Guanidines with Antihypertensive Activity. II[1]

ROBERT P. MULL, RENAT H. MIZZONI, MARY R. DAPERO, AND MARY E. EGBERT

CIBA Pharmaceutical Company, a Division of CIBA Corporation, Summit, New Jersey

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A number of substituted piperazines, hexahydro-1,4-diazepines and octahydro-1,5-diazocines possessing the ethyl guanidine side chain were prepared and found to have cardiovascular properties.

The disclosure that certain amidoximes and guanidines, particularly when associated with large membered heterocyclic systems, possess antihypertensive properties,[2,3] has resulted in a study of other ring systems in the hope that they might give biologically active compounds.[4]

Early in the study it was found that [2-(4-methyl-1-piperazinyl)-ethyl]-guanidine sulfate also manifests interesting cardiovascular properties. This compound suppresses sympathetic nerve impulses, presumably at the efferent nerve terminals; it interferes with powerful vasoconstrictor reflexes to the limb while apparently reducing or eliminating their neurogenic tone. Since it has only mild hypotensive activity in normotensive animals and produces a minimum of early sympathetic-like actions following intravenous administration, it seemed a potential drug against those peripheral vascular diseases where sympathetic hyperactivity is suspected to play a part. As a result of these findings a representative array of related piperazines and higher homologs of piperazine was prepared for pharmacological testing.

In addition to the 4-methyl derivative, several other 4-alkyl and 4-phenyl piperazines proved to have cardiovascular properties. With

(1) For the preceding paper in this series, see R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).

(2) R. P. Mull, R. A. Maxwell, and A. J. Plummer, *Nature*, **180**, 1200 (1957).

(3) R. A. Maxwell, R. P. Mull, and A. J. Plummer, *Experientia*, **15**, 267 (1959).

(4) The compounds were most easily tested by administering 15 to 30 mg./kg. of the test substance to dogs. Active compounds produced the following effects which were graded for their intensity: (a) relaxation of the nictitating membranes, (b) bradycardia, (c) blockade of carotid occlusion reflex pressor responses and (d) suppression of the pressor response to intravenously administered amphetamine. For a more detailed description of the pharmacological test methods see R. A. Maxwell, S. D. Ross, and A. J. Plummer, *J. Pharmacol. Exptl. Therap.*, **123**, 128 (1958), and R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. Daniels, *ibid.*, **128**, 22 (1960).

the latter, introduction of methylene groups betwen the phenyl and piperazine ring caused a decrease of activity. Modifications at the 1-position of piperazine produced variations in activity similar to those noted with the hexahydro-1-azepine and octahydro-1-azocine compounds,[1,5] *i.e.*, optimal activity was associated with the ethyl guanidine side chain. Unlike the postulated factor controlling the activity of pempidine, *i.e.*, the shielding effect of the methyl groups around the basic nitrogen rather than ring size,[6] [2-(4-methyl-*cis*-2,5-dimethyl-1-piperazinyl)-ethyl]-guanidine sulfate was less active than the corresponding unsubstituted ring compound in which the 2 and 5 positions were not substituted. In this regard too it is interesting to note that quaternization of both hexahydro-1-azepinylpropionamidoxime and [2-(octahydro-1-azocinyl)-ethyl]-guanidine hydriodide resulted in a decrease of activity.[7]

To examine the influence of large ring systems, a few hexahydro-1,4-diazepines and octahydro-1,5-diazocines were prepared. Although cardiovascular activity was noted, their pharmacological properties were not greater than the corresponding piperazine compounds. This is in contrast to the remarkable increase in activity obtained with the previously described hexahydro-1-azepine and octahydro-1-azocine series.

Acknowledgment.—The authors wish to express their appreciation to Mr. Louis Dorfman and his associates for the microanalyses.

Experimental[8]

1-Substituted Piperazines.—These intermediates were obtained from commercial sources or prepared by known methods as demonstrated by the examples given for the hexahydro-1,4-diazepines.

Hexahydro-1-methyl-1,4-diazepine.—The formyl compound, which was obtained from commercially available hexahydro-1,4-diazepine according to the method of Horrom and co-workers,[9] was reduced with lithium aluminum hydride[10] to give the desired compound in 42% yield, b.p. 70–73° (32 mm.) [lit.[11] 74–75° (35 mm.)].

1-Benzyl-hexahydro-1,4-diazepine.—Prepared in 56% yield from equal molar

(5) R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.*, **80**, 3769 (1958).

(6) L. Bretherick, G. E. Lee, E. Lunt, and W. R. Wragg, *Nature*, **184**, 1707 (1959).

(7) Previously unpublished results from these laboratories. The methiodide of the former was recrystallized from ethanol, m.p. 115–117°. *Anal.* Calcd. for $C_{10}H_{22}IN_3O$: C, 36.73; H, 6.78; N, 12.85; I, 38.81. Found: C, 36.57; H, 6.80; N, 13.02; I, 38.59. The methiodide of the latter was recrystallized from ethanol, m.p. 167–170°. *Anal.* Calcd. for $C_{11}H_{26}I_2N_4$: C, 28.23; H, 5.60; N, 11.97; I, 54.20. Found: C, 28.46; H, 5.69; N, 12.27; I, 54.52.

(8) Boiling points and melting points are uncorrected.

(9) B. W. Horrom, M. Freifelder and G. B. Stone, *J. Am. Chem. Soc.*, **77**, 753 (1955).

(10) F. F. Blicke and C. J. Lu, *ibid.*, **74**, 3933 (1952).

(11) A. H. Sommers, R. J. Michaels, Jr., and A. W. Weston, *ibid.*, **76**, 5805 (1954).

TABLE I

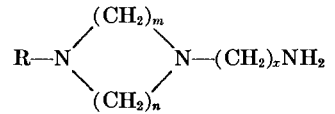
PHYSICAL PROPERTIES OF THE NITRILES $R{-}N\begin{matrix}-(CH_2)_m-\\-(CH_2)_n-\end{matrix}N{-}(CH_2)_xCN$

R	m	n	x	Yield %	M.p. or b.p. °C.	mm.	n^t_D	t	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3[a]	2	2	1	80	120–125[b]	12			$C_7H_{13}N_3$	60.48	60.52	9.43	9.50	30.23	30.34
CH_3	2	2	2	67	88–92[c]	0.7			$C_8H_{15}N_3$	62.80	62.62	9.88	9.78		
C_2H_5	2	2	1	73	117–118	13	1.4732	24	$C_8H_{15}N_3$	62.80	62.55	9.88	9.92		
$(C_2H_5)_2NCH_2CH_2$	2	2	1	69	115–116	0.5	1.4788	26	$C_{12}H_{24}N_4$	64.34	64.74	10.80	10.94	25.01	25.28
NCCH$_2$	2	2	1	90	165–166[d,e]				$C_8H_{12}N_4$	58.59	58.40	6.57	6.48	34.17	33.95
C_6H_5	2	2	1	95	65–66[f]				$C_{12}H_{15}N_3$	71.70	71.53	7.52	7.36	20.91	20.72
o-ClC_6H_4	2	2	1	70	109–111[d]				$C_{12}H_{14}ClN_3$[g]					17.85	17.70
p-ClC_6H_4	2	2	1	67	120–125[h]				$C_{12}H_{14}ClN_3$	61.20	61.24	6.00	5.94	17.85	17.84
o-$CH_3OC_6H_4$	2	2	1	66	68–70[f]				$C_{13}H_{17}N_3O$	67.50	67.88	7.41	7.78		
m-$CH_3OC_6H_4$	2	2	1	68	89–92[d]				$C_{13}H_{17}N_3O$	67.50	67.25	7.41	7.38		
o-$CH_3C_6H_4$	2	2	1	78	114–117[d]				$C_{13}H_{17}N_3$	72.62	72.31	7.97	7.90		
$C_6H_5CH_2$	2	2	1	73	152–155	0.2	1.5422	26	$C_{13}H_{17}N_3$	72.62	72.80	7.97	8.10	19.55	19.33
$C_6H_5CH_2CH_2$	2	2	1	70	170–172	13	1.5319	27	$C_{14}H_{19}N_3$	73.42	73.92	8.36	8.43	18.35	18.69
C_5H_4N[i]	2	2	1	77	120–122	0.5			$C_{11}H_{14}N_4$	65.40	65.81	6.99	6.71	27.74	27.69
C_5H_4N[i]	2	2	3	72	141–143	1			$C_{13}H_{18}N_4$	67.88	67.52	7.89	7.79	24.36	24.56
CH_3	2	3	1	40	68–72	0.2	1.4831	22	$C_8H_{15}N_3$	62.80	62.78	9.88	9.70	27.47	27.32
C_6H_5	2	3	1	88	156–158	1.2	1.5365	27	$C_{14}H_{19}N_3$	73.32	73.67	8.55	8.57	18.33	17.96
CH_3	3	3	1	49	83–85	0.4	1.4837	28	$C_9H_{17}N_3$	67.72	67.32	10.26	10.28	25.16	24.79
C_6H_5	3	3	1	57	147–149	0.25	1.5350	26	$C_{15}H_{21}N_3$	74.14	74.04	8.71	9.09	17.29	16.96

[a] The corresponding *cis*-2,5-dimethylpiperazine was obtained in 53% yield, b.p. 125–126° (13 mm.), $n^{27}D$ 1.4711. *Anal.* Calcd. for $C_9H_{17}N_3$: C, 64.72; H, 10.26; N, 25.16. Found: C, 64.58; H, 10.55; N, 24.77. [b] Solidified on cooling, m.p. 53–56°. [c] Rice, L. M. and Grogan, C. H., *J. Org. Chem.*, **20**, 1687 (1955), recorded b.p. 68–72° (0.3 mm.). [d] Recrystallized from ethanol. [e] Adelson, D. E. and Pollard, C. B., *J. Am. Chem. Soc.*, **57**, 1280 (1935), recorded m.p. 165°. [f] Recrystallized from hexane. [g] *Anal.* Calcd.: Cl, 15.04. Found: Cl, 14.91. [h] Recrystallized from heptane. [i] 2-Pyridyl.

TABLE II

PHYSICAL PROPERTIES OF THE AMINES

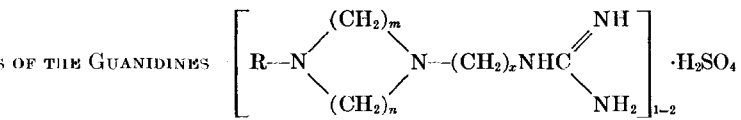


R	m	n	x	Yield %	B.p. °C.	B.p. mm.	n^tD	t	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3[a]	2	2	2	47	87–89	16	1.4779	26	$C_7H_{17}N_3$	58.79	58.50	11.98	11.86	29.39	29.68
CH_3	2	2	3	43	107–109[b]	14			$C_8H_{19}N_3$	61.20	61.18	12.20	12.00	26.77	26.68
C_2H_5	2	2	2	56	97–98	13	1.4777	26	$C_8H_{19}N_3$	61.20	61.07	12.20	11.96	26.77	26.54
$(C_2H_5)_2CH_2CH_2$	2	2	2	68	95–96	0.3	1.4814	26	$C_{12}H_{28}N_4$	63.21	63.12	12.38	12.26	24.58	24.19
$H_2NCH_2CH_2$	2	2	2	38	140–141	15	1.4997	26	$C_8H_{20}N_4$	55.86	55.39	11.72	11.35	32.58	32.50
C_6H_5	2	2	2	37	170–175	14			$C_{12}H_{19}N_3$	70.30	70.15	10.34	10.18	20.50	20.38
o-ClC_6H_5	2	2	2	77	130–134	0.1	1.5694	20	$C_{12}H_{18}ClN_3$	60.11	60.60	7.58	7.58		
p-ClC_6H_5	2	2	2	72	146–158[c]	0.3			$C_{12}H_{18}ClN_3$	60.11	60.89	7.58	7.21	17.51	17.18
o-$CH_3OC_6H_4$	2	2	2	78	133–136	0.05			$C_{13}H_{21}N_3O$	66.35	65.97	9.00	9.17		
m-$CH_3OC_6H_4$	2	2	2	71	152–157	0.05	1.5704	20	$C_{13}H_{21}N_3O$	66.35	66.31	9.00	8.90		
o-$CH_3C_6H_4$	2	2	2	86	104–107	0.05	1.5539	20	$C_{13}H_{21}N_3$					19.19	19.07
$C_6H_5CH_2$	2	2	2	80	180–187	13	1.5361	26	$C_{13}H_{21}N_3$	71.29	71.85	9.67	9.76	19.19	18.83
$C_6H_5CH_2CH_2$	2	2	2	62	157–158	14	1.5362	27	$C_{14}H_{23}N_3$	72.15	72.14	9.95	9.78	18.04	18.22
C_5H_4N[d]	2	2	2	32	112–115	0.05			$C_{11}H_{18}N_4$	64.13	64.15	8.81	8.65	27.20	27.41
C_5H_4N[d]	2	2	2	82	113–115	0.05			$C_{13}H_{22}N_4$	66.72	66.93	9.48	9.43	23.95	24.14
CH_3	2	3	2	76	104–105	13	1.4886	23	$C_8H_{19}N_3$	61.20	60.77	12.20	12.23	26.77	27.41
C_6H_5	2	3	2	67	125–126	0.3	1.5381	27	$C_{14}H_{23}N_3$	72.16	71.44	9.95	10.12	18.04	17.89
CH_3	3	3	2	56	112–117	13	1.4889	28	$C_9H_{21}N_3$	63.21	62.91	12.38	12.41	24.58	25.14
C_6H_5	3	3	2	61	134–137	0.3	1.5347	26	$C_{15}H_{25}N_3$	72.94	72.81	10.20	10.44	17.01	17.11

[a] The corresponding *cis*-2,5-dimethylpiperazine was obtained in 56% yield, b.p. 102–103° (13 mm.), n^{27}D 1.4741. *Anal.* Calcd. for $C_9H_{21}N_3$: C, 63.21; H, 12.38; N, 24.58. Found: C, 63.52; H, 12.42; N, 24.70. [b] Rice, L. M. and Grogan, C. H., *J. Org. Chem.*, **20**, 1687 (1955), recorded b.p. 52° (0.3 mm.). [c] Solidified on cooling, m.p. 97–101°. [d] 2-Pyridyl.

TABLE III

PHYSICAL PROPERTIES OF THE GUANIDINES



R	m	n	x	Yield %	M. p., °[a] dec.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	2	2	2	60	274–340	$C_7H_{19}N_5O_4S$[b,c]	31.25	31.39	7.06	6.92	26.04	26.12
CH_3[d]	2	2	2	51	182–185	$C_{16}H_{40}N_{10}O_4S$[e]	38.13	38.53	8.40	8.14	27.79	27.49
CH_3	2	2	3	80	99–100	$C_9H_{21}N_5O_4S$[b,e]	36.38	35.97	7.80	7.78	23.56	23.24
C_2H_5	2	2	2	90	201–203	$C_{16}H_{44}N_{10}O_4S$[f]	43.58	43.42	8.94	9.14	28.24	28.48
$HOCH_2CH_2$	2	2	0	66	260–290	$C_{14}H_{34}N_8O_5S$	35.10	35.37	8.00	8.04	23.40	23.78
$(C_2H_5)_2NCH_2CH_2$	2	2	2	89	208–212	$C_{26}H_{62}N_{12}O_4S$[f]	48.87	48.79	9.78	10.09	26.31	26.34
$H_2N—C(=NH)$	2	2	2	75	253–300	$C_6H_{21}N_7O_4S$[b,f]	30.84	30.65	6.80	6.71	31.48	30.99
$H_2NC(=NH)NHCH_2CH_2$	2	2	2	68	225–295	$C_{10}H_{24}N_8O_4S$[b]	26.57	26.39	6.24	6.85	24.79	25.02
C_6H_5	2	2	2	78	256–258	$C_{26}H_{44}N_{10}O_4S$[e]	52.66	51.45	7.48	7.29	23.64	23.96
o-ClC_6H_4	2	2	2	87	258–259	$C_{26}H_{42}Cl_2N_{10}O_4S$[g]					21.15	21.01
p-ClC_6H_4	2	2	2	70	250–265	$C_{26}H_{42}Cl_2N_{10}O_4S$	47.17	46.81	6.40	6.72	21.15	20.69
o-$CH_3OC_6H_4$	2	2	2	84	263–265	$C_{28}H_{46}N_{10}O_6S$[h]					20.48	20.16
m-$CH_3OC_6H_4$	2	2	2	84	249–251	$C_{28}H_{46}N_{10}O_6S$[i]					20.48	20.21
o-$CH_3C_6H_4$	2	2	2	79	264–267	$C_{28}H_{48}N_{10}O_4S$[j]					22.59	22.72
$C_6H_5CH_2$	2	2	2	81	185–190	$C_{28}H_{48}N_{10}O_4S$	54.24	53.84	7.80	8.08	22.59	22.29
$C_6H_5CH_2CH_2$	2	2	2	68	266–271	$C_{30}H_{52}N_{10}O_4S$	55.56	55.65	8.02	8.18	21.60	21.30
C_5H_4N[k]	2	2	2	65	272–274	$C_{24}H_{42}N_{12}O_4S$	48.53	48.47	7.13	6.87	28.28	28.61
C_5H_4N[k]	2	2	4	63	280–283	$C_{28}H_{50}N_{12}O_4S$	51.74	51.45	7.75	7.78	25.84	25.92
CH_3	2	3	2	75	142–145	$C_{18}H_{44}N_{10}O_4S$	43.98	44.02	8.94	9.27	28.24	28.39
C_6H_5	2	3	2	51	205–207	$C_{30}H_{52}N_{10}O_4S$[f]	55.60	55.28	8.09	8.27	21.62	21.60
CH_3	3	3	2	54	198–215	$C_{20}H_{48}N_{10}O_4S$[e]	45.84	45.62	9.23	9.17	26.73	26.56
C_6H_5	3	3	2	56	188–191	$C_{32}H_{56}N_{10}O_4S$	56.77	56.86	8.34	8.37	20.73	20.41

FOOTNOTES TO TABLE III

[a] The recrystallizations were from ethanol–water unless otherwise noted. [b] Obtained as Base·H_2SO_4, all others are (Base)$_2$·H_2SO_4. [c] Recrystallized from water. [d] The corresponding *cis*-2,5-dimethylpiperazine was obtained in 70% yield, recrystallized from ethanol–ether, m.p. 225–231°. *Anal.* Calcd. for $C_{20}H_{48}N_{10}O_4S$: C, 45.84; H, 9.23; N, 26.73. Found: C, 45.56; H, 9.04; N, 26.82. [e] Recrystallized from methanol–ether. [f] Recrystallized from ethanol–ether. [g] *Anal.* Calcd.: Cl, 10.74. Found: Cl, 10.41. [h] *Anal.* Calcd.: S, 4.91. Found: S, 4.96. [i] *Anal.* Calcd.: S, 4.91. Found: S, 5.19. [j] *Anal.* Calcd.: S, 5.17. Found: S, 4.83. [k] 2-Pyridyl.

quantities of hexahydro-1,4-diazepine and benzyl chloride in ethanol according to the procedure of Baltzly and co-workers,[12] b.p. 91–101° (0.2 mm.), $n^{26}D$ 1.5484.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.79; H, 9.47; N, 14.74. Found: C, 75.62; H, 9.16; N, 15.04.

Octahydro-1-methyl-1,5-diazocine.—Prepared in 46% yield from octahydro-1,5-diazocine[13] in the manner described for the corresponding hexahydro-1-methyl-1,4-diazepine, b.p. 72–75° (12 mm.), [lit.[14] 76–79° (18 mm.)].

1-Benzyl-octahydro-1,5-diazocine.—Prepared in 36% yield from octahydro-1,5-diazocine in the manner described for the corresponding 1-benzyl-hexahydro-1,4-diazepine, b.p. 97–100° (0.25 mm.), $n^{26}D$ 1.5394.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.53; H, 9.88; N, 13.78. Found: C, 76.09; H, 9.77; N, 13.58.

Preparation of the Nitriles of Table I.—The nitriles were prepared by refluxing equimolecular quantities of the 1-substituted piperazine and a halonitrile in benzene containing an excess of anhydrous sodium carbonate in suspension. Vigorous stirring and heating was continued for 6 hr. The reaction mixture was filtered hot, concentrated *in vacuo* and fractionated.

Preparation of the Amines of Table II.—In a typical example, 0.08 mole of the nitrile in 50 ml. of ether was added slowly to a cooled solution of 0.12 mole of lithium aluminum hydride in 200 ml. of ether. The solution was then refluxed for 3 hr. and stirred at room temperature overnight. The reaction mixture was cooled and decomposed by carefully adding water and 20% sodium hydroxide. After filtration and concentration of the ether solution, the residual oil was fractionated *in vacuo*.

Preparation of the Guanidines of Table III.—A mixture of 0.01 mole of 2-methyl-2-thiopseudourea sulfate and 0.02 mole of the amine in a minimum amount of water was refluxed for 4 hr. The solid which separated upon cooling or concentration was purified by recrystallization.

(12) R. Baltzly, J. S. Buck, E. Lorz, and W. Schön, *ibid.*, **66**, 263 (1944).
(13) E. L. Buhle, A. M. Moore and F. Y. Wiselogle, *ibid.*, **65**, 29 (1943).
(14) J. Hernandez-Mora, Dissertation, University of Michigan, Ann Arbor, 1959.