% protection at 50 mg./kg. s.c.: 2/400/75; 4/450/75; 5/200/69; 6/200/82; 7/300/88; 9/500/63; 11/20/94; 14/20/69; 16/300/100; 17/400/56; 19/150/90; 21/350/50; 24/350/63.

(9) The procedure of C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954) gave the following: compound no./LD_{min}/analgesic ED_{50} mg./kg. s.c.: 4/450/147; 10/1000/225; 19/150/31; 20/400/96.

(10) Descriptive data shown in Table I are not reproduced in the Experimental.

(11) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959).