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.

YONKERS 1, N. Y.

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

Guanamines.[1] IV. Pyridylguanamines

SEYMOUR L. SHAPIRO, VINCENT A. PARRINO, AND LOUIS FREEDMAN

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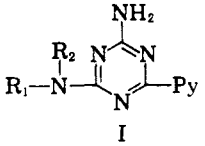
A series of 2-amino-4-substituted amino-6(2-, 3- and 4-pyridyl)-*s*-triazines has been synthesized and examined for pharmacological activity. Significant activity as antiinflammatory, analgesic, and diuretic agents has been noted with selected compounds.

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

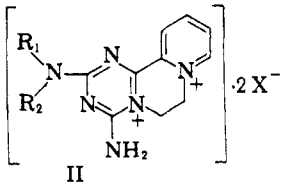


I

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).

TABLE I

PYRIDYLGUANAMINES,[h,j] I

No.	R_1	R_2	M.P., °C.[a,b]	Yield, %	Formula	Analyses[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
					Py = 3-pyridyl						
1	CH_3—	CH_3—	200–202[b1]	43	$C_{10}H_{12}N_6$					38.9	38.8
2	C_3H_5—[d]	H	148–149	44	$C_{11}H_{12}N_6$					36.8	37.2
3	i-C_5H_{11}—	H	120–123	45	$C_{13}H_{18}N_6$	60.4	60.3	7.0	7.0	32.5	32.6
4	—$(CH_2)_5$—		164–166	51	$C_{13}H_{16}N_6$	60.9	60.8	6.3	6.4	32.8	32.8
5	C_6H_{11}—[e]	H	155–157	43	$C_{14}H_{18}N_6$	62.2	62.2	6.7	6.8	31.1	30.8
6	$C_6H_5CH_2CH_2$—	H	154–155	45	$C_{16}H_{16}N_6$	65.7	65.6	5.5	5.8	28.8	28.6
7	C_6H_5—	H	217–218	19	$C_{14}H_{12}N_6$	63.6	63.6	4.6	4.7	31.8	31.9
8[f]	2-CH_3—C_6H_4	H									
9	3-CH_3—C_6H_4—	H	216–218[b2]	18	$C_{15}H_{14}N_6$	64.7	64.8	5.1	5.2	30.2	29.8
10	4-CH_3—C_6H_4—	H	200–201[b3]	35	$C_{15}H_{14}N_6$	64.7	64.8	5.1	4.8	30.2	30.4
11	2,3-di-CH_3—C_6H_3—	H	209–210[b4]	28	$C_{16}H_{16}N_6$					28.8	28.8
12	2,4-di-CH_3—C_6H_3—	H	194–195	27	$C_{16}H_{16}N_6$	65.7	65.7	5.5	5.6	28.8	28.7
13	2,5-di-CH_3—C_6H_3—	H	182–192[b5]	4	$C_{16}H_{16}N_6$	65.7	65.8	5.5	5.9	28.8	28.6
14	2,6-di-CH_3—C_6H_3—	H	204–205	31	$C_{16}H_{16}N_6$	65.7	65.5	5.5	5.6	28.8	28.8
15	2-C_2H_5—C_6H_4—	H	162–163	32	$C_{16}H_{16}N_6$	65.7	65.2	5.5	5.7	28.8	28.8
16	—$C_6H_4CH_2CH_2$—[g]		203–204[b3]	16	$C_{16}H_{14}N_6$	66.2	66.6	4.9	4.9	29.0	28.6
17	2-CH_3—C_6H_4—	C_2H_5—	146–148	37	$C_{17}H_{18}N_6$	66.6	66.9	5.9	5.9	27.4	27.0
18	4-CH_3—C_6H_4	C_2H_5—	183–185	31	$C_{17}H_{18}N_6$	66.6	67.0	5.9	6.1		
19	3-Br—C_6H_4—	H	213–215[b1]	19	$C_{14}H_{11}BrN_6$	49.0	48.7	3.2	3.7	24.5	25.0
20	2-CH_3-4-Cl—C_6H_3—	H	178–180	31	$C_{15}H_{13}ClN_6$	57.6	57.2	4.2	4.1		
21	2-CH_3-5-Cl—C_6H_3—	H	184–186	24	$C_{15}H_{13}ClN_6$	57.6	57.8	4.2	4.3	26.9	27.2
22	2,5-di-CH_3O—C_6H_3—	H	209–211	10	$C_{16}H_{16}N_6O_2$	59.3	59.2	5.0	5.0	25.9	26.2
					Py = 4-pyridyl						
23	CH_3—	CH_3—	229–231[b1]	45	$C_{10}H_{12}N_6$	55.5	55.7	5.6	6.0	38.9	38.5
24	C_3H_5—[d]	H	150–152	52	$C_{11}H_{12}N_6$	57.9	58.0	5.3	4.9		
25	i-C_5H_{11}—	H	155–156	45	$C_{13}H_{18}N_6$	60.4	60.1	7.0	6.8		
26	—$(CH_2)_5$—		170–173	58	$C_{13}H_{16}N_6$	60.9	60.9	6.3	6.2	32.8	33.0
27	C_6H_{11}—[e]	H	186–187	42	$C_{14}H_{18}N_6$	62.2	61.8	6.7	6.5		
28	$C_6H_5CH_2CH_2$—	H	173–174[b1]	50	$C_{16}H_{16}N_6$	65.7	65.5	5.5	5.8	28.8	29.0
29	C_6H_5—	H	211–213	40	$C_{14}H_{12}N_6$	63.6	63.8	4.6	4.5	31.8	32.2
30	3-CH_3—C_6H_4	H	208–210[b3]	41	$C_{15}H_{14}N_6$	64.7	64.8	5.1	5.3	30.2	30.0
31	4-CH_3—C_6H_4—	H	233–234[b3]	21	$C_{15}H_{14}N_6$	64.7	64.5	5.1	5.4	30.2	30.0
32	2,3-di-CH_3—C_6H_3—	H	183–187	9	$C_{16}H_{16}N_6$	65.7	65.4	5.5	5.7	28.8	28.8
33	2,4-di-CH_3—C_6H_3—	H	186–188	30	$C_{16}H_{16}N_6$	65.7	65.3	5.5	5.3		
34	2,5-di-CH_3—C_6H_3—	H	146–188	23	$C_{16}H_{16}N_6$	65.7	65.3	5.5	5.6	28.8	28.7
35	2,6-di-CH_3—C_6H_3—	H	202–203	10	$C_{16}H_{16}N_6$	65.7	65.9	5.5	5.5	28.8	28.4
36	2-C_2H_5—C_6H_4—	H	213–214	31	$C_{16}H_{16}N_6$	65.7	66.0	5.5	5.4	28.8	28.8
37	3-CH_3CHOH—C_6H_4—	H	189–190	12	$C_{16}H_{16}N_6O$	62.3	62.2	5.2	5.0		
38	—$(C_6H_4CH_2CH_2)$—[g]		230–231[b3]	22	$C_{16}H_{14}N_6$	66.2	66.1	4.9	5.0	29.0	29.2
39	2-CH_3—C_6H_4—	C_2H_5—	220–221[b3]	39	$C_{17}H_{18}N_6$	66.6	66.9	5.9	5.5	27.4	27.2

TABLE I (*Continued*)

No.	R_1	R_2	M.P. °C.[a,b]	Yield %	Formula	Analyses[c] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
40[i]	4-CH_3—C_6H_4—	C_2H_5—	170–171[b7]	21	$C_{17}H_{18}N_6$	66.6	66.9	5.9	5.9	27.4	27.0
41	3-Cl—C_6H_4—	H	213–215[b3]	22	$C_{14}H_{11}ClN_6$	56.3	56.4	3.7	3.7	28.1	28.0
42	3-Br—C_6H_4—	H	233–235[b3]	25	$C_{14}H_{11}BrN_6$	49.0	48.7	3.2	3.5	24.5	24.6
43	2-CH_3-4-Cl—C_6H_3—	H	228–229[b4]	29	$C_{15}H_{13}ClN_6$	57.6	57.7	4.2	4.1	26.9	27.2
44	2-CH_3-5-Cl—C_6H_3—	H	234–235[b3]	26	$C_{15}H_{13}ClN_6$	57.6	57.7	4.2	4.4	26.9	27.1
45	2,5-di-CH_3O—C_6H_3—	H	238–239[b3]	8	$C_{16}H_{16}N_6O_2$	59.3	59.4	5.0	4.9	25.9	25.7
			Py = 2-pyridyl								
46	CH_3—	CH_3—	238–240	43	$C_{10}H_{12}N_6$	55.5	55.5	5.6	5.8	38.9	38.8
47	*n*-C_5H_{11}—	H	148–150	62	$C_{13}H_{18}N_6$	60.4	60.9	7.0	6.9	32.5	32.7
48	C_6H_5—	H	234–235	30	$C_{14}H_{12}N_6$	63.6	64.1	4.6	4.7	31.8	31.6
49	2-CH_3—C_6H_4—	H	176–178	34	$C_{15}H_{14}N_6$	64.7	64.8	5.1	4.8	30.2	30.6
50	2,4-di-CH_3—C_6H_3—	H	189–191	29	$C_{16}H_{16}N_6$	65.7	65.2	5.5	5.7	28.8	29.1
51	2-CH_3—C_6H_4—	C_2H_5—	206–208	51	$C_{17}H_{18}N_6$	66.6	67.0	5.9	5.8	27.4	27.4
52	*p*-Cl—C_6H_4—	H	244–246	24	$C_{14}H_{11}ClN_6$	56.3	56.3	3.7	3.7	28.1	28.0
53	*p*-Cl—C_6H_4—	C_2H_5—	215–217	42	$C_{16}H_{15}ClN_6$	58.8	59.4	4.6	4.5	25.7	26.0
54	3-Br—C_6H_4—	H	183–184	29	$C_{14}H_{11}BrN_6$	49.0	49.4	3.2	3.5	24.5	24.2
55	5-Cl-2,4-di-CH_3O—C_6H_2—	H	246–250[b2]	21	$C_{16}H_{15}ClN_6O_2$	53.6	53.9	4.2	4.4	23.4	24.0

[a] Melting points are not corrected. [b] Recrystallizing solvent is acetonitrile unless otherwise shown. [b1] Ethanol. [b2] Methanol. [b3] Propanol. [b4] Isopropyl alcohol. [b5] Benzene. [b6] Water. [b7] Acetic acid–water. [c] Analyses by Weiler and Strauss, Oxford, England. [d] C_3H_5 = Allyl. [e] C_6H_{11} = Cyclohexyl. [f] Compound 8, R_1 = 2-CH_3—C_6H_4, gives compound biguanide complex, m.p. 141–145° (benzene). *Anal.* Calcd. for $C_{24}H_{27}N_{11}$: C, 61.4; H, 5.8; N, 32.8. Found: C, 60.7; H, 6.1; N, 31.9. The compound was identified by isolation of the picrate. [g] —$C_6H_4CH_2CH_2$— with attached nitrogen gives 1-indolino group. [h] The following compounds were characterized as their monopicrates:

Comp. No.	M.P., °C.[a,b]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
2	220[b2]	$C_{17}H_{15}N_9O_7$	44.6	44.6	3.3	3.0	27.6	27.6
8	209–211	$C_{21}H_{17}N_9O_7$	49.7	49.6	3.4	3.4	24.8	25.0
12	212	$C_{22}H_{19}N_9O_7$	50.7	51.0	3.7	3.9		
24	233[b5]	$C_{17}H_{15}N_9O_7$	44.6	44.6	3.3	3.2	27.6	27.6

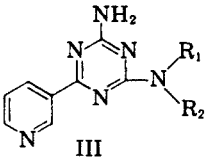
[i] It is of interest that recrystallization from aqueous acetic acid does not yield the acetic acid salt. The basicity of the compound is evidently too low to form acetic acid salts in aqueous media. [j] In the attempted preparation of the subject compounds, in the following instances the product isolated was the nicotinic acid salt of the reactant biguanide:

R_1	M.P., °C.[a,b]	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
3-Cl—C_6H_4—	188–189[b3]	$C_{14}H_{15}ClN_6O_2$	50.2	50.5	4.5	4.3	25.1	25.2
2-CH_3-4-Br—C_6H_3—	192–195	$C_{16}H_{17}BrN_6O_2$	45.8	45.5	4.4	4.4		
3,4-di-Cl—C_6H_3—	228–250[b2]	$C_{14}H_{14}Cl_2N_6O_2$	45.5	45.4	3.8	3.9		
2-CH_3-4-Br—C_6H_3—[k]	194–198[b4]	$C_{15}H_{17}BrN_6O_2$	45.8	45.8	4.4	4.4	21.4	21.4

[k] Isonicotinic acid salt.

The 2-pyridyl guanamines gave colored solutions or precipitates with ferrous ion, whereas the 3- and 4-pyridyl compounds did not.

Since pyridylguanamines can be envisioned as derivatives of nicotinamide and isonicotinamide with the triazine ring supplying the carboxamide type function,[5] as shown for III,



III

a variety of pharmacological effects associated with these pyridine derivatives was evaluated.

No systematic pharmacological response was noted which would permit an analysis of structure *vs.* activity,[6] although in general, the most active structures were found with the alkylamino derivatives of I, Py = 3- and 4-pyridyl. Upon evaluation[7] the following compounds showed antiinflammatory activity: 7(15 units/g.), 26 (4 units/g.); analgesic activity: 27 (33% at 75 mg./kg.), 28 (83% at 330 mg./kg.). Compounds 2 and 24 showed diuretic action in rats, and also lowered blood pressure significantly. Compound 17 had 4+ anticonvulsant activity associated with a negative Evipal sleeping time response.

(5) F. C. Schaefer, J. R. Dudley and J. T. Thurston, *J. Am. Chem. Soc.*, **73**, 3004 (1951).

(6) For pharmacological study of 5-(4-pyridyl)-3-amino-1,2,4-triazols, see K. Biemann and H. Bretschneider, *Monatsch. Chem.*, **89**, 603 (1958).

(7) The following screening techniques applied have been described. (a) Antiinflammatory activity: S. L. Shapiro, H. Soloway, and L. Freedman: *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957); (b) analgesic: C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954); (c) anticonvulsant activity and Evipal sleeping time: S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 1648 (1958); also ref. 1b; (d) diuretic: see ref. 1a; (e) blood pressure: S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

EXPERIMENTAL

Reactants. The biguanides utilized in this study have been described.[8] Ethyl picolinate was prepared in 58% yield, b.p. 118–122° (14 mm.), following the procedure described for ethyl nicotinate.[9]

Pyridylguanamines of Table I. The compounds of Table I 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 the pyridine carboxylic acid ester. The reaction mixture was maintained at 20° for 24–48 hr. and then decanted into 60 ml. of water. After 72 hr., the precipitate was separated, dried, and recrystallized.

Color reactions. Ferrous ion (200 mg./l.)[10] gave brown solutions with compounds 46 and 47, and purple precipitates with compounds 48 and 52. Compound 53 did not react under these test conditions and may have been too insoluble. The 2-pyridylguanamines having an alkylamino substituent give a different color response from those with the arylamino substituent.

The related compounds (1, 2, 7, 18, 23, 29, 24, 40) in the 3- and 4-pyridyl series gave no color with ferrous ion under these conditions.

With cupric ion (500 mg./l.) a brown color was noted with compound 46, and when the hydroxylamine hydrochloride solution was not added, a green color was obtained. Compound 52 under similar conditions gave a brown and green precipitate, respectively.

Acknowledgment. The authors are indebted to Dr. G. Ungar and his staff for the pharmacological screening of the compounds.

YONKERS 1, N. Y.

(8) (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) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **70**, 2755 (1948).

(10) The procedure used was adapted from *Official Methods of Analysis of the Association of Official Agricultural Chemists*, Association of Official Agricultural Chemists, Washington, D. C., 8th Ed., 1955, p. 208; using 1 ml. of test solution, 0.1 ml. of hydroxylamine hydrochloride solution, 0.5 ml. of acetate buffer solution and about 2 mg. of the pyridylguanamine, and heating to boiling.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

A Convenient Synthesis of *t*-Alkyl Esters of Amino Acids[1a]

ARNULF VOLLMAR AND MAX S. DUNN

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The preparation of *t*-alkyl esters of glycine, alanine and phenylalanine *via* the corresponding azido derivatives is described and some of the characteristics of the compounds are pointed out.

A convenient synthesis of *t*-alkyl esters of amino acids, desired for certain kinetic and microbiological investigations, is reported in this paper. Standard procedures for the preparation of amino acid esters of primary and secondary alcohols are well known and have been reviewed recently,[1b] but amino acid esters of *t*-alcohols are less readily accessible because of the lability of *t*-alcohols in acid media. Amino acid esters of *t*-alcohols should be of interest in peptide synthesis in view of their ready hydrolysis under mild acid conditions.

The *t*-butyl and trichloro-*t*-butyl esters of *N*,*N*-