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

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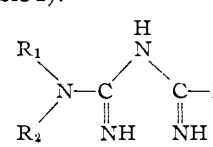
RECEIVED DECEMBER 19, 1958

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).



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).

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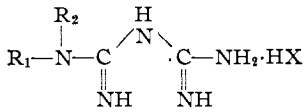
(12) P. Oxley and W. F. Short, *J. Chem. Soc.*, 1252 (1951).

(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.

TABLE I

BIGUANIDES 

No.	R_1 (R_2 = H)	HX	M.p., °C.[a,b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	LD_{min}	Hypoglycemic[e] activity response s.c.	p.o.
1	$CH_2=CHCH_2$–	HCl	178–179[ba]	$C_5H_{12}ClN_5$	33.8	33.4	6.8	7.2			300	2+	2+
2	n-C_4H_9–	HNO_3	125–126[bb]	$C_6H_{16}N_6O_3$	32.7	32.2	7.3	6.8	38.2	38.0	250	4+	4+
3	n-C_4H_9–	2HPic.[d]	190–191[bc]	$C_{18}H_{21}N_{11}O_{14}$	35.1	35.0	3.4	3.8	25.0	25.2			
4	i-C_4H_9–	HCl	222–224[bd]	$C_6H_{16}ClN_5$	37.2	37.3	8.3	7.9	36.2	36.0	300	4+	
5	t-C_4H_9–	HCl	124–128[be]	$C_6H_{16}ClN_5$	37.2	36.6	8.3	7.7	36.2	36.0	750	3+*	
6	n-C_5H_{11}–	HCl	173–174[bd]	$C_7H_{18}ClN_5$	40.5	40.7	8.7	8.8	33.7	33.8	150		4+
7	n-C_5H_{11}–	HNO_3	133–134[be]	$C_7H_{18}N_6O_3$	35.9	36.5	7.7	7.7	35.9	36.5			
8	i-C_5H_{11}–	HCl	188–189[bd]	$C_7H_{18}ClN_5$	40.5	40.8	8.7	8.8	33.7	33.6			
9	i-C_5H_{11}–	HNO_3	134–138[bd]	$C_7H_{18}N_6O_3$	35.9	36.4	7.7	7.4	35.9	36.4	200	3+	3+
10	i-C_5H_{11}–	H_2SO_4	204 dec.[bf]	$C_7H_{19}N_5O_4S$	31.1	30.8	7.1	7.3	26.0	26.8			
11	i-C_5H_{11}–	H_2SO_4[e]	170–172[bf]	$C_{14}H_{36}N_{10}O_4S$	38.2	38.3	8.2	8.5	31.8	31.5			
12	i-C_5H_{11}–	2HPic.[d]	193 dec.[bc]	$C_{19}H_{23}N_{11}O_{14}$	36.3	36.6	3.7	3.8	24.5	24.4			
13	$CH_3CH_2CH_2CHCH_3$–	HCl	217–218[ba]	$C_7H_{18}ClN_5$	40.5	41.0	8.7	8.8	33.7	34.2	100	2+	1+
14	$CH_3CH_2CH_2CHCH_3$–	2HPic.[d]	172–173[bc]	$C_{19}H_{23}N_{11}O_{14}$	36.3	36.5	3.7	4.2	24.5	25.0			
15	$CH_3CH_2CHCH_3CH_2$–	HCl	220–224[bd]	$C_7H_{18}ClN_5$	40.5	40.2	8.7	8.3	33.7	33.5	200		3+
16	$CH_3CHCH_3CHCH_3$–	HCl	220–222[ba]	$C_7H_{18}ClN_5$	40.5	40.9	8.7	8.8	33.7	33.8	300	2+	1+
17	$CH_3CH_2CHCH_2CH_3$–	HCl	231–233[bb]	$C_7H_{18}ClN_5$	40.5	40.8	8.7	8.7	33.7	33.7	200	3+	
18	$(CH_3)_3CCH_2$–	HCl	235–237[bb]	$C_7H_{18}ClN_5$	40.5	40.9	8.7	9.2	33.7	33.7	300		2+
19	n-C_6H_{13}–	HCl	115–127[bb]	$C_8H_{20}ClN_5$	43.3	43.2	9.1	9.0	31.6	32.0	75		0
20	n-$C_4H_9CHCH_3$–	HNO_3	121–123[be]	$C_8H_{20}N_5O_3$	38.7	38.1	8.1	7.9	33.8	34.2	75		0
21	n-$C_4H_9CHCH_3$–	2HPic.[f]	158–159[be]	$C_{20}H_{29}N_{11}O_{16}$	35.4	36.1	4.3	4.3	22.7	22.8			
22	n-$C_4H_7CHCH_3$–[g]	HCl	177–179[be]	$C_8H_{18}ClN_5$	43.6	42.9	8.3	8.0	31.9	31.8	150		0
23	$CH_3CHCH_3(CH_2)_2$–	HCl	141–145[be]	$C_8H_{20}ClN_5$	43.3	43.3	9.1	9.1	31.5	31.5	150		3+
24	$(CH_3)_3CCH_2CH_2$–	HNO_3	136–137[be]	$C_8H_{20}N_6O_3$	38.7	38.8	8.1	8.0	33.9	34.1	200		3+
25	C_6H_{11}–[h]	HCl	225–227[bc]	$C_8H_{18}N_5Cl$	43.7	43.4	8.3	8.2	31.9	32.2	300	4+	2+
26	$CH_3(CH_2)_5$–	HNO_3	119–121[be]	$C_9H_{22}N_5O_3$	41.2	40.9	8.5	8.4	32.0	31.6	100	4+*	
27	C_7H_{13}–[i]	HNO_3	160–161[be]	$C_9H_{20}N_6O_3$	41.5	41.5	7.7	7.7	32.3	31.7	250		1+
28	$CH_3(CH_2)_7$–	HNO_3	126–128[bd]	$C_{10}H_{24}N_6O_3$	43.5	43.6	8.8	8.6	30.4	29.1	150	3+*	
29	C_8H_{17}–[j]	HNO_3	165–167[be]	$C_{10}H_{24}N_8O_3$	43.5	44.0	8.8	8.9	30.4	30.0	100	1+*	
30[k]	C_8H_{17}–[j]	2HPic.[d]	212–213[bc]	$C_{22}H_{29}N_{11}O_{14}$	39.4	38.8	4.4	4.3	22.9	22.9			
33	$CH_3(CH_2)_9$–	HNO_3	85–105[be]	$C_{12}H_{28}N_6O_3$	47.4	47.5	9.3	8.8	27.6	27.5	300	0*	
34	d-$C_{10}H_{17}$–[l]	HCl	223–224[bg]	$C_{12}H_{24}ClN_5$	52.6	52.7	8.8	8.8	25.6	25.8	50	0*	
35	dl-$C_{10}H_{17}$–[l]	HCl	225–227[bg]	$C_{12}H_{24}N_5Cl$	52.6	52.6	8.8	8.6	25.6	25.3	100	0	
38	$C_6H_5CH_2$–	HCl	196–197[be]	$C_9H_{14}ClN_5$	47.5	47.6	6.2	6.0	30.8	30.9	150		3+
41	3-$CH_3C_6H_4CH_2$–	HCl	172–173[bg]	$C_{10}H_{16}ClN_5$	49.7	50.0	6.7	6.9	29.0	29.2	150		0
42	4-$CH_3C_6H_4CH_2$–	HCl	168–170[bo]	$C_{10}H_{16}ClN_5$	49.7	49.5	6.7	6.6	29.0	29.0	200		0
43	4-$ClC_6H_4CH_2$–		118–121[bc]	$C_9H_{12}ClN_5$	47.9	48.0	5.4	5.2					
44	4-$ClC_6H_4CH_2$–	HNO_3	137–138[be]	$C_9H_{13}ClN_5O_3$	37.4	37.6	4.5	4.3	29.1	28.7	150	4+	4+
45	4-$ClC_6H_4CH_2$–	2HPic.[d]	163–164[be]	$C_{21}H_{18}ClN_{11}O_{14}$	36.9	37.4	2.7	2.9	22.5	22.6			
46	3,4-di$ClC_6H_3CH_2$–	HNO_3	139–142[bb]	$C_9H_{12}Cl_2N_6O_3$	33.5	33.9	3.7	4.0	26.0	25.7	150		1+
48	3-$BrC_6H_4CH_2$–	HNO_3	135–137[be]	$C_9H_{13}BrN_5O_3$	32.5	32.4	3.9	3.9	25.2	24.7	200		3+
49	4-$CH_3OC_6H_4CH_2$–		132–134[be]	$C_{10}H_{15}N_5O$	54.3	54.2	6.8	6.7	31.7	32.0	150		2+
50	4-$CH_3OC_6H_4CH_2$–	2HPic.[d]	174–175[be]	$C_{22}H_{21}N_{11}O_{15}$	38.9	38.6	3.1	3.2	22.7	22.6			
51	2-$C_2H_5OC_6H_4CH_2$–	HNO_3	138–140[be]	$C_{11}H_{18}N_6O_4$	44.3	44.7	6.1	6.0	28.2	28.0	75		1+
52	2-$C_2H_5OC_6H_4CH_2$–	2HPic.[d]	158–160[be]	$C_{23}H_{23}N_{11}O_{15}$	39.8	39.9	3.3	3.1	22.2	21.9			
53	$C_6H_5CHCH_3$–	HCl	187–189[be]	$C_{10}H_{16}ClN_5$	49.7	49.6	6.7	6.6	29.0	29.2	100	0	
54	4-Cl-$C_6H_4CHCH_3$–	HCl	216–217[ba]	$C_{10}H_{15}Cl_2N_5$	43.5	43.5	5.5	5.6	25.4	25.4	100	0	
55	$(C_6H_5)_2CH$–	HCl	212–213[bd]	$C_{15}H_{18}ClN_5$	59.3	59.3	6.0	6.2	23.0	23.2	50	0	
56	$(C_6H_5)_2CH$–	2HPic.[d]	167–168[ba]	$C_{27}H_{23}N_{11}O_{14}$	44.7	44.9	3.2	3.6	21.2	21.1			
57	$FurCH_2$–[m]	HCl	161–164[bd]	$C_7H_{12}ClN_5O$	38.6	38.9	5.6	5.7	32.2	32.2	300	3+*	
58	$ThpCH_2$–[n]	HCl	166–168[bd]	$C_7H_{12}ClN_5S$	36.0	36.4	5.2	5.5	30.0	30.0	250	3+*	
59	β-$NpCH_2$–[o]	HNO_3	174–178[be]	$C_{13}H_{18}N_6O_3$	51.0	51.3	5.9	5.4	27.4	27.0	200		0
60	β-$NpCH_2$–[o]	2HPic.[d]	166–168[be]	$C_{25}H_{23}N_{11}O_{14}$					22.0	21.7			
61	$C_6H_5CH_2CH_2$–[p]	HCl	175–178[bd]	$C_{10}H_{16}ClN_5$	49.7	49.7	6.7	6.7	29.0	29.4	200	4+	4+
63	3,4-di$CH_3OC_6H_3CH_2CH_2$–	HCl	190–192[bb]	$C_{12}H_{20}ClN_5O_2$	47.8	47.8	6.7	6.9	23.2	23.2	200	0	0
64	$C_6H_5CH_2CHCH_3$–	HNO_3	146–148[be]	$C_{11}H_{18}N_6O$	46.8	46.7	6.4	6.5	29.8	29.8	300	4+	2+
65	$C_6H_5CH(C_2H_5)CH_2$–	HNO_3	118–121[be]	$C_{12}H_{20}N_6O_3$	48.6	48.7	6.8	6.8	28.4	28.0	100		1+
66	$C_6H_5CHCHC_6H_5$–	HNO_3	165–167[be]	$C_{16}H_{20}N_6O_3$	55.8	55.6	5.9	5.9	24.4	23.8	300	1+*	
67	$C_6H_5OCH_2CH_2$–	HNO_3	154–157[bb]	$C_{10}H_{16}N_5O_4$	42.3	42.2	5.7	5.8	29.6	30.0	200		0
68	$C_6H_5OCHCH_3CH_2$–	HCl	157–159[be]	$C_{11}H_{18}ClN_5O$	48.6	48.4	6.7	6.7	25.8	25.9	250		0
72	$C_6H_5(CH_2)_3$–	HNO_3	109–115[be]	$C_{11}H_{18}N_6O_3$	46.8	47.1	6.4	6.1			200		1+
73	$C_6H_5(CH_2)_3$–	2HPic.[d]	170–171[be]	$C_{23}H_{23}N_{11}O_{14}$	40.8	41.3	3.4	3.6	22.7	22.8			
74	$C_6H_5(CH_2)_4$–	HNO_3	124–126[be]	$C_{12}H_{20}N_6O_3$	48.6	48.7	6.8	6.6	28.4	27.9	100		0

TABLE IA

No.	R_1	R_2	HX	M.p., °C.[a,b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	LD_{min}	Hypoglycemic[e] activity response s.c.	p.o.
75	CH_3–	CH_3–	HCl	218–220[ba]	$C_4H_{12}ClN_5$	29.0	29.2	7.3	7.3			400	3+*	0
76	C_2H_5–	CH_3–	HNO_3	95–104[be]	$C_5H_{14}N_6O_3$	29.1	29.1	6.8	6.8	40.8	40.5	400		0
77	$CH_2=CHCH_2$–	CH_2CHCH_2–	HCl	144–146[be]	$C_8H_{16}ClN_5$	44.1	44.3	7.4	7.2	32.2	32.4	500	3+	1+

TABLE IA (*continued*)

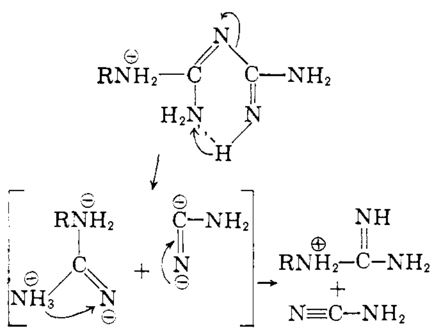
No.	R_1	R_2	HX	M.p., °C.[a,b]	Formula	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	LD_{min}	Hypoglycemic[s] activity response s.c.	p.o.
78	n-C_3H_7–	C_2H_5–	HNO_3	129–131[be]	$C_7H_{18}N_6O_3$	35.9	35.9	7.7	7.8	35.9	36.1	350		0
79	n-C_4H_9–	CH_3–	HCl	181–183[bd]	$C_7H_{18}ClN_5$	40.5	40.6	8.7	8.8	33.7	33.8	200	4+	3+
80	n-C_4H_9–	C_2H_5–	2HPic.[d]	166–169[bd]	$C_{20}H_{25}N_{11}O_{14}$	37.3	37.3	3.9	3.9	23.9	23.7			
81	i-C_4H_9–	CH_3–	HCl	182–184[ba]	$C_7H_{18}ClN_5$	40.5	41.0	8.7	8.8	33.7	33.7	300	3+	2+
82	i-C_4H_9–	CH_3–	2HPic.[d]	195–196[bc]	$C_{19}H_{23}N_{11}O_{14}$	36.3	36.4	3.7	3.9					
83	i-C_4H_9–	i-C_4H_9–	2HPic.[d]	178–180[bb]	$C_{22}H_{29}N_{11}O_{14}$	39.3	39.5	4.4	4.6	22.9	22.6			
84	n-C_5H_{11}–	CH_3–	HCl	132–134[be]	$C_8H_{20}ClN_5$	43.3	43.3	9.1	9.0	31.6	31.6	100	3+	2+
85	i-C_5H_{11}–	CH_3–	HCl	133–135[be]	$C_8H_{20}ClN_5$	43.3	43.5	9.1	8.8	31.6	31.6	200	2+	
88	C_6H_{11}–[h]	CH_3–	2HPic.[d]	212–214[be]	$C_{21}H_{25}N_{11}O_{14}$	38.5	38.8	3.8	3.7	23.5	23.9			
90	–$(CH_2)_5$–		HCl	205–207[bb]	$C_7H_{15}ClN_5$	40.9	40.8	7.8	7.5	34.1	33.8	200	4+*	3+
91	–$(CH_2)_4CHCH_3$–		2HPic.[d]	203–204[bf]	$C_{20}H_{23}N_{11}O_{14}$	37.5	37.5	3.6	3.7	24.0	24.4			
92	–$(CH_2)_6$–		HCl	203–207[bd]	$C_8H_{18}ClN_5$	43.7	43.5	8.3	7.9	31.9	32.0	300	4+	
93	–$(CH_2)_2O(CH_2)_2$–		HCl	189–192[bb]	$C_6H_{14}ClN_5O$	34.7	35.3	6.8	6.9	33.7	33.8	>1000	2+	
94	–$(CH_2)_2O(CH_2)_2$–		2HPic.[d]	223–225[bc]	$C_{18}H_{19}N_{11}O_{15}$	34.4	34.9	3.0	3.2	24.5	24.8			
96	–$(CH_2)_2NCH_3(CH_2)_2$–		2HPic.[d]	245 dec.[bc]	$C_{19}H_{22}N_{12}O_{14}$	35.5	35.7	3.5	3.4	26.2	26.0			
97	$C_6H_5CH_2$–	CH_3–	HCl	201–203[bb]	$C_{10}H_{16}ClN_5$	49.7	49.6	6.7	6.7	29.0	28.9	300	4+	2+
98	$C_6H_5CH_2$–	CH_3–	HAc	178–180[bd]	$C_{12}H_{19}N_5O_2$	54.3	54.1	7.2	7.1	26.4	26.0			
99	$C_6H_5CH_2$–	CH_3–	2HPic.[d]	189–191[be]	$C_{22}H_{21}N_{11}O_{14}$	39.8	40.0	3.2	3.2	23.2	23.2			
100	$C_6H_5CH_2$–	C_2H_5–	HCl	193–195[be]	$C_{11}H_{18}ClN_5$	52.1	52.0	6.4	7.0	27.6	27.2	100		1+
101	$C_6H_5CH_2$–	$CH_2{=}CHCH_2$–	HCl	180–181[bd]	$C_{12}H_{18}ClN_5$	53.8	53.9	6.8	6.8	26.2	26.2	75		1+
102	$C_6H_5CH_2$–	n-C_3H_7–	HCl	188–190[bd]	$C_{12}H_{20}ClN_5$	53.4	53.6	7.5	7.7	26.0	26.0	75		0
103	$C_6H_5CH_2$–	i-C_3H_7–	HCl	169–187[bd]	$C_{12}H_{20}ClN_5$	53.4	53.5	7.5	7.7	26.0	25.8	100		1+
104	$C_6H_5CH_2$–	i-C_3H_7–	2HPic.[d]	165–168[be]	$C_{24}H_{25}N_{11}O_{14}$					22.3	22.0			
105	$C_6H_5CH_2$–	C_6H_5–		76–79[bi]	$C_{15}H_{19}N_5O$[q]	63.1	63.1	6.7	6.9	24.6	24.1	150		1+
106	$C_6H_5CH_2$–	C_6H_5–	HPic.[d]	173–174[ba]	$C_{21}H_{24}N_8O_8$	47.5	47.3	4.5	3.7	21.1	21.4			
107	2-$ClC_6H_4CH_2$–	CH_3–	HNO_3	145–146[bg]	$C_{10}H_{16}ClN_6O_3$	39.7	39.6	5.0	4.8	27.8	28.0	200		2+
108	2-$ClC_6H_4CH_2$–	CH_3–	2HPic.[d]	204–205[be]	$C_{22}H_{20}ClN_{11}O_{14}$	37.9	37.6	2.9	2.6	22.1	21.8			
109	2-$ClC_6H_4CH_2$–	C_2H_5–	HCl	188–190[ba]	$C_{11}H_{17}Cl_2N_5$	45.5	45.8	5.9	5.8	24.1	24.0	100		0
110	2-$ClC_6H_4CH_2$–	$CH_2{=}CHCH_2$–	HCl	166–167[be]	$C_{12}H_{17}Cl_2N_5$	47.7	48.2	5.7	5.8	23.2	22.8	100		1+
111	2-$ClC_6H_4CH_2$–	n-C_3H_7–	HCl	174–176[be]	$C_{12}H_{19}Cl_2N_5$	47.4	47.7	6.3	5.9	23.0	23.4	90		0
112	2-$ClC_6H_4CH_2$–	i-C_3H_7–	HCl	190–191[be]	$C_{12}H_{19}Cl_2N_5$	47.4	47.2	6.3	6.3	23.0	23.0	100		1+
113	2-$ClC_6H_4CH_2$–	i-C_3H_7–	2HPic.[d]	154–156[be]	$C_{24}H_{24}ClN_{11}O_{14}$	39.7	40.4	3.3	3.6	21.2	21.0			
114	4-$ClC_6H_4CH_2$–	CH_3–	HCl	227–228[bb]	$C_{10}H_{15}Cl_2N_5$	43.5	43.9	5.5	5.5	25.4	25.2	150		1+
115	4-$ClC_6H_4CH_2$–	C_2H_5–	HCl	208–209[bg]	$C_{11}H_{17}Cl_2N_5$	45.5	45.3	5.9	5.6	24.1	23.8	125		0
116	4-$ClC_6H_4CH_2$–	C_2H_5–	2HPic.[d]	149–150[bb]	$C_{23}H_{22}ClN_{11}O_{14}$	38.8	38.9	3.1	3.1	21.6	21.6			
117	4-$ClC_6H_4CH_2$–	$CH_2{=}CHCH_2$–	HCl	188–189[bd]	$C_{12}H_{17}Cl_2N_5$	47.7	48.0	5.7	5.6	23.2	23.2	125		0
118	4-$ClC_6H_4CH_2$–	n-C_3H_7–	HCl	195–196[bb]	$C_{12}H_{19}Cl_2N_5$	47.4	47.8	6.3	6.5	23.0	23.3	100		1+
119	4-$ClC_6H_4CH_2$–	i-C_3H_7–	HCl	198–199[be]	$C_{12}H_{19}Cl_2N_5$	47.4	47.4	6.3	6.4	23.0	23.1	75		1+
120	4-$ClC_6H_4CH_2$–	n-C_4H_9–	HCl	182–184[bc]	$C_{13}H_{21}Cl_2N_5$	49.1	49.2	6.7	6.5	22.0	22.1	100		0
121	2,4-di$ClC_6H_3CH_2$–	C_2H_5–	HCl	214–216[bb]	$C_{11}H_{16}Cl_3N_5$	40.7	41.0	5.0	4.9	21.6	21.6	75		0
122	2,4-di$ClC_6H_3CH_2$–	$CH_2{=}CHCH_2$–	HCl	186–188[ba]	$C_{12}H_{16}Cl_3N_5$	42.8	42.9	4.8	4.5	20.8	20.9	100		1+
123	2,4-di$ClC_6H_3CH_2$–	n-C_3H_7–	HCl	192–194[bb]	$C_{12}H_{18}Cl_3N_5$	42.6	43.0	5.4	5.2	20.7	21.0	75		0
124	2,4-di$ClC_6H_3CH_2$–	i-C_3H_7–	HCl	186–188[bc]	$C_{12}H_{18}Cl_3N_5$	42.6	42.2	5.4	5.3	20.7	21.2	50		1+
125	3,4-di$ClC_6H_3CH_2$–	CH_3–	HCl	193–195[bb]	$C_{10}H_{14}Cl_3N_5$	38.7	38.8	4.5	5.0	22.6	22.9	100		2+
126	3,4-di$ClC_6H_3CH_2$–	C_2H_5–	HCl	206–207[bg]	$C_{11}H_{16}Cl_3N_5$	40.7	41.2	5.0	5.0	21.6	21.9	150		2+
127	3,4-di$ClC_6H_3CH_2$–	$CH_2{=}CHCH_2$–	HCl	186–188[bb]	$C_{12}H_{16}Cl_3N_5$	42.8	42.2	4.8	4.5	20.8	20.9	100		1+
128	3,4-di$ClC_6H_3CH_2$–	n-C_3H_7–	HCl	201–202[bb]	$C_{12}H_{18}Cl_3N_5$	42.6	43.3	5.4	5.6	20.7	20.7	75		0
129	3,4-di$ClC_6H_3CH_2$–	n-C_3H_7–	2HPic.[d]	147–149[be]	$C_{24}H_{23}Cl_2N_{11}O_{14}$	37.9	38.4	3.1	3.3	20.3	19.9			
130	3-$BrC_6H_4CH_2$–	CH_3–	HCl	135–137[be]	$C_{10}H_{15}BrClN_5$	37.5	37.9	4.7	4.6	21.8	22.0	150		1+
131	3-$BrC_6H_4CH_2$–	C_2H_5–	HCl	222–224[bb]	$C_{11}H_{17}BrClN_5$	39.5	39.2	5.1	5.2	20.9	21.1	85		0
132	4-$BrC_6H_4CH_2$–	C_2H_5–	HCl	206–208[be]	$C_{11}H_{17}BrClN_5$	39.5	39.4	5.1	5.0	20.9	21.4	100		1+
133	4-$BrC_6H_4CH_2$–	$CH_2{=}CHCH_2$–	HCl	184–186[ba]	$C_{12}H_{17}BrClN_5$	41.6	41.6	4.9	4.5	20.2	20.4	150		0
134	4-$BrC_6H_4CH_2$–	i-C_3H_7–	HNO_3	178–180[be]	$C_{12}H_{19}BrN_6O_3$	38.4	38.4	5.1	4.9	22.4	22.1	100		1+
135	4-$BrC_6H_4CH_2$–	n-C_4H_9–	HCl	173–176[ba]	$C_{13}H_{21}BrClN_5$	43.0	43.2	5.8	5.6	19.3	18.9	75		0
136	2-$C_2H_5OC_6H_4CH_2$–	CH_3–	HNO_3	154–155[be]	$C_{12}H_{20}N_6O_4$	46.1	45.9	6.5	6.2	26.9	26.8	50		1+
137	2-$C_2H_5OC_6H_4CH_2$–	CH_3–	2HPic.[d]	159–160[be]	$C_{24}H_{25}N_{11}O_{15}$	40.7	40.9	3.6	3.8	21.8	22.1			
138	4-$C_2H_5OC_6H_4CH_2$–	CH_3–	HCl	180–182[ba]	$C_{12}H_{20}ClN_5O$	50.4	50.6	7.1	7.2	24.5	24.8	100		2+
139	$FurCH_2$–[m]	CH_3–	HCl	227–230[bd]	$C_8H_{14}ClN_5O$	41.5	41.7	6.1	6.0	30.2	30.1	300	3+*	
140	$FurCH_2$–[m]	C_2H_5–	HCl	149–152[be]	$C_9H_{16}ClN_5O$	44.0	44.2	6.6	6.1	28.5	28.6	150	0*	
141	$ThpCH_2$–[n]	CH_3–	HCl	197–200[bb]	$C_8H_{14}ClN_5S$	38.8	39.1	5.7	5.7	28.3	28.6	350	0	
142	$ThpCH_2$–[n]	C_2H_5–	HCl	186–188[bd]	$C_9H_{16}ClN_5S$	41.3	41.2	6.2	6.1	26.7	26.8	300	0	
143	$C_6H_5CH_2CH_2$–	CH_3–	HCl	161–164[bd]	$C_{11}H_{18}ClN_5$	51.7	51.4	7.1	6.8	27.4	27.0	50	1+	
144	$C_6H_5CH_2CH_2$–	C_2H_5–	HCl	166–168[be]	$C_{12}H_{20}ClN_5$	53.4	53.6	7.5	8.0	26.0	26.4	150		0
145	$C_6H_5CH_2CH_2$–	C_2H_5–	2HPic.[d]	158–160[bc]	$C_{24}H_{25}N_{11}O_{14}$					22.3	22.1			
146	$C_6H_5CH_2CH_2$–	$CH_2{=}CHCH_2$–	HCl	143–145[bc]	$C_{13}H_{20}ClN_5$	55.0	55.1	7.3	7.0	24.8	24.6	75		1+
147	$C_6H_5CH_2CH_2$–	n-C_3H_7–	HCl	125–127[bd]	$C_{13}H_{22}ClN_5$	55.0	55.0	7.8	7.9	24.7	24.6	100		0
148	$C_6H_5CH_2CH_2$–	i-C_3H_7–	2HPic.[d]	176–177[be]	$C_{25}H_{27}N_{11}O_{14}$	42.5	42.9	3.9	3.8	21.8	21.8			
149	$C_6H_5CH_2CHCH_3$–	CH_3–		60[bc]	$C_{12}H_{19}N_5$[q,u]	55.4	55.4	8.5	8.5	26.9	27.0	100	0	
150	$C_6H_5CH_2CHCH_3$–	CH_3–	2HPic.[d]	91–95[bc]	$C_{24}H_{25}N_{11}O_{14}$	41.7	41.9	3.6	3.9					
153	$C_6H_5OCHCH_3CH_2$–	CH_3–	HCl	148–152[be]	$C_{12}H_{20}ClN_5O$	50.4	50.8	7.1	7.1	24.5	24.6	150		1+
154	–$CH_2C_6H_3CH_2CH_2$–[r]		HCl	220–223[bb]	$C_{11}H_{16}ClN_5$	51.8	51.9	6.3	6.5	27.6	27.5	150	1+	

[a] Melting points are not corrected. [b] Recrystallizing solvent: [ba]propanol, [bb]ethanol, [bc]water, [bd]isopropyl alcohol, [be]acetonitrile, [bf]methanol, [bg]ethanol–hexane, [bh]methanol–ether, [bi]propanol–hexane, [bj]ethyl acetate–hexane, [bk]ethyl acetate, [bl]isopropyl alcohol–hexane, [bm]methanol–water, [bn]benzene, [bo]xylene. [c] Analyses by Weiler and Strauss, Oxford, England. [d] HPic. = picric acid. The picrates isolated usually indicated two moles of picric acid per mole of biguanide and this has been shown as 2HPic. throughout the table wherever applicable. [e] Dibasic sulfate. [f] Isolated as dihydrate. [g] R =

1-methyl-pentene-4. [h] Cyclohexyl. [i] Cycloheptyl. [j] *t*-Octyl. [k] Numerical sequence not retained. [l] Bornyl. [m] Fur = 2-furyl. [n] Thp = 2-thiophene. [o] Np = naphthyl. [p] A variety of other salts of this biguanide are reported in ref. 2. [q] Crystallizes as monohydrate; [qa] 1.5 water. [r] Compound derived from tetrahydroisoquinoline as reactant amine. [s] The hypoglycemic activity was determined in normal guinea pigs by established methods and has been outlined in ref. 6. In screening the compounds in the course of the study, oral or subcutaneous testing was used. Usually, a subcutaneous test was run at one-fifth of the LD_{min} (minimum lethal dose subcutaneous in mice) and when otherwise established at one-third of the LD_{min}, the response has been shown with an asterisk. The oral activity was established at one-third of the LD_{min}. In the table the numerical values shown have been classified in terms of percentage reduction of blood sugar from the normal blood sugar of the animal; 0 = less than 10% reduction; 1+ = 10–20% reduction; 2+ = 21–35% reduction; 3+ = 36–60% reduction and 4+ = over 60% reduction.

could conceivably react through its intermolecular hydrogen-bonded form[2] through hydrogen transfer to yield the guanidine and cyanamide as shown in Scheme I.[12]

SCHEME I

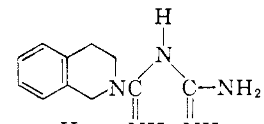


Pharmacology.—The relationship of structure to hypoglycemic activity is discussed on the basis of screening experiments in the guinea pig.[15]

In the series R_1 = alkyl, the activity reaches a peak with *n*-amyl (compound 6), then diminishes through *n*-octyl and disappears with *n*-decyl. Compared to the active *n*-alkyl structures, branched or cyclic structures reflect a diminished response. The oxygen isostere of *n*-amylbiguanide, β-methoxypropylbiguanide (see Experimental), was inactive. The most desirable variant of R_2 was hydrogen, although some structures having R_2 as methyl, and the N^1,N^1-polymethylenebiguanides (compounds 90, 92) were effective. The data indicate a dependence on the molecular bulk of R_1 plus R_2.

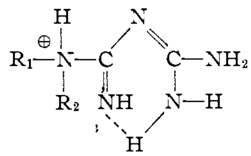
In the aralkyl series good activity was noted with R_1 = benzyl and peak effects were obtained with β-phenethyl (compound 61 (DBI)).[2] Lengthening or substitution on the alkylene chain diminished or abolished activity. The phenyl ring of the aralkyl could be substituted by pyridine, thiophene or furan rings with retention of activity, while use of a larger aryl moiety, β-naphthyl (compound 59), was ineffective. In active aralkyl compounds, substitution on the phenyl ring with halogen or alkoxy yielded active structures without enhancing the hypoglycemic effect. In turn, methyl substituents on the ring and substitution of R_2 as alkyl diminished the activity (however, see compound 97). The few (β-phenoxyethyl)-biguanide structures evaluated proved to be inactive (compounds 67, 68).

The tetrahydroisoquinoline derivative II (compound 154) which embodies the structural elements of the active compounds 61, 90 and 97, was relatively ineffective.



II

The data suggest that hypoglycemic activity is associated with selected biguanides in the form of an intramolecular hydrogen-bonded cation[2] (III).



III

$R_1 = C_4$–C_5 alkyl
$Ar(CH_2)_n$ where n = 1, 2
Ar = phenyl, furyl, thienyl, pyridyl, chlorophenyl, methoxyphenyl

R_2 = H, CH_3

Experimental[16]

Materials.—Many of the amines used in this work were obtained from commercial sources. The preparation of certain of the amines has been detailed elsewhere[11] while the following amines were processed as described in the literature: β-(2-furyl)-ethylamine,[17] N-methyl-β-phenethylamine,[18] 2-thenylamine.[19] The remainder of the amines were prepared by either of three general procedures: **Procedure A.**—Reduction of amides (Table II) with lithium aluminum hydride[20] (Table III). **Procedure B.**—Reduction of nitriles with lithium aluminum hydride–aluminum chloride (Table IV). **Procedure C.**—Reaction of aralkyl halides with amines (Table V).

Some typical examples are given wherein the experimental details warrant some comment.

***m*-Methylbenzylamine** (Compound 2, Table IV).—To a stirred suspension of 11.4 g. (0.3 mole) of lithium aluminum hydride in 300 ml. of ether was added dropwise over a 2-hour period 47.0 g. (0.35 mole) of aluminum chloride in 350 ml. of ether. A solution of 35.0 g. (0.3 mole) of *m*-toluonitrile in 600 ml. of ether was then added over 1.5 hours. Stirring was continued for 0.5 hours followed by the cautious addition of 60 ml. of water and 19.8 ml. of 40% sodium hydroxide.

The gray granular precipitate which formed was separated and rinsed with 200 ml. of ether. Under these conditions of neutralization, the formed amine was still bound in the precipitate as a lithio-aluminum complex.[21] The separated precipitate was suspended in 230 ml. of saturated sodium chloride, and 105 ml. of 40% sodium hydroxide was added. The gelatinous mass which formed was extracted with five successive 150-ml. portions of ether, the ether extracts combined and dried (calcium sulfate). After filtration, the ether solution of the amine was saturated with dried hydrogen chloride, there being obtained 41.8 g. of the hydrochloride.

N-*n*-Propyl-2,4-dichlorobenzylamine (Compounds 43, 44, 45, Table V).—In this procedure and in the other compounds described in Table V, some tertiary amine was formed in each instance. While the tertiary amines thus

(15) Not all of the compounds were tested by the same route of administration although sufficient data are at hand to characterize structure–activity relationships. Many more compounds would undoubtedly show activity if evaluated at higher levels.

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

(17) W. C. McCarthy and R. J. Kahl, *J. Org. Chem.*, **21**, 1118 (1956).

(18) H. Decker and P. Becker, *Ber.*, **45**, 2408 (1913).

(19) H. D. Hartough, S. J. Lukasiewicz and E. H. Murray, Jr., THIS JOURNAL, **70**, 1146 (1948).

(20) W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 469.

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TABLE II

AMIDES $R_1-C(=O)-NH-R_2$

No.	R_1	R_2	M.p., °C.[a,b]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	C_6H_5-	$n-C_4H_9-$	[aa]	94	$C_{11}H_{15}NO$	7.9	8.3
2	$2-ClC_6H_4-$	H	139–141	81	C_7H_6ClNO	9.0	9.0
3	$2-ClC_6H_4-$	CH_3-	119–120[bj]	97	C_8H_8ClNO	8.3	8.0
4	$2-ClC_6H_4-$	$n-C_3H_7-$	75–77[bj]	81	$C_{10}H_{12}ClNO$	7.1	6.9
5	$2-ClC_6H_4-$	$CH_2=CHCH_2-$	63–67[bm]	66	$C_{10}H_{10}ClNO$	7.2	6.9
6	$2-ClC_6H_4-$	$n-C_4H_9-$	69–71[bj]	95	$C_{11}H_{14}ClNO$	6.6	7.0
7	$4-ClC_6H_4-$	CH_3-	158–159[bk]	97	C_8H_8ClNO	8.3	8.2
8	$4-ClC_6H_4-$	$C_6H_5CH_2CH_2-$	133–134[bk]	98	$C_{15}H_{14}ClNO$	5.4	5.0
9	$4-ClC_6H_4-$	3,4-diCH_3O-$C_6H_3CH_2CH_2-$	129–131[bk]	100	$C_{17}H_{18}ClNO_3$	[ab]	
10	$3-BrC_6H_4-$	H	153–155[bj]	100	C_7H_6BrNO	7.0	7.2
11	$3-BrC_6H_4-$	CH_3-	93–94[hj]	100	C_8H_8BrNO	6.5	6.7
12	$3-BrC_6H_4-$	C_2H_5-	81–82[bj]	98	$C_9H_{10}BrNO$	6.1	5.9
13	3,4-diClC_6H_3-	H	140–142[bk]	50	$C_7H_5Cl_2NO$	7.4	7.0
14	3,4-diClC_6H_3-	CH_3-	131–132[bk]	50	$C_8H_7Cl_2NO$	6.9	6.9
15	$4-FC_6H_4-$	H	148–152[be]	55	C_7H_6FNO	10.1	9.8
16	$2-C_2H_5OC_6H_4-$	H	132–134[bj]	75	$C_9H_{11}NO_2$	8.5	8.1
17	$2-C_2H_5OC_6H_4-$	CH_3-	53–55[bj]	62	$C_{10}H_{13}NO_2$	7.8	7.9
18	$4-C_2H_5OC_6H_4-$	H	202–204[bb]	100	$C_9H_{11}NO_2$	8.5	8.3
19	$4-C_2H_5OC_6H_4-$	CH_3-	142–144[bb]	94	$C_{10}H_{13}NO_2$	7.8	7.9
20	Thp-[n]	CH_3-	110–112[bj]	95	C_6H_7NOS	9.9	10.0
21	Thp-[n]	C_2H_5-	75–77[bi]	76	C_7H_9NOS	9.0	8.9
22	$4-ClC_6H_4CH_2-$	CH_3-	114–116[bj]	89	$C_9H_{10}ClNO$	7.6	8.0
23	$C_6H_5CH_2CH_2-$	H	98–99[bk]	80	$C_9H_{11}NO$	9.4	9.1
24	$C_6H_5CH_2CH_2-$	$n-C_4H_9-$	[ac]	80	$C_{12}H_{19}NO$	6.8	6.8
25	$C_6H_5OCH_2-$	H	102–104[bi]	89	$C_8H_9NO_2$	9.3	9.0
26	$C_6H_5OCH_2-$	CH_3-	69–70[bj]	65	$C_9H_{11}NO_2$	8.5	8.1
27	$C_6H_5OCHCH_3-$	H	128–130[bj]	84	$C_9H_{11}NO_2$	8.5	8.3
28	$C_6H_5OCHCH_3-$	CH_3-	91–92[bj]	82	$C_{10}H_{13}NO_2$	7.8	7.9
29	$C_6H_5OCHCH_3-$	C_2H_5-	69–70[bj]	80	$C_{11}H_{15}NO_2$	7.3	7.0

The footnotes in this table have the same significance as those shown in Table I. [aa] Boiling point 125–137° (0.1 mm.). [ab] Calcd.: C, 63.9; H, 5.7. Found: C, 64.0; H, 5.7. [ac] Boiling point 145–157° (0.5 mm.).

obtained were not germane to the study at hand, their formation and properties have been included in the table as an indication of the scope[22] of this type of synthesis in the preparation of amines and to indicate the influence of structural effects[23] on the ratio of *sec*:*tert*-amine formed.

A mixture of 29.5 g. (0.3 mole) of *n*-propylamine, 70 ml. of water, 30 ml. of 40% sodium hydroxide and 50 ml. of acetonitrile was treated with a solution of 58.5 g. (0.3 mole) of 2,4-dichlorobenzyl chloride in 40 ml. of acetonitrile. The reaction mixture was securely stoppered, and after 10 minutes, a mild exothermic reaction was noted. After standing for 4 days, a liter of water was added, and 61.0 g. of a colorless oil which separated was removed, dissolved in 100 ml. of ether and dried (sodium sulfate). No appreciable increase in yield was effected by extraction of the aqueous phase of the reaction mixture with additional ether.

After filtration of the ether solution of the products, removal of ether, and distillation, there was obtained 46.2 g. of the secondary amine (compound 43, Table V), b.p. 82–85° (0.35–0.5 mm.), and 7.7 g. of the di-(2,4-dichlorobenzyl)-propylamine (compound 45, Table V), b.p. 161–175° (0.05 mm.).

Treatment of a solution of 45.8 g. of compound 43 in 1.2 liters of ether with hydrogen chloride yielded 49.2 g. of the hydrochloride (compound 44, Table V) of N-*n*-propyl-2,4-dichlorobenzylamine.

Preparation of Biguanides.—Representative examples of the synthesis for structural variants of the compounds in Table I are given below.

(22) C. G. Swain and D. C. Dittmer, THIS JOURNAL, 77, 3924 (1955).

(23) (a) J. C. Charlton and E. D. Hughes, *J. Chem. Soc.*, 850, 855 (1956); (b) G. Baddeley, J. Chadwick and H. T. Taylor, *ibid.*, 448 (1956).

N[1],N[1]-Hexamethylenebiguanide Hydrochloride (Compound 92, Table I).—An equimolar mixture of hexamethyleneimine hydrochloride and dicyandiamide (0.15 mole) was slowly heated with stirring (oil-bath). The mixture began to melt at 97° (bath, 127°) and fused completely at 120° (bath, 132°). The bath temperature was raised gradually over a 1-hour period to 170° and heating was continued at this temperature for 50 minutes. When cool, the product was dissolved in 130 ml. of ethanol and filtered (carbon). The filtrate, after addition of 300 ml. of ether, yielded 18.9 g. (57%) of product.

***m*-Bromobenzylbiguanide Nitrate** (Compound 48, Table I).—An equimolar mixture of *m*-bromobenzylamine hydrochloride and dicyandiamide (0.05 mole) was heated as above. The mixture began to melt at 125° (bath, 139°) and fused completely at 153°. Heating was continued (bath, 150–160°) for 1 hour. The cooled fusion product was dissolved in 250 ml. of water and filtered (carbon). After removal of 200 ml. of water at 18 mm., the aqueous solution of the reaction product was treated with a solution of 5.0 g. of sodium nitrate in 5 ml. of water, and after chilling at 5°, 14.9 g. of product separated and was recrystallized from acetonitrile. There was obtained 8.8 g. (50%).

N[1]-(3,4-Dichlorobenzyl)-N[1]-ethylbiguanide Hydrochloride (Compound 126, Table I).—An equimolar mixture of N-ethyl-3,4-dichlorobenzylamine hydrochloride (compound 53, Table V) and dicyandiamide (0.1 mole) was heated as above. The mixture began to melt at 142° (bath, 156°). Heating was continued with gradual raising of bath temperature to 167° over a 1-hour period. The cooled fusion product was recrystallized from ethanol giving 20.4 g (64%).

***p*-Methoxybenzylbiguanide** (Compound 49, Table I).—An equimolar mixture of *p*-methoxybenzylamine hydro-

TABLE III

AMINES BY LITHIUM ALUMINUM HYDRIDE REDUCTION OF AMIDES $R_1—N(R_2)—H \cdot HCl$

No.	R_1	R_2	M.p., °C.[a,b]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	$(CH_3)_3CCH_2$–	H	288–289	45	$C_5H_{14}ClN$	11.3	11.2
2	$(CH_3)_3CCH_2CH_2$–	H	314 dec.	62	$C_6H_{16}ClN$	10.2	10.0
3	$CH_3CHCH_3(CH_2)_3$–	H	186–188[bk]	54	$C_6H_{16}ClN$	10.2	9.7
4	2-$ClC_6H_4CH_2$–	H	216–218[bb]	59	$C_7H_9Cl_2N$	7.9	8.3
5	2-$ClC_6H_4CH_2$–	n-C_4H_9–	107–115[bk]	50	$C_{11}H_{17}Cl_2N$	6.0	5.7
6	4-$ClC_6H_4CH_2$–	$C_6H_4CH_2CH_2$–	>260[bb]	92	$C_{15}H_{17}Cl_2N$	5.0	4.7
7[ca]	4-$ClC_6H_4CH_2$–	3,4-diCH_3O-$C_6H_3CH_2CH_2$–	139–141[ba]		$C_{23}H_{23}ClN_4O_9$	[cb]	
8	3-$BrC_6H_4CH_2$–	H	212–214[be]	74	C_7H_9BrClN	6.3	5.7
9	3-$BrC_6H_4CH_2$–	CH_3–	159–160[be]	93	$C_8H_{11}BrClN$	5.9	5.8
10	3-$BrC_6H_4CH_2$–	C_2H_5–	171–172[be]	100	$C_9H_{13}BrClN$	5.6	6.0
11	3,4-di$ClC_6H_3CH_2$–	H	230–234[bb]	29			
12[ca]	3,4-di$ClC_6H_3CH_2$–	H	214–215[be]		$C_{13}H_{10}Cl_2N_4O_7$	13.8	14.0
13	3,4-di$ClC_6H_3CH_2$–	CH_3–	225–227[bb]	44	$C_8H_{10}Cl_3N$	6.2	6.1
14	2-$C_2H_5OC_6H_4CH_2$–	H	165–167[be]	64	$C_9H_{14}ClNO$	7.5	7.1
15	2-$C_2H_5OC_6H_4CH_2$–	CH_3–	125–138	97	$C_{10}H_{16}ClNO$	7.0	7.1
16	4-$C_2H_5OC_6H_4CH_2$–	H	231–233[ba]	68	$C_9H_{14}ClNO$	7.5	7.1
17	4-$C_2H_5OC_6H_4CH_2$–	CH_3–	162–163[be]	97	$C_{10}H_{16}ClNO$	7.0	6.9
18	FurCH_2–	CH_3–	145–147[bl]	52	$C_6H_{10}ClNO$	9.5	9.2
19	FurCH_2–	C_2H_5–	120–122[bl]	52	$C_7H_{12}ClNO$	8.7	8.8
20	ThpCH_2–	CH_3–	190–192[bb]	77	$C_6H_{10}ClNS$	8.6	8.8
21	ThpCH_2–	C_2H_5–	137–138[be]	74	$C_7H_{12}ClNS$	7.9	8.2
22	4-$ClC_6H_4(CH_2)_2$–	CH_3–	147–154[be]	78	$C_9H_{13}Cl_2N$	6.8	7.0
23	$C_6H_5(CH_2)_3$–	H	218–220[be]	65	$C_9H_{14}ClN$	8.2	7.8
24	$C_6H_5(CH_2)_3$–	n-C_4H_9–	218–219[be]	85	$C_{13}H_{22}ClN$	6.2	5.9
25	$C_6H_5(CH_2)_4$–	H	164–165[be]	67	$C_{10}H_{16}ClN$	7.5	7.8
26	α-NpCH_2–[o]	H	249–250[be]	37	$C_{11}H_{12}ClN$	7.2[cc]	6.8
27	β-NpCH_2–[o]	H	266–268[bb]	73	$C_{11}H_{12}ClN$	7.2	6.8
28	$C_6H_5OCH_2CH_2$–	H	214–216[bb]	58	$C_8H_{12}ClNO$	8.1	8.1
29	$C_6H_5OCH_2CH_2$–	CH_3–	175–176[be]	79	$C_9H_{14}ClNO$	7.5	7.0
30	$C_6H_5OCH_2CH_2$–	C_2H_5–	178–180[be]	85	$C_{10}H_{16}ClNO$	7.0	6.8
31	$C_6H_5OCHCH_3CH_2$–	H	156–158[be]	66	$C_9H_{14}ClNO$	7.5	7.1
32	$C_6H_5OCHCH_3CH_2$–	CH_3–	116–117[bh]	58	$C_{10}H_{16}ClNO$	7.0	7.0

The footnotes in this table have the same significance as those shown in Table I. [ca] Picrate of the compound shown. [cb] Calcd.: C, 51.6; H, 4.4. Found: C, 51.8; H, 4.3. [cc] Calcd.: C, 68.2; H, 6.3. Found: C, 68.3; H, 6.3.

TABLE IV

AMINES BY $AlCl_3$-$LiAlH_4$ REDUCTION OF NITRILES R_1-$NH_2 \cdot HCl$

No.	R_1	M.p., °C.[a,b]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	2-$CH_3C_6H_4CH_2$–	222–223[bb]	83	$C_8H_{12}ClN$	[da]	
2	3-$CH_3C_6H_4CH_2$–	214–215[ba]	89	$C_8H_{12}ClN$	8.9	8.8
3	4-$CH_3C_6H_4CH_2$–	220–224[aa]	90	$C_8H_{12}ClN$	8.9	8.8
4	$C_6H_5(CH_2)_4$–	161–163[be]	79	$C_9H_{14}ClN$	8.2	7.7
5	α-NpCH_2CH_2–[o]	249–250[bb]	74	$C_{12}H_{14}ClN$	6.7	6.9

The footnotes in this table have the same significance as those shown in Table I. [da] Calcd.: C, 61.0; H, 7.7. Found: C, 60.7; H, 7.4.

chloride and dicyandiamide (0.1 mole) was heated as above. The mixture began to melt at 143° (bath, 158°) and fused completely at 167° with a rise of mixture temperature to 170° (bath, 164°). Heating (bath, 164–169°) was maintained for 1.3 hours. The cooled fusion product was dissolved in 200 ml. of water, treated with carbon and filtered. The filtrate was concentrated to 125 ml. under vacuum (18 mm.), cooled and 10 ml. of 40% sodium hydroxide was added with continued stirring and cooling. After storage at 5° for 20 hours, 10.8 g. of product separated and was recrystallized from acetonitrile. There was obtained 5.7 g. (26%).

N^1-(3-Methoxypropyl)-biguanide Hydrochloride.—Equimolar portions (0.1 mole) of 3-methoxypropylamine hydrochloride and dicyandiamide were fused as previously described. The mixture softened at 78° (bath, 120°) and fused completely at 122°. Within 15 minutes of complete fusion, an exothermic reaction occurred and the internal temperature rose to 142° (bath, 136°). The reaction mixture was maintained at 142° for 1 hour, cooled and dissolved in 140 ml. of ethanol. After addition of carbon, the solution was filtered and the filtrate treated with 140 ml. of hexane. There was obtained 11.5 g. (55%) of product, m.p. 155–157°.

Anal. Calcd. for $C_6H_{16}ClN_5O$: C, 34.4; H, 7.7; N, 33.4. Found: C, 34.2; H, 8.1; N, 33.1.

N^1-(2-Picolyl)-biguanide Hydrochloride.—A solution of 10.8 g. (0.1 mole) of 2-picolylamine in 34.3 ml. of 3 *N* hydrochloric acid was evaporated to dryness and the residue dried and slurried with ether. There was obtained 14.3 g. of the monohydrochloride of 2-picolylamine, m.p. 121–124°.

A mixture of 13.3 g. (0.09 mole) of the hydrochloride and 8.4 g. (0.1 mole) of dicyandiamide was fused in an oil-bath. The mixture began to melt at 67° (bath, 105°) and fused completely at 126° (bath, 132°). After 5 minutes, an exothermic reaction occurred, the temperature rose to 143° (bath, 141°) and the reaction mixture darkened considerably. Heating was discontinued. When the cooled reaction product was dissolved in 90 ml. of ethanol, and 85 ml. of hexane was added, an oil precipitated. The supernatant was decanted and on standing gave 2.2 g. of product, m.p. 134–142°. After resolution in ethanol and precipitation with hexane, the oil gave an additional 3.64 g., m.p. 130–132°. Recrystallization (isopropyl alcohol–hexane) gave the product in 10% yield, m.p. 177–178°. The compound had an LD_{min} of 500 mg./kg. and showed 4+ hypoglycemia (s.c.).

TABLE V

AMINES FROM ARYLALKYL HALIDES $R_1—N(R_3)—R_2$

No.	R_1 [eb]	R_2 [ef]	R_3	M.p. or b.p.,[a,b] °C.	Mm.	Yield, %	Formula	Nitrogen, % Calcd.	Found
1	$C_6H_5CH_2$–	C_2H_5–	H	55–64	6.0–7.0	24[ea]	$C_9H_{13}N$	10.4	10.0
2		HCl		181–183[be]					
3	$C_6H_5CH_2$–	C_2H_5–	R_1	127–131	3.5	68[ea]			
4	$C_6H_5CH_2$–	n-C_3H_7–	H	69–74	4.0	47[ea]	$C_{10}H_{15}N$	9.4	9.2
5		HCl		182–184[be]			$C_{10}H_{16}ClN$	7.5	7.9
6	$C_6H_5CH_2$–	n-C_3H_7–	R_1	102–130	1.75	45[ea]	$C_{17}H_{21}N$	5.9	5.9
7	$C_6H_5CH_2$–	i-C_3H_7–	H	64–66	4.0	66[ea]			
8		HCl		190–191[be]			$C_{10}H_{16}ClN$	7.6	7.9
9	$C_6H_5CH_2$–	i-C_3H_7–	R_1	104–110	0.3	27[ea]	$C_{17}H_{21}N$	5.9	5.8
10	$C_6H_5CH_2$–	CH_2=$CHCH_2$–	H	70–79	5.5	33			
11		HCl		145–146[be]			$C_{10}H_{14}ClN$	7.6	7.8
12	$C_6H_5CH_2$–	CH_2=$CHCH_2$–	R_1	118–135	2.0	60	$C_{17}H_{19}N$	5.9	6.0
13	2-$ClC_6H_4CH_2$–	C_2H_5–	H	54–58	0.1	40			
14		HCl		138–140[be]			$C_9H_{13}Cl_2N$	6.8	6.8
15	2-$ClC_6H_4CH_2$–	C_2H_5–	R_1	132–140	0.24	43			
16		HCl		181–186[be]			$C_{16}H_{18}Cl_3N$	4.2	4.1
17	2-$ClC_6H_4CH_2$–	i-C_3H_7–	H	67–92	5.0	71			
18		HCl		170–172[be]			$C_{10}H_{15}Cl_2N$	6.4	6.0
19	2-$ClC_6H_4CH_2$–	i-C_3H_7–	R_1	Res.[ec]		21			
20	2-$ClC_6H_4CH_2$–	CH_2=$CHCH_2$–	H	68–70	0.04	59			
21		HCl		116–117[be]			$C_{10}H_{13}Cl_2N$	6.4	6.2
22	2-$ClC_6H_4CH_2$–	CH_2=$CHCH_2$–	R_1	Res.[ec]		27	$C_{17}H_{17}Cl_2N$	4.6	4.7
23	4-$ClC_6H_4CH_2$–	CH_3–	R_1	180–182	3.0	74	$C_{15}H_{15}Cl_2N$	5.0	5.2
24	Metho-perchlorate			140			$C_{16}H_{18}Cl_3NO_4$	3.6	3.7
25	4-$ClC_6H_4CH_2$–	C_2H_5–	H	112–114	9.0	35	$C_9H_{12}ClN$	8.3	8.0
26		HCl		235–237[bb]			$C_9H_{13}Cl_2N$	6.8	6.7
27	4-$ClC_6H_4CH_2$–	C_2H_5–	R_1	212–216	10.0	50	$C_{16}H_{17}Cl_2N$	4.8	4.7
28	4-$ClC_6H_4CH_2$–	n-C_3H_7–	H	123–126	9.0	47			
29		HCl		221–223[ba]			$C_{10}H_{15}Cl_2N$	6.4	6.2
30	4-$ClC_6H_4CH_2$–	n-C_3H_7–	R_1	216–220	9.0	49			
31	4-$ClC_6H_4CH_2$–	i-C_3H_7–	H	65–68	0.25	73			
32		HCl		196–198[be]			$C_{10}H_{15}Cl_2N$	6.4	5.9
33	4-$ClC_6H_4CH_2$–	i-C_3H_7–	R_1	162–166	0.75	15	$C_{17}H_{19}Cl_2N$	4.5	4.8
34	4-$ClC_6H_4CH_2$–	CH_2=$CHCH_2$–	H	115–118	8.0	50	$C_{10}H_{12}ClN$	7.7	7.9
35		HCl		189–190			$C_{10}H_{13}Cl_2N$	6.4	6.3
36	4-$ClC_6H_4CH_2$–	CH_2=$CHCH_2$–	R_1	Res.[ec]		37			
37	4-$ClC_6H_4CH_2$–	n-C_4H_9–	H	104–107	3.0	47			
38		HCl		243–244[bb]			$C_{11}H_{17}Cl_2N$	6.0	5.9
39	4-$ClC_6H_4CH_2$–	n-C_4H_9–	R_1	Res.[ec]		33	$C_{18}H_{21}Cl_2N$	4.4	4.3
40	2,4-di$ClC_6H_3CH_2$–	C_2H_5–	H	106–111	3.2	55	$C_9H_{11}Cl_2N$	6.9	6.7
41		HCl		182–183[bb]			$C_9H_{12}Cl_3N$	5.8	5.7
42	2,4-di$ClC_6H_3CH_2$–	C_2H_5–	R_1	145–200	1.0	21	$C_{16}H_{15}Cl_4N$	3.9	4.1
43	2,4-di$ClC_6H_3CH_2$–	n-C_3H_7–	H	82–85	0.35–0.5	71			
44		HCl		155–157[be]			$C_{10}H_{14}Cl_3N$	5.5	5.9
45	2,4-di$ClC_6H_3CH_2$–	n-C_3H_7–	R_1	161–175	0.05	14	$C_{17}H_{17}Cl_4N$	3.7	3.8
46	2,4-di$ClC_6H_3CH_2$–	i-C_3H_7–	H	112–117	4.0	74			
47		HCl		188–189[be]			$C_{10}H_{14}Cl_3N$	5.5	5.7
48	2,4-di$ClC_6H_3CH_2$–	i-C_3H_7–	R_1	56–62	0.05	16	$C_{17}H_{17}Cl_4N$	3.7	3.8
49	2,4-di$ClC_6H_3CH_2$–	CH_2=$CHCH_2$–	H	100–121	3.5	65	$C_{10}H_{11}Cl_2N$	6.5	6.7
50		HCl		148–149[bb]			$C_{10}H_{12}Cl_3N$	[ed]	
51	2,4-di$ClC_6H_3CH_2$–	CH_2=$CHCH_2$–	R_1	Res.[ec]		18			
52	3,4-di$ClC_6H_3CH_2$–	C_2H_5–	H	114–118	4.0	49	$C_9H_{11}NCl_2$	6.9	6.9
53		HCl		227–229[bb]			$C_9H_{12}Cl_3N$	5.8	5.8
54	3,4-di$ClC_6H_3CH_2$–	C_2H_5–	R_1	185–200	0.3–0.7	35	$C_{16}H_{15}Cl_4N$	3.9	4.0
55	3,4-di$ClC_6H_3CH_2$–	n-C_3H_7–	H	125–131	4.5–5.0	65	$C_{10}H_{13}Cl_2N$	6.4	6.5
56		HCl		231–233[bb]			$C_{10}H_{14}Cl_3N$	5.5	5.9
57	3,4-di$ClC_6H_3CH_2$–	n-C_3H_7–	R_1	Res.[ec]		23	$C_{17}H_{17}Cl_4N$	3.7	3.9
58	3,4-di$ClC_6H_3CH_2$–	i-C_3H_7–	H	120–122	4.0	85	$C_{10}H_{13}Cl_2N$	6.4	6.0
59		HCl		204–205[be]			$C_{10}H_{14}Cl_3N$	5.5	5.9
60	3,4-di$ClC_6H_3CH_2$–	i-C_3H_7–	R_1	Res.[ec]		7			
61	3,4-di$ClC_6H_3CH_2$–	CH_2=$CHCH_2$–	H	130–135	3.3	63	$C_{10}H_{11}Cl_2N$	6.5	6.7

TABLE V (*continued*)

No.	R_1[eb]	R_2[ef]	R_3	M.p. or b.p.,[a,b] °C.	Mm.	Yield, %	Formula	Nitrogen, % Calcd.	Found
62	HCl			222–224[bb]			$C_{16}H_{12}Cl_5N$	[ee]	
63	3,4-diClC$_6$H$_3$CH$_2$-	CH$_2$=CHCH$_2$-	R_1	86–167	0.25–0.33	24	$C_{17}H_{15}Cl_4N$	3.7	3.9
64	4-BrC$_6$H$_4$CH$_2$-	C$_2$H$_5$-	H	108–111	6.0	27[ea]	$C_9H_{12}BrN$	6.5	6.7
65	HCl			238–240[bb]			$C_9H_{13}BrClN$	5.6	5.8
66	HBr			238–241[be]					
67	4-BrC$_6$H$_4$CH$_2$-	C$_2$H$_5$-	R_1	Res.[ec]		4[ea]			
68	4-BrC$_6$H$_4$CH$_2$-	*i*-C$_3$H$_7$-	H	80–84	0.65–0.8	66	$C_{10}H_{14}BrN$	6.1	6.4
69	HCl			190–191			$C_{10}H_{15}BrClN$	5.3	4.9
70	4-BrC$_6$H$_4$CH$_2$-	*i*-C$_3$H$_7$-	R_1	Res.[ec]		19			
71	4-BrC$_6$H$_4$CH$_2$-	CH$_2$=CHCH$_2$-	H	82–89	0.06	44	$C_{10}H_{12}BrN$	6.2	6.4
72	HCl			194–196[be]			$C_{10}H_{13}BrClN$	5.3	4.9
73	4-BrC$_6$H$_4$CH$_2$-	*n*-C$_4$H$_9$-	H	84–94	0.08	57			
74	HCl			233–235[be]			$C_{11}H_{17}BrClN$	5.0	4.8
75	C$_6$H$_5$CH$_2$CH$_2$-	C$_2$H$_5$-	H	50–75	2.8	43			
76	HCl			182–184[be]					
77	C$_6$H$_5$CH$_2$CH$_2$-	C$_2$H$_5$-	R_1	115–130	0.15–0.25	38	$C_{18}H_{23}N$	5.5	5.9
78	C$_6$H$_5$CH$_2$CH$_2$-	*n*-C$_3$H$_7$-	H	78–87	3.0–3.5	63	$C_{11}H_{17}N$	8.6	8.7
79	HCl			215–216[be]			$C_{11}H_{18}ClN$	7.0	7.3
80	C$_6$H$_5$CH$_2$CH$_2$-	*n*-C$_3$H$_7$-	R_1	90–119	0.1–0.12	21	$C_{19}H_{25}N$	5.2	4.8
81	C$_6$H$_5$CH$_2$CH$_2$-	*i*-C$_3$H$_7$	H	76–78	3.5–4.0	79			
82	HCl			168–169[be]			$C_{11}H_{18}ClN$	7.0	6.8
83	C$_6$H$_5$CH$_2$CH$_2$-	*i*-C$_3$H$_7$-	R_1	126–134	0.3–0.4	15	$C_{19}H_{25}N$	5.2	5.3
84	C$_6$H$_5$CH$_2$CH$_2$-	CH$_2$=CHCH$_2$-	H	85–92	4.0	58	$C_{11}H_{15}N$	8.7	8.8
85	HCl			175–176[be]			$C_{11}H_{16}ClN$	7.1	7.3
86	C$_6$H$_5$CH$_2$CH$_2$-	CH$_2$=CHCH$_2$-	R_1	105–130	0.4–0.7	24	$C_{19}H_{23}N$	5.3	4.8

The footnotes in this table have the same significance as those shown in Table I. [ea] The aralkyl halide used was the bromide. In other instances the aralkyl chloride was used. [eb] HCl where shown indicates the hydrochloride of the compound immediately above. [ec] Res. = residue which was not distilled. [ed] Calcd.: Cl, 42.1. Found: Cl, 42.0. [ee] Calcd.: Cl, 42.1. Found: Cl, 42.1. [ef] A consideration of the utility of this method indicates that improved yields of the desired secondary amines are obtained as the steric hindrance in the amine (*i.e.*, isopropylamine) and aralkyl halide (*i.e.*, *o*-chloro groups on the benzene ring) is increased. The phenethyl group as compared to the benzyl group gives more secondary amine when used as the alkylating agent. The data do not reflect any significant improvement when an aralkyl bromide is used as compared to an aralkyl chloride. The results obtained have been tabulated as percentage yield of amines (% secondary amines/% tertiary amines) as a function of initial reactants and are shown in Table Va.

TABLE Va

% YIELDS OF *sec-/tert-*AMINE AS FUNCTION OF REACTANTS

Aralkyl halide	Amines used: Ethyl	Propyl	*i*-Propyl	Allyl
C$_6$H$_5$CH$_2$Br	24/68	47/45	66/27	33/60
2-ClC$_6$H$_4$CH$_2$Cl	40/43		71/21	59/27
4-ClC$_6$H$_4$CH$_2$Cl	35/50	47/49	73/15	50/37
2,4-diClC$_6$H$_3$CH$_2$Cl	55/21	71/14	74/16	65/18
3,4-diClC$_6$H$_3$CH$_2$Cl	49/35	65/23	85/7	63/24
4-BrC$_6$H$_4$CH$_2$Br	27/54		66/19	44/57
C$_6$H$_5$CH$_2$CH$_2$Br	43/38	63/21	79/15	58/24

Anal. Calcd. for $C_8H_{13}ClN_6$: C, 42.0; H, 5.7; N, 36.8. Found: C, 41.0; H, 5.6; N, 37.1.

The dipicrate melted at 210–214° dec.

Anal. Calcd. for $C_{20}H_{18}N_{12}O_{14}$: N, 25.8. Found: N, 25.5.

N[1]-(3-Picolyl)-biguanide Hydrochloride.—In a manner similar to the procedure above, there was prepared N[1]-(3-picolyl)-biguanide hydrochloride, m.p. 168–171° (ethanol-acetonitrile), in 20% yield.

Anal. Calcd. for $C_8H_{13}ClN_6$: C, 42.0; H, 5.7. Found: C, 42.2; H, 5.5.

The dipicrate melted at 177–180° (ethanol–hexane).

Anal. Calcd. for $C_{20}H_{18}N_{12}O_{14}$: C, 36.9; H, 2.8; N, 25.8. Found: C, 37.0; H, 3.2; N, 25.6.

N[1]-(2-[4-Pyridyl]-ethyl)-biguanide Sulfate.—Attempted fusions of the pyridylethylamines as their hydrochlorides with dicyandiamide did not prove to be a convenient procedure for the synthesis of the corresponding biguanides. For compounds of this type, the procedure of Slotta and Tschesche[4] was more serviceable.

A mixture of 12.2 g. (0.1 mole) of 2-(4-pyridyl)-ethylamine, 8.48 g. (0.1 mole) of dicyandiamide and 12.5 g. (0.05 mole) of copper sulfate pentahydrate in 75 ml. of water was heated at 100° for 10 hours. When cool, the brown-red precipitate (18.5 g.) which had formed was separated, suspended in 500 ml. of water and saturated with hydrogen sulfide. The formed cupric sulfide (8.8 g.) was separated and the filtrate evaporated to dryness. The residue obtained was boiled with 100 ml. of ethanol and the insoluble product, 2.35 g., separated. Upon recrystallization (methanol–acetonitrile), there was obtained 1.22 g. (5%), m.p. 221–222°, which the analysis indicated to be the dibasic sulfate monohydrate. The compound had an LD_{min} of 750 mg./kg. and showed 4+ hypoglycemia (s.c.).

Anal. Calcd. for $C_{18}H_{32}N_{12}O_6S$: C, 40.8; H, 6.0; N, 31.8. Found: C, 40.1; H, 5.0; N, 31.7.

The dipicrate melted at 199–200° (water).

Anal. Calcd. for $C_{21}H_{10}N_{12}O_{14}$: C, 38.0; H, 3.1. Found: C, 38.4; H, 2.8.

N[1]-(2-Cyclohexylethyl)-guanidine Nitrate.—The critical character of the fusion process is reflected in the isolation of guanidines, in some runs using virtually the same conditions which afforded the biguanides.

Equimolar portions (0.13 mole) of β-cyclohexylethylamine

TABLE VI

GUANIDINES $R_1R_2NC(=NH)NH_2\cdot HX$[fa]

R_1	HX	M.p.,[a,b] °C.	Analyses[c] Nitrogen, % Calcd.	Found
C_8H_{15}-[fb]	HNO$_3$	173–174[bd]	24.1	24.0
CH$_3$(CH$_2$)$_{11}$-	HNO$_3$	82–83[be]	19.3	18.8
CH$_3$(CH$_2$)$_{11}$-	HPic.[d]	141–143[be]	18.4	18.5
α-NpCH$_2$CH$_2$-[c]	HNO$_3$	172–173[ba]	20.3	20.6
i-C$_5$H$_{11}$-[fc]	HCl	111–114[be]	23.4	23.6

The footnotes have the same significance as those shown in Table I. [fa] R_2 = hydrogen unless otherwise shown. [fb] C_8H_{15} — = cyclohexylethyl. [fc] R_2 = methyl.

hydrochloride and dicyandiamide were fused as shown. After softening at 108° (bath, 148°), complete fusion occurred at 143° (bath, 150°). The bath temperature was raised gradually to 182° while heating was maintained for 1.25 hours. The cooled reaction product was dissolved in 225 ml. of water, carbon added and the reaction mixture filtered. Addition of 25.0 g. of sodium nitrate precipitated 25.2 g. of oily crystals which were separated and recrystallized from 250 ml. of water. There was obtained 11.6 g. (38%) of the guanidine, m.p. 164–167°; recrystallized (isopropyl alcohol), m.p. 173–174°.

The guanidines isolated in this study are shown in Table VI.

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

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH AND VARIAN ASSOCIATES]

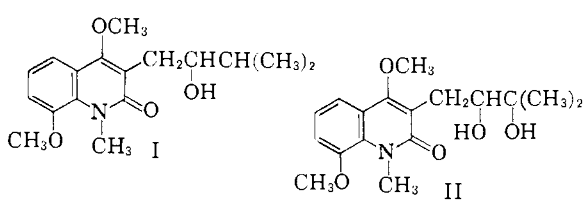
Alkaloids of *Lunasia amara* Blanco. Hydroxylunacridine

BY SIDNEY GOODWIN, J. N. SHOOLERY AND E. C. HORNING

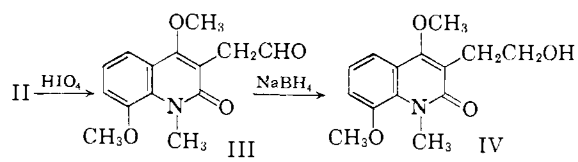
RECEIVED DECEMBER 1, 1958

Hydroxylunacridine has been shown to have the structure II.

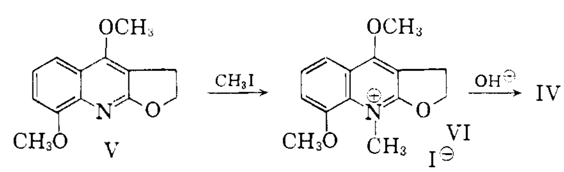
One of the leaf alkaloids of *Lunasia amara* Blanco[1] was found to have the empirical formula $C_{17}H_{23}O_5N$ and to contain two methoxyl groups, one N-methyl group and two active hydrogen atoms. The ultraviolet absorption spectrum was identical with that of lunacridine (I), indicating that the aromatic system was that of a 3-alkyl-4,8-dimethoxy-1-methyl-2-quinolone. The nuclear magnetic resonance spectrum confirmed this relationship; the signals of the aromatic hydrogen nuclei, and of the methoxyl and N-methyl hydrogen nuclei, were identical with those observed for lunacridine. In addition, the n.m.r. spectrum indicated that the side chain arrangement was $-CH_2CHOHCOH(CH_3)_2$. The compound was therefore given the name hydroxylunacridine and considered to be II.



Periodic acid oxidation of hydroxylunacridine yielded acetone, isolated and identified as the 2,4-dinitrophenylhydrazone, and a second carbonyl-containing cleavage product which was also isolated as a 2,4-dinitrophenylhydrazone. The analytical data for the latter compound corresponded to those for an aldehyde derivative of the expected structure III. When the periodic acid oxidation was followed by sodium borohydride reduction *in situ*, a crystalline compound, $C_{14}H_{17}O_4N$, m.p. 120–121.5°, was isolated and was presumed to be the alcohol IV.



This alcohol, a key compound in the structure determination of the alkaloid, may be prepared from γ-fagarine by a sequence of reactions suggested by *Lunasia* chemistry; specifically the dihydrofurano ring opening reaction analogous to the observed conversion of the methyl lunacrinium ion to lunacridine.[2] The requisite dihydro-γ-fagarine (V) may be obtained either by the Grundon–McCorkindale synthesis[5] or from the catalytic reduction of γ-fagarine. The natural material was used here to prepare V which in turn was converted to the methiodide VI. Treatment of the methiodide with dilute sodium hydroxide solution yielded the alcohol IV, m.p. 120–121°, which proved to be identical with the compound isolated



from the degradation of hydroxylunacridine. In addition to the usual comparison, IV from γ-fagarine was converted to the aldehyde 2,4-dinitrophenylhydrazone which was identical with the product obtained through the periodic acid oxidation of hydroxylunacridine.

Nuclear Magnetic Resonance Spectrum.[6]—Although the n.m.r. spectrum was used to predict the structure of the side chain of hydroxylunacridine, it

(1) The leaves and bark of *Lunasia* sp. contain a number of alkaloids not previously described or studied. A summary of the alkaloids isolated from *L. amara* leaves, including hydroxylunacridine, is in preparation. References to earlier work, and a review of current knowledge relating to the "water-soluble" quaternary *Lunasia* bases, the major alkaloid lunacrine, and the related compound lunacridine, are included in a summary by J. R. Price.[2] Structures have been proposed for lunacrine and lunacridine.[3,4]

(2) J. R. Price, "Recent Advances in Heterocyclic Chemistry," Academic Press, Inc., New York, N. Y., 1958, p. 92.

(3) S. Goodwin and E. C. Horning, THIS JOURNAL, **81**, 1908 (1959).

(4) S. Goodwin, J. N. Shoolery and L. F. Johnson, *ibid.*, **81**, 3065 (1959).

(5) M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, 2177 (1957).

(6) The resonance frequencies are given relative to benzene at 60 mc. and the solvent was deuterio-chloroform. The equipment and operating conditions were the same as those described for lunacrine and lunine.[4]