[CONTRIBUTION FROM THE ORGANIC RESEARCH DIVISION OF THE U. S. VITAMIN AND PHARMACEUTICAL CORPORATION]

Guanamines.[1] III. Perfluoroalkylguanamines and Related Compounds

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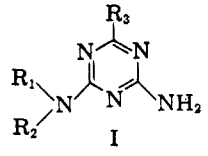
A series of guanamines of type I has been synthesized for pharmacological evaluation. The ultraviolet absorption spectra of a selected series of these compounds have been determined and are discussed.

Our investigation of guanamine derivatives[1] is extended to triazines of type I which have been



I

R_3 = $-CF_3$, $-C_2F_5$, $-C_3F_7$, $-CFCl_2$, $-CHBr_2$

prepared for pharmacological study,[2] particularly as anti-bacterial[3] and anti-viral agents.[4] The compounds which have been prepared[5,6,7] are described in Table I.

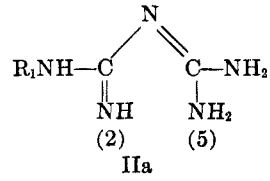
The synthesis of the required guanamines I was effected by reaction of the biguanide[8] with the appropriate ethyl ester.

While reaction of phenyl biguanide with ethyl trichloroacetate gave virtually only I, R_3 = OH, R_1 = C_6H_5—, R_2 = H and merely traces of I, R_3 = $-CCl_3$, R_1 = C_6H_5—, R_2 = H, it is relevant that none of the variants of R_3 employed in this study gave any of I, R_3 = OH compounds.[9]

Distinctions in the nature of the reactivity of ethyl trichloroacetate and ethyl trifluoroacetate have been noted by others.[10]

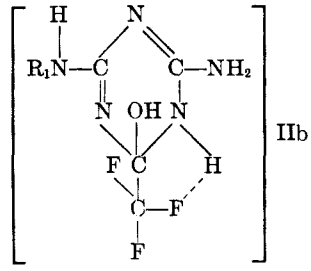
In this system the selectivity of reactivity of the ethyl trichloroacetate may be a function of steric factors.

From other studies[11] it would appear that the active species for the biguanide in methanol would be associated with a form IIa which could react with



IIa

the ester $R_3COOC_2H_5$ at N^2 or N^5 to give the acylated intermediate. Either acylated form in turn undergoes nucleophilic attack by the alternative nitrogen with proton transfer to give IIb (R_3 = $-CF_3$)[12] which permits *trans* elimination of water



IIb

and isolation of I, R_3 = CF_3.

In turn, the ester R_3 = $-CCl_3$ could give the transition state intermediate IIc with elimination of chloroform and isolation of I, R_3 = OH.

(1) (a) Paper I of this series, S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin, and L. Freedman, *J. Am. Chem. Soc.*, **79**, 5064 (1957); (b) paper II, S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3996 (1959).

(2) A. F. Lindenstruth, J. H. Fellman, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **72**, 1886 (1950).

(3) H. M. Walborsky, M. Baum, and D. F. Loncrini, *J. Am. Chem. Soc.*, **77**, 3637 (1955).

(4) W. Cutting and A. Furst, *Antibiotics & Chemotherapy*, **8**, 441 (1958).

(5) A variety of papers and patents have described 2,4,6-trisperhaloalkyltriazines; (a) E. T. McBee, O. R. Pierce, and R. O. Bolt, *Ind. Eng. Chem.*, **39**, 391 (1947); (b) E. Ghigi, *Gazz. chim. ital.*, **71**, 641 (1941); (c) D. D. Coffman, U. S. Patent **2,442,995** (June 8, 1948); (d) G. W. Rigby, U. S. Patent **2,484,528**, (Oct. 11, 1949); (e) T. R. Norton, *J. Am. Chem. Soc.*, **72**, 3527 (1950); (f) T. L. Cairns, A. W. Larchar, and B. C. McKusick, *J. Am. Chem. Soc.*, **74**, 5633 (1952); (g) E. Kober and C. Grundmann, *J. Am. Chem. Soc.*, **81**, 3769 (1959).

(6) For I. R_1 = C_6H_5, R_2 = H, R_3 = $-CCl_3$, see S. L. Shapiro and C. G. Overberger, *J. Am. Chem. Soc.*, **76**, 97 (1954).

(7) Since the completion of our work, W. F. Cockburn and R. A. B. Bannard, *Can. J. Chem.*, **35**, 1285 (1957), have reported on several analogs of I (see Table I).

(8) The biguanides used as initial reactants have been previously described; (a) S. L. Shapiro, V. A. Parrino, E. Rogow, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3725 (1959); (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3728 (1959).

(9) (a) A. Kreutzberger, *J. Am. Chem. Soc.* **79**, 2629 (1957) observed that the $-CCl_3$ group attached to the triazine ring is readily removed as chloroform in nucleophilic displacements using ammonia, amines, water or ethanol, with ethanol being the most powerful nucleophile; (b) S. Birtwell and G. J. Stacey, U. S. Patent **2,830,052** (April 8, 1958), obtained guanamines of the class R_3 = $-CCl_3$ upon reaction of biguanides with trichloroacetic anhydride.

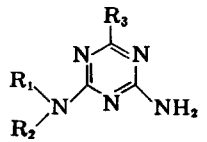
(10) (a) M. M. Joullié, *J. Am. Chem. Soc.*, **77**, 6662 (1955); (b) M. M. Joullié and A. R. Day, **76**, 2990 (1954), found that ethyl trichloroacetate reacts with secondary amine to give the urethane with elimination of chloroform.

(11) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 2220 (1959).

(12) For somewhat similar hydrogen bonding in chloral hydrate, see B. Stehlík and A. Tháč, *Chem. Zvesti*, **3**, 164 (1949) [*Chem. Abstr.*, **44**, 7218^e (1950)].

TABLE I

GUANAMINES



No.	R_1	R_2	M.P.[a]	RS[b]	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	R_3 = —$CFCl_2$											
1	CH_3—	CH_3—	187–190	A	68	$C_6H_8Cl_2FN_5$	30.0	30.2	3.4	3.5	29.2	29.2
2	C_3H_5—[d]	H	105–107	A	64	$C_7H_8Cl_2FN_5$	33.4	33.3	3.2	3.2	27.8	28.0
3	*i*-C_5H_{11}—	H	132–134	B	32	$C_9H_{14}Cl_2FN_5$	38.3	38.6	5.0	5.0	24.8	25.0
4	—$(CH_2)_5$—		159–162	A	20	$C_9H_{12}Cl_2FN_5$	38.6	38.8	4.3	4.4	25.0	24.8
5	C_6H_{11}—[e]	H	133–135	A	85	$C_{10}H_{14}Cl_2FN_5$	41.8	42.0	4.8	5.1	23.8	24.0
6	$C_6H_5CH_2CH_2$—	H	118–120	A	66	$C_{12}H_{12}Cl_2FN_5$	45.6	45.8	3.8	4.0	22.2	22.0
7	C_6H_5—	H	178–179	A	42	$C_{10}H_8Cl_2FN_5$	41.7	41.8	2.8	2.9	24.3	24.0
8	2-CH_3—C_6H_4—	H	179–182	B	27	$C_{11}H_{10}Cl_2FN_5$	43.7	44.3	3.3	3.5	23.2	23.0
9	3-CH_3—C_6H_4—	H	119–125	B	8	$C_{11}H_{10}Cl_2FN_5$	43.7	44.3	3.3	3.5	23.2	23.2
10	4-CH_3—C_6H_4—	H	153	A	58	$C_{11}H_{10}Cl_2FN_5$	43.7	43.7	3.3	4.5	23.2	23.2
11	2,3-di-CH_3—C_6H_3—	H	178–180	A	12	$C_{12}H_{12}Cl_2FN_5$	45.6	45.8	3.8	3.7	22.2	22.3
12	2,4-di-CH_3—C_6H_3—	H	211–212	A	27	$C_{12}H_{12}Cl_2FN_5$	45.6	45.9	3.8	3.9	22.2	22.0
13	2,5-di-CH_3—C_6H_3—	H	152–163	C	22	$C_{12}H_{12}Cl_2FN_5$	45.6	46.0	3.8	4.0	22.2	21.7
14	2,6-di-CH_3—C_6H_3—	H	207–209	D	30	$C_{12}H_{12}Cl_2FN_5$	45.6	45.5	3.8	4.3	22.2	21.7
15	2-C_2H_5—C_6H_4—	H	144–145	C	38	$C_{12}H_{12}Cl_2FN_5$	45.6	46.1	3.8	3.9	22.2	22.2
16	—C_6H_4—CH_2—CH_2—[f]		211–213	A	38	$C_{12}H_{10}Cl_2FN_5$	45.9	46.2	3.2	3.4	22.3	22.4
17	2-CH_3—C_6H_4—	C_2H_5—	95–99	C	42	$C_{13}H_{14}Cl_2FN_5$	47.3	47.4	4.3	4.1	21.2	21.2
18	4-CH_3—C_6H_4—	C_2H_5—	143–144	A	26	$C_{13}H_{14}Cl_2FN_5$	47.3	47.2	4.3	4.4	21.2	21.2
19	3-Cl—C_6H_4—	H	165–168	A	29	$C_{10}H_7Cl_3FN_5$	37.2	37.5	2.2	2.5	21.7	22.3
20	3-Br—C_6H_4—	H	166–168	C	32	$C_{10}H_7BrCl_2FN_5$	32.7	33.2	1.9	2.5	19.1	18.9
21	2-CH_3—3-Cl—C_6H_3—	H	172–173	A	17	$C_{11}H_9Cl_3FN_5$	39.3	40.0	2.7	2.7	20.8	20.2
22	2-CH_3—4-Cl—C_6H_3—	H	179–181	A	23	$C_{11}H_9Cl_3FN_5$	39.3	39.5	2.7	3.0	20.8	21.1
23	2-CH_3—5-Cl—C_6H_3—	H	168–170	E	16	$C_{11}H_9Cl_3FN_5$	39.3	39.1	2.7	2.1	20.8	21.0
24	2-CH_3—4-Br—C_6H_3—	H	182–184	A	27	$C_{11}H_9BrCl_2FN_5$	34.7	35.1	2.4	2.6	18.4	18.2
25	3,4-di-Cl—C_6H_3—	H	171–172	A	30	$C_{10}H_6Cl_4FN_5$	33.6	33.9	1.7	1.8	19.6	19.3
26	2-CH_3—5-OH—C_6H_3—	C_2H_5—	231–233	E	29	$C_{13}H_{15}Cl_2FN_5O$	45.0	45.2	4.4	4.5		
27	2,5-di-CH_3O—C_6H_3—	H	184–185	A	17	$C_{12}H_{12}Cl_2FN_5O_2$	41.4	41.8	3.5	3.5	20.1	20.5
28	R_3 = —CF_3 CH_3—	CH_3—	154–156	C	50	$C_6H_8F_3N_5$					33.8	33.8
29	C_3H_5—[d]	H	116–118	C	36	$C_7H_8F_3N_5$	38.4	38.5	3.7	4.1	32.0	32.0
30[g]	—$(CH_2)_5$—		156–158	A	40	$C_9H_{12}F_3N_5$	43.7	43.9	4.9	5.5	28.3	28.0
31[h]	C_6H_{11}—[e]	H	157–161	A	65	$C_{10}H_{14}F_3N_5$	46.0	46.4	5.4	5.6	26.8	26.9
32	$C_6H_5CH_2CH_2$—	H	159–161	C	65	$C_{12}H_{12}F_3N_5$	50.9	51.4	4.3	4.5	24.7	24.8
33	C_6H_5—	H	183–185	B	27	$C_{10}H_8F_3N_5$					27.4	28.0
34	3-CH_3—C_6H_4—	H	150–152	C	32	$C_{11}H_{10}F_3N_5$	49.1	49.3	3.7	4.2	26.0	26.1

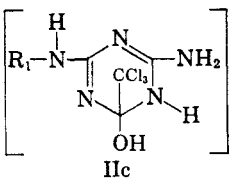
TABLE I (*Continued*)

No.	R_1	R_2	M.P.[a]	RS[b]	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
35	4-CH_3—C_6H_4—	H	185–187	A	44	$C_{11}H_{10}F_3N_5$	49.1	49.4	3.7	4.1	26.0	25.7
36	2,3-di-CH_3—C_6H_3—	H	203–205	A	34	$C_{12}H_{12}F_3N_5$					24.7	25.0
37	2,4-di-CH_3—C_6H_3—	H	219–221	A	36	$C_{12}H_{12}F_3N_5$	50.9	51.2	4.3	4.5	24.7	25.0
38	2,6-di-CH_3—C_6H_3—	H	222–224	A	32	$C_{12}H_{12}F_3N_5$	50.9	51.2	4.3	4.3	24.7	23.5
39[d]	2-C_2H_5—C_6H_4—	H	172–173	C	34	$C_{12}H_{12}F_3N_5$	50.9	51.0	4.3	4.4	24.7	24.7
40	2-CH_3—C_6H_4—	C_2H_5—	89– 97	C	44	$C_{13}H_{14}F_3N_5$	52.5	52.9	4.7	5.4	23.6	24.0
41	4-CH_3—C_6H_4—	C_2H_5—	136–138	A	18	$C_{13}H_{14}F_3N_5$	52.5	53.2	4.7	4.9	23.6	23.7
42	3-Cl—C_6H_4—	H	166–169	C	42	$C_{10}H_7ClF_3N_5$	41.5	41.8	2.4	2.6	24.2	24.2
43	3-Br—C_6H_4—	H	149–151	C	20	$C_{10}H_7BrF_3N_5$					21.0	20.8
44	2-CH_3—5-Cl—C_6H_3— R_3 = —C_2F_5	H	207–209	A	23	$C_{11}H_6ClF_3N_5$					23.1	23.0
45	CH_3—	CH_3—	178–180	A	40	$C_7H_8F_5N_5$	32.7	33.1	3.1	3.4	27.2	27.2
46	C_3H_5—[d]	H	112–114	C	48	$C_8H_8F_5N_5$	35.7	35.7	3.0	3.5	26.0	25.8
47	—$(CH_2)_5$—		130–131	A	51	$C_{10}H_{12}F_5N_5$					23.6	23.9
48[f]	$C_6H_5CH_2CH_2$—	H	106–108	C	45	$C_{13}H_{12}F_5N_5$	46.8	47.2	3.6	4.0	21.0	20.8
49	C_6H_5—	H	184–185	B	39	$C_{11}H_8F_5N_5$	43.3	43.2	2.6	2.9	22.9	23.2
50[k]	3-CH_3—C_6H_4—	H	159–161	A	28	$C_{12}H_{10}F_5N_5$	45.1	45.4	3.2	3.2	21.9	22.0
51	4-CH_3—C_6H_4—	H	180–181	A	38	$C_{12}H_{10}F_5N_5$					21.9	22.2
52	2,3-di-CH_3—C_6H_3—	H	176–182	A	22	$C_{13}H_{12}F_5N_5$	46.8	47.3	3.6	4.2	21.0	21.0
53[l]	2,4-di-CH_3—C_6H_3—	H	175–176	C	21	$C_{13}H_{12}F_5N_5$	46.8	47.0	3.6	4.0	21.0	21.0
54	2,5-di-CH_3—C_6H_3—	H	150–153	C	24	$C_{13}H_{12}F_5N_5$	46.8	47.0	3.6	4.0	21.0	21.0
55[m]	2,6-di-CH_3—C_6H_3—	H	190–191	A	10	$C_{13}H_{12}F_5N_5$	46.8	46.7	3.6	4.1	21.0	21.1
56	2-CH_3—C_6H_4—	C_2H_5—	109–111	C	43	$C_{14}H_{14}F_5N_5$	48.4	48.5	4.1	4.4	20.2	20.2
57	4-CH_3—C_6H_4—	C_2H_5—	143–145	A	28	$C_{14}H_{14}F_5N_5$	48.4	48.6	4.1	4.5	20.2	19.7
58	3-Cl—C_6H_4—	H	117–119	C	31	$C_{11}H_7ClF_5N_5$					20.6	21.0
59	3-Br—C_6H_4—	H	131–134	C	29	$C_{11}H_7BrF_5N_5$					18.2	17.8
60	2-CH_3—4-Cl—C_6H_3— R_3 = —C_3F_7	H	166–169	D	43	$C_{12}H_9ClF_5N_5$					19.8	20.1
61	CH_3—	CH_3—	151–153	C	54	$C_8H_8F_7N_5$	31.3	31.7	2.6	2.8	22.8	22.8
62	C_3H_5—[d]	H	101–103	C	47	$C_9H_8F_7N_5$	33.9	34.4	2.5	3.1	21.9	21.8
63	—$(CH_2)_5$—		136–137	A	49	$C_{11}H_{12}F_7N_5$	38.1	38.4	3.5	4.3	20.2	19.7
64	C_6H_{11}—[e]	H	65– 68	A	55	$C_{12}H_{14}F_7N_5$	39.9	40.3	3.9	4.1	19.4	19.2
65	$C_6H_5CH_2CH_2$—	H	112–114	A	31	$C_{14}H_{12}F_7N_5$	43.9	43.9	3.2	3.1	18.3	17.9
66	C_6H_5—	H	122–124	B	29	$C_{12}H_8F_7N_5$	40.6	40.8	2.3	2.5	19.7	20.2
67[n]	3-CH_3—C_6H_4—	H	105–107	A	19	$C_{13}H_{10}F_7N_5$					19.0	18.9
68[o]	2,3-di-CH_3—C_6H_3—	H	158–159	B	29	$C_{11}H_{12}F_7N_5$	43.9	44.3	3.2	3.6	18.3	18.2
69	2,6-di-CH_3—C_6H_3—	H	186–188	D	22	$C_{14}H_{12}F_7N_5$	43.9	44.5	3.2	3.4	18.3	18.4
70	2-CH_3—C_6H_4—	C_2H_5—	96– 98	C	30	$C_{15}H_{14}F_7N_5$	45.3	45.5	3.6	3.8	17.6	17.8
71	4-CH_3—C_6H_4—	C_2H_5—	112–114	A	27	$C_{15}H_{14}F_7N_5$	45.3	45.3	3.6	3.7	17.6	17.7
72	3-Cl—C_6H_4—	H	132–134	C	49	$C_{12}H_7ClF_7N_5$	37.0	37.0	1.8	2.3	18.0	18.2
73	3-Br—C_6H_4—	H	129–130	C	36	$C_{12}H_7BrF_7N_5$					16.1	15.9
74	2-CH_3—4-Cl—C_6H_3—	H	122–124	D	25	$C_{13}H_9ClF_7N_5$	38.7	38.7	2.2	2.9	17.3	17.2
75	2-CH_3—5-Cl—C_6H_3— R_3 = —$CHBr_2$	H	151–153	C	31	$C_{13}H_9ClF_7N_5$	38.7	38.9	2.2	2.3	17.4	17.0
76	CH_3—	CH_3—	196–198	E	56	$C_6H_9Br_2N_5$	23.2	23.5	2.9	3.4	22.5	22.6

TABLE I (*Continued*)

No.	R_1	R_2	M.P.[a]	RS[b]	Yield, %	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
77	C_3H_5—[d]		145–147	A	60	$C_7H_9Br_2N_5$	26.0	26.3	2.8	2.6	21.7	22.0
78	—$(CH_2)_5$—		184	A	54	$C_9H_{13}Br_2N_5$	30.8	30.3	3.7	4.0	20.0	19.9
79	$C_6H_5CH_2CH_2$—	H	114–116	F	52	$C_{12}H_{13}Br_2N_5$	37.2	37.7	3.4	3.8	18.1	17.7
80	C_6H_5—	H	165–168	A	38	$C_{10}H_9Br_2N_5$	33.5	33.7	2.5	2.6	19.5	19.7
81	3-CH_3—C_6H_4—	H	183–185	A	23	$C_{11}H_{11}Br_2N_5$					18.8	18.9
82	2,3-di-CH_3—C_6H_3—	H	179–180	A	32	$C_{12}H_{13}Br_2N_5$	37.2	37.6	3.4	3.7	18.1	18.2
83	2,4-di-CH_3—C_6H_3—	H	183–185	A	4	$C_{12}H_{13}Br_2N_5$	37.2	37.2	3.4	3.7	18.1	18.2
84	2,6-di-CH_3—C_6H_3—	H	227–228	E	5	$C_{12}H_{13}Br_2N_5$	37.2	37.4	3.4	3.8	18.1	17.8
85[p]	2-C_2H_5—C_6H_4—	H	173–174	A	25	$C_{12}H_{13}Br_2N_5$	37.2	37.3	3.4	3.6	18.1	18.3
86	2-CH_3—C_6H_4—	C_2H_5—	133–136	C	40	$C_{13}H_{15}Br_2N_5$	38.9	39.4	3.8	3.8	17.5	17.0
87	4-CH_3—C_6H_4—	C_2H_5—	142–144	A	23	$C_{13}H_{15}Br_2N_5$	38.9	39.4	3.8	4.5	17.5	16.9
88[q]	3-Cl—C_6H_4—	H	146–148	A	17	$C_{10}H_9Br_2ClN_5$					17.8	18.3
89	2-CH_3—4-Cl—C_6H_3—	H	175–176	A	27	$C_{11}H_{10}Br_2ClN_5$					17.2	17.5

[a] Melting points are not corrected. [b] RS = recrystallizing solvent: A = acetonitrile; B = benzene; C = acetonitrile-water; D = isopropyl alcohol; E = propanol; F = ethanol. [c] Analyses by Weiler and Strauss, Oxford, England. [d] C_3H_5— = allyl. [e] C_6H_{11}— = cyclohexyl. [f] —$C_6H_4CH_2CH_2$— with attached *N* is 1-indolinyl. [g] Ref. 7 reports m.p. 160°. [h] Ref. 7 reports m.p. 165–168°. [i] The initially isolated compound was an equimolar complex of compound 39 and the reactant biguanide, m.p. 133–135° (benzene). *Anal.* Calcd. for $C_{21}H_{27}F_2N_{10}$: C, 54.1; H, 5.6; N, 28.7. Found: C, 54.3; H, 5.5; N, 29.2. On treatment with boiling water the product (insoluble) is obtained. [j] The picrate melted 155–156° (propanol). *Anal.* Calcd. for $C_{19}H_{15}F_5N_8O_7$: C, 40.6; H, 2.7; N, 19.9. Found: C, 40.3; H, 3.1; N, 20.0. [k] Initially isolated as an equimolar complex with reactant biguanide, m.p. 129–135° (benzene). Not obtained analytically pure. Upon treatment with boiling water the biguanide component dissolved (and was identified as the dipicrate) and the insoluble portion dried and recrystallized as shown in the table afforded the product. [l] Equimolar complex with biguanide, m.p. 168–170° (acetonitrile) (see footnote *k*). [m] Equimolar complex with biguanide, m.p. 167–168° (acetonitrile). *Anal.* Calcd. for $C_{23}H_{27}F_5N_{10}$: C, 51.3; H, 5.1; N, 26.0. Found: C, 51.8; H, 5.5; N, 26.3 (see footnote *i*). [n] Equimolar complex with biguanide, m.p. 93–97° (benzene). *Anal.* Calcd. for $C_{22}H_{23}F_7N_{10}$; C, 47.2; H, 4.1. Found: C, 47.9; H, 4.7 (see footnote *k*). [o] Equimolar complex with biguanide, m.p. 134–137° (benzene). *Anal.* Calcd. for $C_{24}H_{27}F_7N_{10}$: N, 23.8. Found: N, 23.2 (see footnote *k*). [p] Equimolar complex with the reactant biguanide, m.p. 125–135° (benzene) (see footnote *k*). [q] An acceptable carbon-hydrogen analysis was not obtained. When a picrate derivative was made, it apparently dissociated on attempted recrystallization from water.



IIc

Paralleling the oxyalkylguanamine study,[8b] this series also showed molar complexes with the product I and the reactant biguanide (compounds 50, 53, 55, 67, 68, 85). The formation of such complexes was confined to R_1 = *ortho*- substituted or 3-methylphenyl. However, all variants of R_3 with the exception of R_3 = $-CFCl_2$ gave such complexes. These complexes were readily dissociated into the constituent biguanide and guanamine by boiling with water.

A number of effects are indicated by the ultraviolet absorption data (Table II), particularly in relation to spectra of triazines previously established.[1a,13]

When R_1 is phenyl, R_2 is hydrogen and R_3 is varied as perfluoroalkyl, the spectra parallel R_3 = $-CH_2Cl$ while R_3 = $-CCl_2F$ is virtually the same as R_3 = $CHCl_2$.[13] In turn, I as above, R_3 = $-CHBr_2$ shows a non-specific absorption suggestive of neither aniline type nor triazine type spectra.[1a]

Trial with molecular models indicates with selected conformations that *ortho* substituents on the R_1 phenyl group can interact sterically with the halogens on the R_3 group. In the instance where R_3 contains bromine even the *ortho* hydrogens of the R_1 phenyl group will interact, and consequently the phenyl group assumes a position noncoplanar with the triazine ring with the dibromomethyl compounds.

Another interesting effect is the bathochromic shift noted relative to R_3 = H[1a] using the R_3 substituents of this series with the alkylaminoguanamines. A shift of approximately 12 mμ is noted with the β-phenethyl compounds and approximately 10 mμ with the cyclohexyl compound. Moreover, a bathochromic effect is noted with the R_1R_2 substituted compounds in this series as, for example, in the piperidino structures (numbers 4, 30, 47, 63) and the dimethylamino structures (1, 45, 61) compared to the mono-substituted such as the allyl (2, 29) or the β-phenethyl (6, 32, 48, 65) and the cyclohexyl compounds (31, 64). While the extinction coefficients are relatively the same and also parallel those where R_3 = hydrogen, the λ_{max} for the di-substituted amino derivatives shows a bathochromic effect of approximately 5 mμ.

An additional effect is shown by the three characteristic spectral patterns with aryl structures:

1) Those which parallel the unsubstituted phenyl group with relatively hypsochromic absorption maxima and high extinction coefficients and which provide no steric hindrance to the coplanarity of the anilino group with the triazine ring.

2) Those showing essentially a shoulder type of absorption having a partial steric hindrance between the anilino group and the triazine ring. These include the structures throughout wherein R_1 is *o*-tolyl, 2,3-dimethylphenyl, *N*-ethyl; *p*-tolyl, and *o*-ethylphenyl (with the exception of compound 56).

3) Those with well defined specific absorption maxima, hypsochromic and hyperchromic to the R_1-alkyl substituted compounds with structures conventionally considered to have high steric hindrance about the anilino nitrogen.[8a] These include

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a,b]

No.[c]	λ max,[d] mμ	ε × 10^{-3}	No.[c]	λ max,[d] mμ	ε × 10^{-3}
1	282	3.33	42	253	18.5
				273–284	13.6
2	278	3.63			
			45	280	3.4
4	229	28.7			
	285	3.52	47	228	27.1
				282	3.48
6	278	3.74			
			48	275	4.03
7	255	20.4			
			49	254	18.5
8	267–287	3.32			
			51	254	19.1
10	254	19.2			
			52	263–275	6.1
11	260–280	6.01			
			55	272	4.72
14	270	4.35			
			56	274	4.51
15	n.s.a.[e]				
			58	251	18.2
17	276	4.56		276–282	11.7
19	255	20.6	61	280	3.46
	276–282	11.7			
			63	229	22.7
29	272	3.89		283	3.11
30	227	27.7	64	276	3.72
	280	3.8			
			65	278	4.01
31	217	28.5			
	272	3.69	66	254	18.5
32	273	4.0	68	258–278	6.32
33	254	18.3	69	272	4.79
35	255	17.7	70	272	4.52
	275–285	11.8			
			71	262–284	5.67
36	265–278	2.97			
			72	252	18.7
38	268	4.85		272–286	10.9
39	260–273	8.5	80	280–300	7.72
40	269	4.62	85	240–270	4.83
41	262–272	6.32	86	281	4.25

[a] The spectra were measured in methanol using a Beckman Model DK ultraviolet recording spectrophotometer. [b] The authors wish to thank M. Blitz and his staff for establishing the ultraviolet spectra. [c] The number corresponds to the compound number of Table I. [d] Where a range is shown, the data are for a shoulder and the ε value has been calculated at the center of the shoulder range. [e] n.s.a. = non-specific absorption.

(13) C. G. Overberger and S. L. Shapiro, *J. Am. Chem. Soc.*, **76**, 1855 (1954).

compounds where R_1 = 2,6-dimethylphenyl (compounds 14, 38, 55, 69) and *N*-ethyl, *o*-tolyl (compounds 17, 40, 70, 86) as well as compound 56 mentioned above. Here, it is likely that there is no interaction between the substituted phenyl group, its attached nitrogen and the triazine ring and the noted spectrum would be largely a function of triazine absorption.[14]

The anti-bacterial and anti-fungal studies have been hampered by the relatively poor solubility of the compounds of Table I in aqueous systems at physiological *p*H values.

(14) For related observations, see (a) H. Lumbroso and R. Dabard, *Bull. soc. chim. France*, 749 (1959); (b) A. Arcoria, H. Lumbroso and R. Passerini, *Bull. soc. chim. France*, 754 (1959); (c) S. L. Shapiro, I. M. Rose, F. C. Testa, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 6498 (1959).

EXPERIMENTAL

Guanamines of Table I. These were prepared by the same general procedure.

A solution of 0.025 mole of the biguanide hydrochloride (or nitrate) in 25 ml. of methanol was treated with 24 ml. (0.05 mole) of 23% sodium methoxide in methanol followed by 0.025 mole of ester. The reaction mixture was maintained at 20° for 24–48 hr. and then decanted in 60 ml. of water. After 72 hr., the formed precipitate of product was separated, dried and recrystallized.

In those instances where analyses indicated that the isolated material was a complex with the reactant biguanide (compounds 50, 53, 55, 67, 68, 85), this complex was dissociated by a 2–3 hr. reflux in water. The biguanide dissolved in the hot water, and the insoluble guanamine was separated and recrystallized.

Acknowledgement. The authors wish to thank R. Levinton for the data on the anti-bacterial activity.

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[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORPORATION]

Guanamines.[1] IV. Pyridylguanamines

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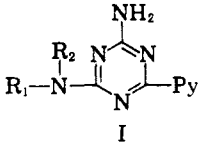
A series of 2-amino-4-substituted amino-6(2-, 3- and 4-pyridyl)-*s*-triazines has been synthesized and examined for pharmacological activity. Significant activity as antiinflammatory, analgesic, and diuretic agents has been noted with selected compounds.

Our investigations of guanamines with pharmacological activity are extended to pyridylguanamines of the type I.[2]

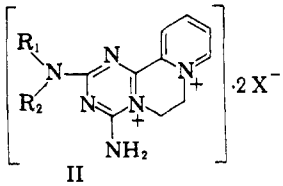


I

Py = 2-, 3-, and 4-pyridyl
R_1 = alkyl, alkenyl, aryl, substituted aryl
R_2 = hydrogen, alkyl
R_1R_2N = heterocyclic structures

The synthesis of the guanamines (Table I) was effected by reaction of the substituted biguanide in methanol with the appropriate pyridine carboxylic acid ester under sodium methoxide catalysis. Yields of product I were considerably better when R_1R_2N— was derived from aliphatic amines than from aryl amines. This may be associated with the formation of complexes between the product and the reactant biguanide,[1b,1c] and one such complex was isolated in this series. In selected instances (with arylbiguanides), the only isolable product was the nicotinic or isonicotinic acid salt of the biguanide.

Structures such as I, Py = 2-pyridyl, suggested chelation with iron and other metallic ions,[2d,3] and attempted preparation of bisquanternary structures of type II, as herbicides.[4]



II

The attempt to convert I, Py = 2-pyridyl, to the corresponding bisquaternary salt with ethylene dibromide yielded only unchanged reactant.

(1) For previous papers in this series, see (a) S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin, and L. Freedman, *J. Am. Chem. Soc.* **79**, 5064 (1957); (b) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 3996 (1959); (c) S. L. Shapiro, V. A. Parrino, and L. Freedman, *J. Org. Chem.*, **25**, 379 (1960).

(2) Compounds of type I have not been previously reported. For compounds having more than one pyridyl nucleus on the triazine ring, see (a) S. Saure, *Chem. Ber.*, **83**, 335 (1950); (b) H. J. Kahn, V. A. Petrow, R. Wien, and J. Harrison, *J. Chem. Soc.*, 858 (1945); (c) P. B. Russel and G. H. Hitchings, *J. Am. Chem. Soc.*, **72**, 4922 (1950); (d) F. H. Case and E. Koft, *J. Am. Chem. Soc.*, **81**, 905 (1959); for pyridylamino-*s*-triazine compounds, see (d) J. T. Thurston, U. S. Patent **2,474,194** (June 21, 1949); (e) W. O. Foye and A. E. Buckpitt, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 385 (1952).

(3) G. Maerker and F. H. Case, *J. Am. Chem. Soc.*, **80**, 2745 (1958).

(4) R. J. Fielden, R. F. Homer, and R. L. Jones, U. S. Patent **2,823,987** (Feb. 18, 1958).