these reactions in cell-free systems, it is hoped that methods can be developed for a more rapid and efficient production of this whole series of oligosaccharides.

Acknowledgments.—I wish to thank Professor J. Fruton, Department of Biochemistry, Yale University, for the use of the polarimeter and Dr. G. Taborsky for making the measurements. Thanks are also due to Dr. W. S. McNutt and Dr. I. Zelitch for helpful advice and to Dr. H. B. Vickery for assistance with the manuscript.

NEW HAVEN, CONN.

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

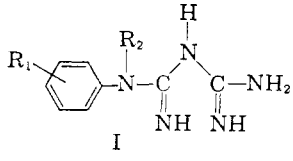
Hypoglycemic Agents. II.[1-3] Arylbiguanides

BY SEYMOUR L. SHAPIRO, VINCENT A. PARRINO, ELAINE ROGOW AND LOUIS FREEDMAN

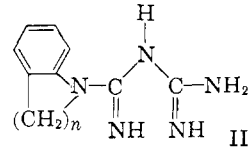
RECEIVED DECEMBER 19, 1958

Arylbiguanides of the type I have failed to yield compounds with outstanding hypoglycemic activity. The ultraviolet absorption spectra are interpreted to indicate "acetanilide resonance" or "biguanide resonance" depending on the steric factors in the aryl ring of I. Arylbiguanides are characterized as fairly stable to basic but vulnerable to acidic hydrolysis, in contrast to aralkylbiguanides.

In continuation of our study of hypoglycemic biguanides[1-3] a series of arylbiguanides of the types I and II have been prepared[4,5] and examined for

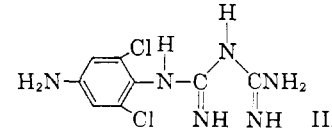


I



II

hypoglycemic activity, ultraviolet absorption characteristics and hydrolytic stability. Most of the arylbiguanides (Table I) were prepared by the aqueous method of Curd and Rose,[6] although in several instances (compounds 1 and 2) pyridine[7] was employed as the solvent. In a few cases, the product was preferably isolated as the nitrate or the free base (see Table I). With *p*-aminosalicylic acid as the reactant amine, decarboxylation[8] occurred to yield *m*-hydroxyphenylbiguanide. The product from the monohydrochloride of 2,6-dichloro - *p* - phenylenediamine was assigned the structure III.[9]



III

Many of the biguanides were characterized as the dipicrates, although a monopicrate[2,10] of the 2,6-dimethylphenylbiguanide was obtained by controlling the quantity of aqueous picric acid used.

The hydrolytic stability of the arylbiguanides in aqueous systems contrasted with observations under comparable conditions with β-phenethylbiguanide.[2] Phenylbiguanide proved to be fairly stable to basic hydrolysis, while treatment of (*m*-chlorophenyl)-biguanide with 3 *N* hydrochloric acid yielded 1-amidino-3-(*m*-chlorophenyl)-urea[11] and *m*-chloroaniline.

The ultraviolet absorption data (Table II) show that compared to I, R_2 = H, hypsochromic shifts are obtained with R_2 as methyl and ethyl, with the latter contributing a hyperchromic effect[12] (see compound 2 *vs. e;* 5 *vs.* 3; 8 *vs.* 6).

Many spectral characteristics similar to those of the acetanilides,[13,14] are noted although certain differences exist. Thus the effect of a single *o*-substituent is not nearly so marked with arylbiguanides, and while 2,6-disubstituted-acetanilides would not show any specific absorption[15] the 2,6-

(1) Presented in part at the Meeting of the American Chemical Society, New York, N. Y., September, 1957.

(2) S. L. Shapiro, V. A. Parrino and L. Freedman, THIS JOURNAL, **81**, 2220 (1959).

(3) S. L. Shapiro, V. A. Parrino and L. Freedman, *ibid.*, **81**, 3728 (1959).

(4) Structural variation of the substituted phenyl group as dimethyl, ethyl, halo and methoxyphenyl was indicated by analogy with congeners of such compounds having high hypoglycemic activity in the aralkylbiguanide series.[1-3].

(5) The evaluation of *p*-aminophenylbiguanide (compound 21, Table I) was suggested by the work of C. E. Braun, *J. Biol. Chem.*, **89**, 97 (1930), who reported hypoglycemic effects in rabbits with an *impure* preparation of *p*-aminophenylguanidine hydroiodide. Pure preparations of this salt or of other salts were found to be ineffective by T. B. Parks and C. E. Braun, *ibid.*, **91**, 629 (1931). Although the mode of processing (C. E. Braun, THIS JOURNAL, **54**, 1511 (1932)), would reflect an authentic preparation of the desired guanidine, a possibility existed that the impure preparations which showed hypoglycemic action may have been converted in part to the *p*-aminophenylbiguanide, which in turn might have been the active product. Thus, for example, C. E. Braun, *ibid.*, **55**, 1280 (1933), isolated *p*-tolylbiguanide hydrochloride in the preparation of *p*-tolylguanidine.

(6) F. H. S. Curd and F. L. Rose, British Patent 581,346 [*C. A.*, **41**, 3125 (1947)].

(7) B. R. Jacobs and Z. E. Jolles, British Patent 587,907 [*C. A.*, **42**, 214 (1948)].

(8) For instability of *p*-aminosalicylic acid in aqueous system, see C. Ghilmatti, *Farm. sci. e tec. (Pavia)*, **3**, 652 (1948) [*C. A.*, **43**, 2973b (1949)].

(9) Other syntheses in this series indicate that 2,6-substituents on the reactant aniline do not critically restrict biguanide formation. Assuming that the proton would be attached at the more basic amino group in position 1 (steric inhibition of resonance), the resultant biguanide would have the structure III.

(10) T. Callan and N. Strafford, *J. Soc. Chem. Ind.* (*London*), **43**, 1 (1924), found that while *o*-tolylbiguanide forms a dipicrate, only one mole is firmly bound.

(11) See ref. 13 of ref. 2 for pertinent data on this hydrolysis.

(12) J. C. Gage, *J. Chem. Soc.*, 221 (1949).

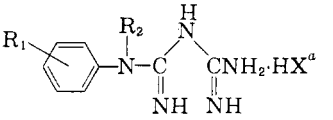
(13) H. E. Ungnade, THIS JOURNAL, **76**, 5133 (1954).

(14) The spectral data for acetanilides corresponding to the phenyl substitution shown in Table I, compound number, λ_{max} $\epsilon \times 10^{-3}$ are reproduced from ref. 13: *e*, 242, 14.4; 3, 230, 6.28; 6, 245, 14.0; 9, 245, 14.85; 12, 240, 10.4; 13, 245, 14.9; 14, 249, 17.8; 15, 234, 7.6; 16, 246, 14.0; 17, 252, 18.7; 18, 246, 13.6; 24, 245, 11.7.

(15) B. M. Wepster, "Progress in Stereochemistry," Vol. 2, Academic Press, Inc., New York, N. Y., 1958, pp. 115–120.

TABLE I

SUBSTITUTED ARYLBIGUANIDES



No.[b]	R_1	HX	M.p., °C.	RS[d]	Formula	Analyses[e] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H[a1]		107–110	A	$C_9H_{13}N_5$	56.5	56.5	6.9	6.8		
2	H[a2]		124–126	B	$C_{10}H_{15}N_5$	58.5	58.8	7.4	7.4	34.1	33.7
4	2-CH_3–[a2]	HCl	201–203	B	$C_{11}H_{18}ClN_5$	51.6	51.9	7.1	7.0	27.4	27.2
5	2-CH_3–[a2]	HNO_3	202–203	B	$C_{11}H_{18}N_6O_3$	46.8	46.9	6.4	6.3	29.8	30.0
7	3-CH_3–	2Pic.	173–175	B	$C_{21}H_{19}N_{11}O_{14}$	38.9	38.8	3.0	3.0	23.7	23.8
8	3-CH_3–[a2]	HCl	190–192	C	$C_{11}H_{18}ClN_5$	51.7	51.6	7.1	6.5	27.4	27.4
10	2-C_2H_5–		148–150	A	$C_{10}H_{15}N_5$	58.5	58.5	7.4	7.2	34.1	34.2
11	3-F	HCl	232–233	C	$C_8H_{11}ClFN_5$					30.2	30.0
15	2-Br	HCl	224–225	B	$C_8H_{11}BrClN_5$	32.8	33.3	3.8	3.9	23.9	23.4
18	3-I	HCl	203–204	C	$C_8H_{11}ClIN_5$	28.3	28.6	3.3	3.6	20.7	20.9
19	3-CF_3–	HCl	199–200	A	$C_9H_{11}ClF_3N_5$					24.9	24.4
20	4-NH_2–	2HNO_3	>300	B	$C_8H_{14}N_8O_6$	30.2	30.9	4.4	4.0	35.2	35.0
21	4-NH_2–	2Pic.	210	B	$C_{20}H_{18}N_{12}O_{14}$	37.4	37.0	2.9	2.8	25.9	26.2
22	4-C_6H_5NH–	HCl	220–221	C	$C_{14}H_{17}ClN_6$	55.2	55.2	5.6	5.7	27.6	27.5
23	3-OH	HCl	183–185	F	$C_8H_{12}ClN_5O$	41.8	41.3	5.3	5.4	30.5	30.6
24	3-CH_3O–	HCl	206–209	C	$C_9H_{14}ClN_5O$	44.5	44.2	5.8	5.5	28.8	29.1
25	3-(HO)$CHCH_3$–	HCl	185–187	E	$C_{10}H_{16}ClN_5O$	46.6	46.5	6.3	6.2	27.2	26.9
26	4-$HOCH_2CH_2$–	HNO_3	134–135	A	$C_{10}H_{16}N_6O_4$	42.3	42.1	5.7	5.3	29.6	29.6
27	4-$HOCH_2CH_2$–	2Pic.	173–174	B	$C_{22}H_{21}N_{11}O_{15}$	38.9	38.8	3.1	3.2	22.7	22.8
28	2,3-diCH_3–	HCl	232–233	B	$C_{10}H_{16}ClN_5$	49.7	49.9	6.7	6.7		
29	2,3-diCH_3–	2Pic.	203–204	B	$C_{22}H_{21}N_{11}O_{14}$	39.8	40.3	3.2	3.3	23.2	23.0
31	2,4-diCH_3–	2Pic.	201–202	B	$C_{22}H_{21}N_{11}O_{14}$	39.9	39.7	3.2	2.9		
33	2,6-diCH_3–	H_2O	84–89	B	$C_{10}H_{17}N_5O$[f]	53.8	54.0	7.7	7.6		
34	2,6-diCH_3–	Pic.	170–172	B	$C_{16}H_{18}N_8O_7$	44.2	44.5	4.2	4.4	25.8	25.9
35	2,6-diCH_3–	2Pic.	177–179	B	$C_{22}H_{23}N_{11}O_{15}$[f]	38.8	38.5	3.4	3.4	22.6	22.7
36	2,6-diC_2H_5–	HCl	192–194	B	$C_{12}H_{20}ClN_5$	53.5	52.9	7.5	7.3	25.9	25.8
37	2-CH_3-5-*i*-C_3H_7–	HCl	222–223	B	$C_{12}H_{20}ClN_5$	53.5	53.8	7.5	7.6	25.9	26.2
38	2-CH_3–3-Cl	HCl	238–239	B	$C_9H_{13}Cl_2N_5$	41.2	41.6	5.0	4.9	26.7	26.3
39	2-CH_3–4-Cl	H_2O	144–170	B	$C_9H_{14}ClN_5O$[f]	44.4	43.8	5.8	5.3		
40	2-CH_3–4-Cl	2Pic.	194–195	B	$C_{21}H_{18}ClN_{11}O_{14}$	36.9	37.3	2.7	2.6	22.5	22.2
41	2-CH_3–5-Cl	HCl	199–201	B	$C_9H_{13}Cl_2N_5$	41.2	41.0	5.0	5.0		
42	2-CH_3–6-Cl	HCl	204–205	C	$C_{19}H_{13}Cl_2N_5$	41.2	40.9	5.0	5.3	26.7	27.1
43	4-CH_3–3-Cl	HCl	208–211	C	$C_9H_{13}Cl_2H_5$	41.3	41.2	5.0	5.3		
44	2-CH_3–4-Br	HCl	241–243	B	$C_9H_{13}BrClN_5$	35.3	35.5	4.3	4.3	22.8	22.7
45	2,3-di-Cl	HNO_3	211–212	A	$C_8H_{10}Cl_2N_6O_3$	31.1	30.8	3.3	3.8		
46	2,5-di-Cl	HCl	209–212	F	$C_8H_{10}Cl_3N_5$	33.9	33.3	3.6	3.6		
48	2-CH_3O–5-Cl	HCl	232–234	C	$C_9H_{13}Cl_2N_5O$	38.9	39.0	4.7	4.6	25.2	25.3
49	2,5-diCH_3O–	HCl	228–229	E	$C_{10}H_{16}ClN_5O_2$	43.9	43.9	5.9	6.1	25.6	25.9
50	2,5-diC_2H_5O–	HNO_3	169–172	A	$C_{12}H_{20}N_6O_5$	43.9	43.7	6.1	6.2	25.6	25.7
51	2,5-diC_2H_5O–	2Pic.	153–155	F	$C_{24}H_{25}N_{11}O_{16}$	39.8	40.0	3.5	3.8	21.3	21.4
52	2,4,6-triCH_3–	HCl	225–227	C	$C_{11}H_{18}ClN_5$	51.7	52.0	7.1	7.3		
53	2,6-diCl-4-NH_2–	HCl	229–231	H	$C_8H_{11}Cl_3N_6$	32.3	32.3	3.7	4.0	28.3	28.0
54	2,4-diCH_3O-5-Cl	HCl	226–227	G	$C_{10}H_{15}Cl_2N_5O_2$	39.1	38.8	4.9	5.3		
55	–$C_6H_4CH_2CH_2$–[g]	HCl	228–230	C	$C_{10}H_{14}ClN_5$	50.1	50.6	5.9	5.9	29.2	29.3
56	–$C_6H_4(CH_2)_3$–[h]	HCl	206–208	F	$C_{11}H_{18}ClN_5O$[f]	48.6	48.3	6.7	6.7		

[a] R_2 is hydrogen unless otherwise shown; [a1] R_2 = CH_3; [a2] R_2 = C_2H_5. [b] Biguanide hydrochlorides previously reported which were prepared for the ultraviolet absorption work are described by compound number, (R_1), m.p., and reference, respectively: 3, (2-CH_3), 224–226°, "Beilstein," Vol. 12, p. 803; 6, (3-CH_3), 209–211°, H. King and I. M. Tonkin, *J. Chem. Soc.*, 1063 (1946); 9, (4-CH_3), 239–240°, C. E. Braun, THIS JOURNAL, **55**, 1280 (1933); 12, (2-Cl), 224–225°, T. Takahashi and A. Niino, *J. Pharm. Soc. Japan*, **63**, 249 (1943) [*C. A.*, **45**, 5120c (1951)]; 13, (3-Cl), 199–200°, (see (4-CH_3)); 14, (4-Cl), 239–241°, F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 362 (1946); 16, (3-Br), 187–188°, A. F. Crowther, F. H. S. Curd and F. L. Rose, *ibid.*, 1780 (1951); 17, (4-Br), 235–236°, (see (3-CH_3)); 30, (2,4-di-CH_3), 235–237°, (*ibid*); 32, (2,5-di-CH_3), 210–213°, (*ibid.*); 47, (3,5-di-Cl), 248–250°, A. F. Crowther, British Patent 709,906. [c] Melting points are not corrected. [d] Recrystallizing solvent: A = acetonitrile; B = water; C = ethanol–hexane; D = ethanol; E = methanol–ether; F = isopropyl alcohol–hexane; G = methanol; H = methyl Cellosolve–acetonitrile. [e] Analyses by Weiler and Strauss, Oxford, England. [f] Crystallizes as monohydrate. [g] Derived from indoline. [h] Derived from tetrahydroquinoline.

dialkylphenylbiguanides show characteristic absorption and higher extinctions as the hindrance about the anilino nitrogen is increased (compounds 33, 36, 52 *vs.* 3).

The hypsochromic influence of the *o*-methyl group prevails with disubstituted biguanides wherein the other substituent is methyl (compounds 28, 30, 32) or halo (compounds 38, 39, 41, 42, 44), with

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF ARYLBIGUANIDES[a,b]

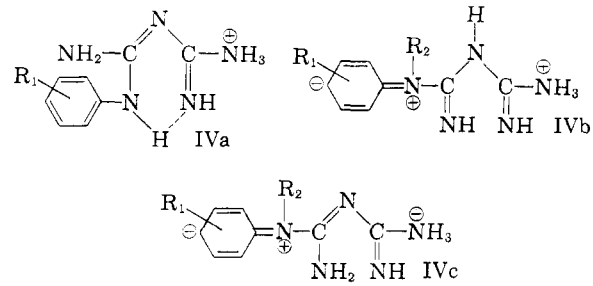
No.[c]	R_1	λ_{max},[d] mμ	ε × 10⁻³
[e]	H	242	14.6
1	H[c1]	237	14.4
2	H[c2]	236	16.5
3	2-CH_3–	236	15.6
5	2-CH_3–[c2]	235	19.0
6	3-CH_3–	240	13.8
8	3-CH_3–[c2]	236	17.4
9	4-CH_3–	240	15.0
12	2-Cl	236	14.9
13	3-Cl	249	13.7
14	4-Cl	252	15.2
15	2-Br	235	15.2
16	3-Br	249	14.1
17	4-Br	254	16.6
18	3-I	228	25.0
		243–261	14.2
19	3-CF_3	248	14.3
23	3-OH	233–245	13.1
		275–280	5.3
24	3-CH_3O–	235–251	13.4
		274–287	4.6
20	4-NH_2	257	18.0
28	2,3-diCH_3–	235	17.5
30	2,4-diCH_3–	235	17.5
32	2,5-diCH_3–	236	16.4
33	2,6-diCH_3–	235	17.9
52	2,4,6-triCH_3–	235	20.4
36	2,6-diC_2H_5–	235	18.2
38	2-CH_3–3-Cl	234	16.9
39	2-CH_3–4-Cl	236	19.3
41	2-CH_3–5-Cl	237	14.4
42	2-CH_3–6-Cl	236	16.8
44	2-CH_3–4-Br	236	19.7
45	2,3-di-Cl	232–244	14.1
47	3,5-di-Cl	254	14.7
48	5-Cl-2-CH_3O–	287	4.7
53	4-NH_2–2,6-diCl	243–252	13.1
49	2,5-diCH_3O–	238–246	12.2
		295	5.3

[a] The spectra were determined in water using a Beckman spectrophotometer (model DK). [b] The authors are grateful to Mr. M. Blitz and his associates for providing the ultraviolet absorption data. [c] The compound number shown in the table corresponds to the number used in Table I. R_2 is hydrogen throughout unless otherwise shown; [c1] R_2 is methyl; [c2] R_2 is ethyl. [d] Where a range is shown under λ it describes a shoulder in the ultraviolet absorption curve, and the extinction coefficient reported represents the noted absorption at the center of the range. [e] Phenylbiguanide hydrochloride.

para-halogen having the expected hyperchromic influence.

The spectra suggest the form IVa[2] for the arylbiguanide cation where the aryl group is sterically hindered or R_2 is alkyl ("biguanide resonance"), while "acetanilide resonance," typified by IVb, contributes significantly where R_2 = hydrogen and R_1 = phenyl or non-hindered phenyl structures. Forms such as IVc should show greater bathochromic shifts and extinction coefficients than have been noted.

Pharmacology.—A more detailed description of the noted hypoglycemic effects with the arylbiguanides will be given at a later date. In general,



IVa IVb

IVc

however, following procedures described previously,[2,3] none of the arylbiguanides examined showed oral hypoglycemic activity approaching that noted with β-phenethylbiguanide.

Experimental[16]

2-Methyl-5-(*i*-propyl)-phenylbiguanide Hydrochloride (Compound 37).—A solution of 25.0 g. (0.16 mole) of 2-methyl-5-(*i*-propyl)-aniline, 52.8 ml. of 3 *N* hydrochloric acid (0.16 mole) and 13.4 g. (0.16 mole) of dicyandiamide was heated under reflux for 5 hours. (The precipitate of the product began to form after the first hour of reaction time.) The formed precipitate was separated from the cool reaction mixture, there being obtained 31.1 g. (74%) of product, m.p. 218–220°.

N^1-Ethyl-N^1-(*o*-tolyl)-biguanide.—A solution of 50.8 g. (0.29 mole) of *N*-ethyl-*o*-toluidine hydrochloride and 24.4 g. (0.29 mole) of dicyandiamide in 200 ml. of pyridine was heated under reflux for 5.5 hours. When cool, the formed product was separated, rinsed with ether to remove entrained pyridine and dried. There was obtained 73.2 g. (100%). Addition of 40% sodium hydroxide to an aqueous solution of the hydrochloride precipitated the free base, m.p. 138–140°.

Anal. Calcd. for $C_{11}H_{17}N_5$: C, 60.3; H, 7.8; N, 31.9. Found: C, 60.1; H, 7.9; N, 31.9.

The compound was also characterized as its hydrochloride (compound 4) and the nitrate (compound 5). The other biguanides prepared using the pyridine procedure were compounds 1 and 2.

2,6-Dimethylphenylbiguanide (Compound 33).—A solution of 121 g. (1.0 mole) of 2,6-dimethylaniline in 330 ml. of 3 *N* hydrochloric acid (1.0 mole) was treated with 84.0 g. (1.0 mole) of dicyandiamide and heated under reflux for 6 hours. No precipitate formed on cooling. The reaction mixture was filtered (carbon), and with continued cooling and stirring, treated with 200 ml. of 40% sodium hydroxide. To the thick precipitate which had formed there was added an additional 400 ml. of water. After storage at 10° for 20 hours, the product, 172 g. (77%), was separated.

The dipicrate was prepared by treatment of a methanol solution of the biguanide with an excess of saturated aqueous picric acid (compound 35).

A solution of 223 mg. (0.001 mole) of the biguanide in 5 ml. of methanol was treated with 270 mg. of 85% picric acid and the solution diluted to 100 ml. with water. The reaction mixture was heated, filtered (carbon) and reheated to remove the methanol. Upon standing, the monopicrate of the product (compound 34) was obtained.

***p*-(2-Hydroxyethyl)-phenylbiguanide Nitrate** (Compound 26).—A solution of 8.2 g. (0.06 mole) of *p*-aminophenylethyl alcohol, 20 ml. (0.06 mole) of 3 *N* hydrochloric acid and 5.0 g. (0.06 mole) of dicyandiamide was heated under reflux for 5 hours. The purple reaction mixture, when cooled, was treated with a solution of 15.3 g. (0.18 mole) of sodium nitrate in 25 ml. of water. The reaction mixture was filtered (carbon) and after standing 2 hours the formed precipitate was separated, rinsed with acetone and dried. The product was dissolved in 110 ml. of ethanol and 100 ml. of hexane was added. The product, 9.5 g. (56%), was separated, m.p. 125–127°.

4-Amino-2,6-dichlorophenylbiguanide Hydrochloride (Compound 53).—A solution of 9.5 g. (0.05 mole) of 1,4-diamino-2,6-dichlorobenzene in 17 ml. of 3 *N* hydrochloric acid (0.05 mole) and 100 ml. of water was heated and

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

filtered (carbon). The filtrate was treated with 4.2 g. (0.05 mole) of dicyandiamide and heated under reflux for 7 hours. When cool, 5.7 g. (38%) of crude product was obtained.

A similar run using two equivalents of hydrochloric acid yielded, as the only isolable product, the monohydrochloride of the reactant amine.

3-Hydroxyphenylbiguanide Hydrochloride (from *p*-Aminosalicylic Acid) (Compound 23).—To a clear solution of 15.3 g. (0.1 mole) of *p*-aminosalicylic acid in 34 ml. (0.1 mole) of 3 *N* hydrochloric acid and 150 ml. of water, there was added 8.4 g. (0.1 mole) of dicyandiamide. The reaction mixture was heated under reflux for 7 hours. When cool, the clear solution was evaporated to yield a gummy residue which after trituration with acetone, and drying, weighed 17.1 g. Recrystallization (propanol–hexane) yielded 11.4 g. (50%) of product, m.p. 183–185°.

The same biguanide was obtained from *m*-aminophenol, m.p. 182–184°, mixed m.p. 183–185°.

1-Amidino-3-(*m*-chlorophenyl)-urea Hydrochloride.—A solution of 24.8 g. (0.1 mole) of *m*-chlorophenylbiguanide hydrochloride in 70 ml. of 3 *N* hydrochloric acid (total, 3.1 moles of hydrogen chloride) was heated under reflux for 1 hour. When cool, 9.4 g. of insoluble material was separated, which after recrystallization (ethanol–hexane) yielded 6.9 g. (28%) of product, m.p. 207–208° dec.

Anal. Calcd. for $C_8H_{10}Cl_2N_4O$: C, 38.6; H, 4.4; N, 22.2. Found: C, 38.6; H, 4.1; N, 22.4.

The picrate melted at 224–228° (ethanol–hexane).

Anal. Calcd. for $C_{14}H_{12}ClN_7O_8$: C, 38.1; H, 2.7; N, 22.2. Found: C, 38.1; H, 2.7; N, 22.5.

The filtrate, after separation of the product, was treated with 40 ml. of saturated aqueous sodium nitrate solution, and 18.9 g. (47%) of the nitrate salt of *m*-chloroaniline separated; recrystallized (acetonitrile), m.p. 191–194° dec.

Anal. Calcd. for $C_6H_7ClN_2O_3$: N, 14.7. Found: N, 14.2.

It was further identified as the picrate, m.p. 174–177° (propanol), which did not depress when admixed with authentic picrate of *m*-chloroaniline, m.p. 175–176°,[17] mixed m.p. 177–180°.

Alkaline Hydrolysis of Phenylbiguanide.—A solution of 17.7 g. (0.1 mole) of phenylbiguanide in 75 ml. of water containing 4.0 g. (0.1 mole) of sodium hydroxide was heated under reflux for 0.5 hours. When cool, 14.1 g. (80%) of crude phenylbiguanide, m.p. 123–130°, separated. On recrystallization from water, 6.2 g. of pure phenylbiguanide was obtained, m.p. 140–142°; not depressing when admixed with an authentic sample, m.p. 140–142°; mixed m.p. 140–142°.

Acknowledgment.—The authors are grateful to Dr. G. Ungar and his staff for the reports on the hypoglycemic activity of the compounds.

(17) The melting point of *m*-chloroaniline picrate is reported as 177° by E. Hertel, *Ber.*, **57B**, 1559 (1924); *C. A.*, **19**, 258 (1925).

YONKERS 1, N. Y.

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

Hypoglycemic Agents. III.[1–3] N^1-Alkyl- and Aralkylbiguanides

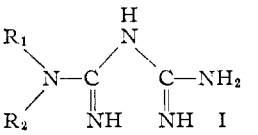
BY SEYMOUR L. SHAPIRO, VINCENT A. PARRINO AND LOUIS FREEDMAN

RECEIVED DECEMBER 19, 1958

A series of N^1-alkyl- and aralkylbiguanides has been synthesized and examined for hypoglycemic activity in guinea pigs. The relationship between structure and hypoglycemic activity is discussed.

In 1929, Slotta and Tschesche[4] synthesized a series of biguanides (I) which was examined[5] for hypoglycemic activity with the conclusion that even the most active compound of that series, N^1,N^1-dimethylbiguanide, was not indicated for use as an insulin substitute in humans.[6]

Recent work from these laboratories[2,6] described a selected compound, I, $R_1 = C_6H_5CH_2CH_2$– (DBI),[7] with outstanding hypoglycemic activity. These findings have been confirmed pharmacologically[8] and also clinically on a broad spectrum level[9] by others. In this paper the synthesis of a variety of alkyl- and aralkylbiguanides of the type I is described (Table I).



The preparation of the biguanide hydrochlorides[10–12] was effected by fusion of equimolar mixtures of the amine hydrochloride and dicyandiamide with the reaction temperatures desirably maintained at 130–150° for 0.5–2 hours. In a few cases the product was isolated as the nitrate, acetate or the free base (see Table I)

An infrequent side reaction was the formation of the guanidine, rather than the biguanide under the conditions used (see Table VI). Although biguanides are stronger bases than the aliphatic amines,[2,13] the basicity[14] of the related guanidine may be sufficiently high so that it is the protonated form of the final product. The formed biguanide

(1) Presented in part at the New York City Meeting of the American Chemical Society, September, 1957.

(2) S. L. Shapiro, V. A. Parrino and L. Freedman, THIS JOURNAL, **81**, 2220 (1959). Paper I of this series describes the properties of β-phenethylbiguanide.

(3) S. L. Shapiro, V. A. Parrino, E. Rogow and L. Freedman, *ibid.*, **81**, 3725 (1959). Paper II of this series describes the properties of arylbiguanides.

(4) K. H. Slotta and R. Tschesche, *Ber.*, **62B**, 1398 (1929).

(5) E. Hesse and G. Taubmann, *Arch. exp. Pathol. Phamakol., Naunyn-Schmiedeberg's*, **142**, 290 (1929).

(6) G. Ungar, L. Freedman and S. L. Shapiro, *Proc. Soc. Exp. Biol. Med.*, **95**, 190 (1957).

(7) U. S. Vitamin Corp. brand name for β-phenethylbiguanide hydrochloride.

(8) (a) A. N. Wick, E. R. Larson and G. S. Serif, *J. Biol. Chem.*, **233**, 296 (1958); (b) R. H. Williams, J. M. Tyberghein, P. M. Hyde and R. L. Nielsen, *Metabolism*, **6**, 311 (1957); (c) S. S. Bergen, J. G. Hilton and W. S. Norton, *Proc. Soc. Exp. Biol. Med.*, **98**, 625 (1958).

(9) (a) J. Pomeranze, H. Fuiji and G. T. Mouratoff, *ibid.*, **95**, 193 (1957); (b) L. P. Krall and R. Camerini-Davalos, *ibid.*, **95**, 345 (1957); (c) R. H. Williams, D. C. Tanner and W. D. O'Dell, *Diabetes*, **7**, 87 (1958).

(10) S. L. Shapiro, V. A. Parrino and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 689 (1957).

(11) S. L. Shapiro, V. A. Parrino, K. Geiger, S. Kobrin and L. Freedman, THIS JOURNAL, **79**, 5064 (1957).

(12) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1252 (1951).

(13) J. C. Gage, *J. Chem. Soc.*, 221 (1949).

(14) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 355.