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# Cardiovascular Activity of Aromatic Guanidine Compounds

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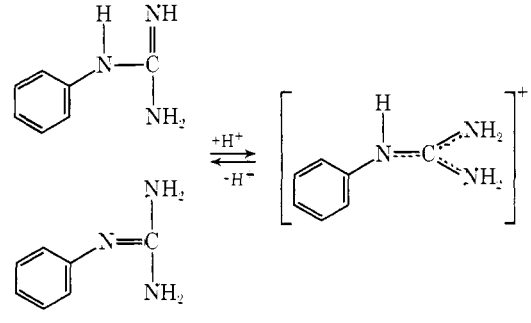
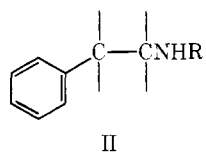
A series of aromatic guanidines and several 1-phenylbiguanides was prepared and tested for cardiovascular (CV) effects in anesthetized dogs measuring heart rate, blood pressure, carotid artery blood flow, and myocardial force changes. The predominant CV effect at minimally effective dose was vasoconstriction unassociated with cardiac stimulation. The structure–activity relationships of the compounds were discussed comparing their structural similarities to the β-phenylethylamines. The most potent members of the series were phenylguanidines substituted in the 3 and 4 positions on the aromatic nucleus with hydroxy or chloro groups. Preliminary mechanism studies indicated that the 3,4-dihydroxyphenylguanidines act at least partially by a direct α-adrenergic mechanism.

During a general screening program of organic compounds several phenylguanidine compounds were found to exhibit biological activity similar to the familiar adrenergic action of the β-phenylethylamine series. Examination of the two significant tautomeric structures and the protonated species of phenylguanidine I, which would be expected to exist at physiologic pH, reveals obvious structural similarity to the β-phenylethylamine series II.



I



II

Both structures I and II have aromatic groups and basic amino groups separated by similar distances. The bond distance between the central carbon and each nitrogen of the guanidine nucleus has been reported to be 1.32 Å[1] in contrast to 1.46 Å for an aliphatic carbon to carbon bond. The guanidine compounds would, however, be planar and thus more rigid than the aliphatic portion of the β-phenylethylamine series. Using these considerations as a rationale, a large series of aromatic guanidine and several 1-phenylbiguanide compounds were prepared. The pharmacological actions of these compounds were investigated to determine if they possessed potentially useful cardiovascular effects.

**Chemistry.** The guanidine and biguanide moieties of the compounds described in Tables I and II were prepared using five different methods. The method selected for each compound was dependent upon the location and number of substituents on the guanidine or biguanide nitrogens. For the preparation of the monosubstituted guanidine compounds and the 1,1-disubstituted compounds in Tables I and II, the well-known reaction of an aromatic amine mineral acid salt and hydrogen cyanamide in a refluxing solution of water or aqueous ethanol was used (method 1).[2]

The aromatic amines were obtained commercially or

**Table I**

Ar—NH—C(=NH)—NH$_2$

| No. | Ar | Recrystn solvent[a] | Salt | Mp, °C | Method | Yield, % | Formula | Analyses[b] | Dose, mg/kg iv | Blood pressure increase[c] | Change in carotid blood flow[d] | Change in heart rate[e] | Change in contractile force[f] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | A | $HNO_3$ | 125–127[g] | 1 | 40 | $C_7H_{10}N_4O_3$ | | 0.1 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.5 | 3 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | 1.0 | 3 (2) | − (2) | + (2) | + (2) |
| | | | | | | | | | 4.0 | 3 (1) | + (1) | + (1) | + (1) |
| 2 | 2-$ClC_6H_4$ | A | $HNO_3$ | 167–169[h] | 1 | 35 | $C_7H_9ClN_4O_3$ | C, H, N, Cl | 0.1 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 1.0 | 0 (1) | − (1) | + (1) | + (1) |
| 3 | 3-$ClC_6H_4$ | B | $HNO_3$ | 170–172 dec[i] | 1 | 45 | $C_7H_9ClN_4O_3$ | | 0.01 | 2 (2) | − (2) | − (2) | 0 (2) |
| | | | | | | | | | 0.1 | 2 (2) | − (2) | − (2) | − (2) |
| | | | | | | | | | 1.0 | 4 (2) | − (2) | − (2) | + (1) |
| | | | | | | | | | 2.0 | 3 (1) | − (1) | + (1) | + (1) |
| 4 | 4-$ClC_6H_4$ | B | $HNO_3$ | 170–172[j] | 1 | 48 | $C_7H_9ClN_4O_3$ | | 0.01 | 2 (2) | − (2) | 0 (2) | 0 (2) |
| | | | | | | | | | 0.1 | 3 (2) | − (2) | − (2) | + (2) |
| | | | | | | | | | 1.0 | 3 (1) | − (1) | − (1) | + (1) |
| 5 | 2,3-$Cl_2C_6H_3$ | B | $HNO_3$ | 169–172 dec | 1 | 55 | $C_7H_8Cl_2N_4O_3$ | C, H, N | 0.1 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 1.0 | 0 (1) | − (1) | + (1) | + (1) |
| 6 | 3,4-$Cl_2C_6H_3$ | A | HCl | 178–180[k] | 1 | 30 | $C_7H_8Cl_3N_3$ | C, H, N | 0.001 | 1 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | 0.01 | 2 (2) | − (2) | − (2) | + (2) |
| | | | | | | | | | 0.1 | 4 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | − (1) | + (1) |
| 7 | 2,6-$Cl_2C_6H_3$ | B | $HNO_3$ | 216 dec | 1 | 25 | $C_7H_8Cl_2N_4O_3$ | C, H, N | 0.1 | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 1.0 | 1 (2) | − (1) | − (2) | 0 (2) |
| | | | | | | | | | 5.0 | 3 (1) | | − (1) | |
| 8 | 3,5-$Cl_2C_6H_3$ | B | $HNO_3$ | 199–201 | 1 | 20 | $C_7H_8Cl_2N_4O_3$ | C, H, N | 0.1 | 2 (2) | − (2) | − (2) | − (2) |
| | | | | | | | | | 1.0 | 3 (2) | − (2) | − (2) | 0 (2) |
| 9 | 2-$CH_3$-4-$ClC_6H_3$ | A | HCl | 198–201 | 1 | 40 | $C_8H_{11}Cl_2N_3$ | C, H, N, Cl | 0.01 | 0 (2) | − (2) | 0 (1) | 0 (2) |
| | | | | | | | | | 0.05 | 1 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.1 | 2 (2) | − (2) | 0 (2) | 0 (2) |
| | | | | | | | | | 0.5 | 3 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | 2.0 | 4 (1) | − (1) | + (1) | + (1) |
| 10 | 2-$CH_3$-5-$ClC_6H_3$ | B | $HNO_3$ | 185–187 | 1 | 60 | $C_8H_{11}ClN_4O_3$ | C, H, N, Cl | 0.01 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.05 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.1 | 2 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.5 | 3 (1) | − (1) | − (1) | − (1) |
| 11 | 4-$CH_3$-3-$ClC_6H_3$ | B | $HNO_3$ | 193–195 | 1 | 55 | $C_8H_{11}ClN_4O_3$ | C, H, N, Cl | 0.01 | 2 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 0.1 | 4 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | + (1) | + (1) |
| 12 | 3-F-4-$CH_3C_6H_3$ | B | $HNO_3$ | 180–182 | 1 | 60 | $C_8H_{11}FN_4O_3$ | C, H, N, F | 0.01 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.1 | 3 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | 1.0 | 5 (1) | 0 (1) | − (1) | + (1) |
| 13 | 2,5-$(CH_3O)_2$-4-$ClC_6H_2$ | C | $HNO_3$ | 191 dec | 1 | 35 | $C_9H_{13}ClN_4O_5$ | C, H, N, Cl | 0.1 | 1 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 1 (1) | − (1) | 0 (1) | 0 (1) |
| 14 | 3-$CH_3OC_6H_4$ | A | Base | 151–153 | 1 | 78 | $C_8H_{11}N_3O$ | C, H, N | 0.1 | 1 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 2 (1) | − (1) | − (1) | + (1) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **15** | 3,4-$(CH_3O)_2C_6H_3$ | C | $HNO_3$ | 137–138 | 1 | 61 | $C_9H_{14}N_4O_5$ | C, H, N | 0.1 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.5 | 1 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | 1.0 | 3 (1) | 0 (1) | − (1) | + (1) |
| **16** | 3,4,5-$(CH_3O)_3C_6H_2$ | D | $HNO_3$ | 199–201 dec | 1 | 28 | $C_{10}H_{16}N_4O_6$ | C, H, N | 0.1 | 1 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 1.0 | 3 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 4.0 | 3 (1) | − (1) | − (1) | − (1) |
| **17** | 2-$CH_3C_6H_4$ | B | $HNO_3$ | 128–130[l] | 1 | 20 | $C_8H_{12}N_4O_3$ | | 1.0 | 2 (2) | − (2) | − (2) | 0 (1) |
| | | | | | | | | | 2.0 | 3 (1) | − (1) | − (1) | + (1) |
| **18** | 2,3-$(CH_3)_2C_6H_3$ | D | $HNO_3$ | 225 dec | 1 | 51 | $C_9H_{14}N_4O_3$ | C, H, N | 0.1 | 1 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 2 (2) | − (1) | + (2) | + (1) |
| | | | | | | | | | 2.0 | 3 (1) | − (1) | + (1) | + (1) |
| **19** | 3-$HOC_6H_4$ | E | HCl | 155–157 | 1 | 22 | $C_7H_{10}ClN_3O$ | C, H, N, Cl | 0.01 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.1 | 2 (2) | − (2) | − (2) | 0 (2) |
| | | | | | | | | | 1.0 | 5 (2) | 0 (2) | − (2) | + (2) |
| | | | | | | | | | 2.0 | 5 (1) | 0 (1) | + (1) | + (1) |
| **20** | 4-$HOC_6H_4$ | B | HCl | 198–200[m] | 1 | 34 | $C_7H_{10}ClN_3O$ | | 0.01 | 0 (2) | − (2) | 0 (2) | 0 (2) |
| | | | | | | | | | 0.1 | 2 (3) | − (3) | − (3) | + (2) |
| | | | | | | | | | 0.2 | 4 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | 1.0 | 5 (4) | − (1) | + (4) | + (1) |
| **21** | 3,4-$(HO)_2C_6H_3$ | F | HCl | 153–156 | 11 | 85 | $C_7H_{10}N_4O_5$ | C, H, N, Cl | 0.001 | 0 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 0.01 | 2 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 0.1 | 4 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | + (1) | + (1) |
| **22** | 3-Cl-4-$HOC_6H_3$ | B | HCl | 244–246 dec | 1 | 29 | $C_7H_9Cl_2N_3O$ | C, H, N | 0.001 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.01 | 2 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | 0.1 | 3 (1) | − (1) | 0 (1) | + (1) |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | + (1) | + (1) |
| **23** | 3-$CH_3$-4-$HOC_6H_3$ | C | $0.5H_2SO_4$ | 268–270 | 1 | 64 | $C_{16}H_{24}N_6O_6S$ | C, H, N, S | 0.01 | 0 (1) | − (1) | 0 (1) | |
| | | | | | | | | | 0.1 | 3 (1) | − (1) | + (1) | |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | + (1) | |
| **24** | 3-$HOCH_2$-4-$HOC_6H_3$ | A | HCl | 157–159 | 1 | 30 | $C_8H_{12}ClN_3O_2$ | C, H, N | 0.01 | 0 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 0.1 | 4 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 2.0 | 5 (1) | − (1) | − (1) | + (1) |
| **25** | 3-$CH_3SO_2NH$-4-$HOC_6H_3$ | C | HCl | 267–270 dec | 1 | 51 | $C_8H_{13}ClN_4O_3S$ | C, H, N, Cl, S | 0.01 | 2 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 0.1 | 4 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | − (1) | − (1) |
| **26** | 3,5-$(Br)_2$-4-$HOC_6H_2$ | B | HCl | 285 dec | 1 | 65 | $C_7H_8Br_2ClN_3O$ | C, H, N, Br, Cl | 0.1 | 2 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | 1.0 | 4 (1) | − (1) | − (1) | − (1) |
| **27** | 3-$CH_3SO_2NHC_6H_4$ | C | Base | 241–243 dec | 1 | 61 | $C_8H_{12}N_4O_2S$ | C, H, N, S | 1.0 | 1 (1) | + (1) | − (1) | 0 (1) |
| | | | | | | | | | 2.0 | 2 (1) | 0 (1) | − (1) | − (1) |
| | | | | | | | | | 4.0 | 2 (1) | 0 (1) | − (1) | − (1) |
| **28** | 4-$CH_3SO_2NHC_6H_4$ | G | HCl | 249–251 | 1 | 63 | $C_8H_{13}ClN_4O_2S$ | C, H, N, Cl | 1.0 | 0 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 2.0 | 1 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 8.0 | 1 (1) | − (1) | − (1) | − (1) |
| **29** | 3-$CH_3COC_6H_4$ | A | HCl | 152–154 | 1 | 20 | $C_9H_{12}ClN_3O$ | C, H, N, Cl | 0.5 | 2 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | 1.0 | 3 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | 2.0 | 4 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | 4.0 | 5 (1) | 0 (1) | − (1) | + (1) |

**Table I** (*Continued*)

| No. | Ar—NH—C(=NH)—NH$_2$ Ar | Recrystn solvent[a] | Salt | Mp, °C | Method | Yield, % | Formula | Analyses[b] | Dose, mg/kg iv | Change in Blood pressure increase[c] | Change in carotid blood flow[d] | Change in heart rate[e] | Change in contractile force[f] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 4-$CH_3COC_6H_4$ | A | HCl | 212–214[n] | 1 | 25 | $C_9H_{12}ClN_3O$ | | 0.1 | 1 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 1.0 | 3 (1) | − (1) | − (1) | |
| | | | | | | | | | 4.0 | 3 (1) | − (1) | − (1) | + (1) |
| 31 | 3,4-$(C_6H_5CH_2O)_2C_6H_3$ | H | Base | 138–139 | 1 | 64 | $C_{21}H_{21}N_3O_2$ | C, H, N | 0.5 | 1 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 1 (1) | 0 (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 2.0 | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| 32 | 1-Naphthyl | B | $HNO_3$ | 197–199 | 1 | 30 | $C_{11}H_{12}N_4O_3$ | | 0.01 | 0 (1) | − (1) | 0 | 0 |
| | | | | | | | | | 0.1 | 3 (3) | − (3) | − (3) | − (2) |
| | | | | | | | | | 0.5 | 4 (1) | 0 (1) | − (1) | |
| 33 | 1-(5,6,7,8-Tetrahydro)naphthyl | | | | | | | | 2.0 | 3 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | 5.0 | 3 (1) | + (1) | + (1) | + (1) |
| | | A | HCl | 214–217 | 1 | 32 | $C_{11}H_{16}ClN_3$ | C, H, N | 0.01 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.1 | 2 (2) | − (2) | − (2) | − (2) |
| | | | | | | | | | 1.0 | 3 (1) | − (1) | − (1) | − (1) |
| 34 | 2-Pyrimidyl | D | HCl | 280–282 | 1 | 15 | $C_5H_8ClN_5$ | C, H, N | 0.1 | 0 (1) | 0 (1) | + (1) | − (1) |
| | | | | | | | | | 1.0 | 1 (2) | 0 (2) | 0 (2) | 0 (2) |
| | | | | | | | | | 8.0 | 1 (1) | − (1) | − (1) | 0 (1) |
| 35 | 2-Benzimidazolyl | | Base | 242–244 | *p* | | $C_8H_9N_5$ | | 1.0 | 0 (2) | − (2) | 0 (2) | 0 (1) |
| | | | | | | | | | 2.0 | 0 (2) | − (2) | 0 (1) | + (1) |
| | | | | | | | | | 4.0 | 2 (2) | − (1) | 0 (2) | + (1) |
| | | | | | | | | | 8.0 | 3 (1) | − (2) | − (1) | + (1) |
| 36 | 5-Quinolyl | B | HCl | 292–294 | 1 | 55 | $C_{10}H_{11}N_4Cl$ | C, H, N, Cl | 0.1 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | 0.5 | 0 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | 1.0 | 1 (1) | − (1) | − (1) | − (1) |
| 37 | 5-(8-Hydroxy)quinolyl | D[o] | HCl | 310–312 | 1 | 28 | $C_{10}H_{11}ClN_4O$ | C, H, N, Cl | 0.01 | 1 (1) | − (1) | -- (1) | − (1) |
| | | | | | | | | | 0.1 | 4 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | 1.0 | 5 (1) | − (1) | − (1) | − (1) |
| 38 | 2-(4-Methyl)quinazolyl | | HCl | 330 dec[q] | *p* | | $C_{10}H_{12}ClN_5$ | | 1.0 | 3 (1) | 0 (1) | − (1) | − (1) |
| | | | | | | | | | 2.5 | 2 (1) | 0 (1) | − (1) | − (1) |
| 39 | 3-(1-Methylbenzo[*f*]quinzolyl) | | HCl | 312–313 dec[r] | *p* | | $C_{14}H_{14}ClN_5$ | | 1.0 | 0 (2) | − (2) | − (1) | 0 (1) |
| | | | | | | | | | 2.0 | 1 (2) | − (2) | 0 (2) | 0 (1) |
| | | | | | | | | | 4.0 | 0 (2) | − (2) | 0 (2) | 0 (1) |

[a] A, *i*-PrOH; B, EtOH; C, $H_2O$; D, MeOH; E, *n*-PrOH; F, *i*-PrOH–cyclohexane; G, EtOH–MeOH; H, benzene. [b] Analytical results were within ±0.4% of the theoretical values. [c] Blood pressure increases rated as follows: 0 (0–3 mmHg); 1 (4–10 mmHg); 2 (11–25 mmHg); 3 (26–50 mmHg); 4 (51–75 mmHg); 5 (>75 mmHg). The integer in parentheses is the number of determinations made. [d] Change in carotid blood flow at the time of maximal pressor effect: −, decrease in flow; 0, no change; +, increase in flow. The integer in parentheses is the number of determinations made. [e] Change in heart rate at the time of maximal pressor effect: −, decrease in heart rate; 0, no change; +, increase in heart rate. The integer in parentheses is the number of determinations made. [f] Change in contractile force of the heart at the time of maximal pressor effect: −, decrease in contractile force; 0, no change; +, increase in contractile force. The integer in parentheses is the number of the determinations made. [g] A. Kampf, *Ber.*, 37, 1684 (1904), mp 128°. [h] G. S. Dawes and J. C. Mott, *Br. J. Pharmacol.*, 5, 65–76 (1950), no melting point reported. [i] H. King and I. Tonkin, *J. Chem. Soc.*, 1063 (1946), mp 171–172°. [j] Meister, Lucius und Bruning, Hoechst A. M., German Patent 172,979 (Nov 7, 1906), mp 166°. [k] A. F. Crowther and F. H. S. Hurd, I.C.I. Ltd., British Patent 667,116 (Feb 27, 1952); *Chem. Abstr.*, 47, 5435e (1953), mp 170–171°. [l] Footnote *i*, mp 131–132°. [m] H. Schotte, Shering-Kahlbaum, A.G., German Patent 565,881 (Jan 13, 1925); *Chem. Abstr.*, 27, 2456 (1933), mp 197–198°. [n] Footnote *i*, mp 211°. [o] R. Klingner, *Z. Physiol. Chem.*, 155, 237 (1926), mp 196–197°. [p] Aldrich Chemical Co. [q] L. F. Theiling and R. L. McKee, *J. Am. Chem. Soc.*, 74, 1835 (1952), mp 319–320° dec. [r] A. Rosowsky et al., *J. Org. Chem.*, 29, 2881–2887 (1964), mp 313–314° dec.

were synthesized from available starting materials. The intermediates obtained by synthesis are listed in Table III. The primary aromatic amines in this table were prepared by catalytic hydrogenation of the corresponding substituted nitrobenzene using either 10% palladium on carbon (method 2) or platinum dioxide (method 3) as catalyst. Compound **72** was prepared by the reaction of **71** with trimethyl orthoformate followed by dilute hydrochloric acid hydrolysis using the method of Roberts and Vogt.[3]

The 1,3-di- and the 1,1,3-trisubstituted guanidines **47, 48, 51-53** were prepared by the reaction of the appropriate 1-aryl-2-methyl-2-thiopseudourea hydriodide with primary aliphatic amines in refluxing ethanol solution (method 4).[4]

The intermediate 1-aryl-2-methyl-2-thiopseudourea hydriodides **74, 77, 79,** and **81** were obtained by the reaction of methyl iodide with the arylthioureas **73, 76, 78,** and **80** in refluxing ethanol solution (method 5).[4,5] These intermediates are listed in Table III. The thioureas were prepared from aromatic amine hydrochloride salts and potassium thiocyanate (method 6)[6] or in two steps from the aromatic amine and benzoylisothiocyanate (method 7).[7]

The 1,2,3-trisubstituted guanidines **54** and **55** were prepared by the reaction of diisopropylcarbodiimide with the appropriate aromatic amine hydrochloride in alcohol solution (method 8).

2-Anilino-2-imidazolines were prepared by two methods. These compounds contain a guanidine moiety with two of the nitrogens connected by an ethylene bridge. Compounds **60** and **61** were obtained by heating the thioureas **84** and **85** with an excess of ethylenediamine (method 9).[8] Compound **62** was obtained by heating the *S*-methylthiopseudourea hydriodide **83** with an excess of ethylenediamine at 65°.[8]

The aromatic biguanides **64** and **65** were prepared by the reaction of the aromatic amine hydrochlorides with dicyandiamide in refluxing isopropyl alcohol solution (method 10).[5]

The 3,4-dihydroxyphenylguanidine hydrochlorides and the 1-(3,4-dihydroxyphenyl) biguanide nitrate were prepared by hydrogenolytic cleavage in the presence of 5% palladium-on-carbon catalyst of the corresponding 3,4-dibenzyloxyphenylguanidine and biguanide hydrochlorides (method 11). Direct synthesis of the 3,4-dihydroxyphenylguanidines from 3,4-dihydroxyaniline was not possible because of the instability of the dihydroxyaniline intermediates. The dihydroxyphenylguanidine and biguanide hydrochloride and nitrate salts were stable and could be easily isolated and purified. The free bases of these compounds, however, were very unstable and formed dark oxidation products when exposed to air.

**Pharmacology.** The cardiovascular effects of the aromatic guanidines and biguanides were determined in mongrel dogs of either sex anesthetized with pentobarbital sodium (30 mg/kg iv); anesthesia was maintained at a constant level by continuous infusion of 0.1 mg/kg/min of pentobarbital sodium. The following parameters were measured: respiration, lead II electrocardiogram, heart rate, myocardial contractile force (Walton-Brodie strain gage), central aortic systolic/diastolic and mean blood pressure, and carotid artery blood flow.

Graded doses (usually 0.001, 0.01, 0.1, and 1.0 mg/kg) of the test compounds in 0.9% saline solution were administered intravenously; the lowest dose was administered first followed by the next highest dose when the response to the first dose had subsided. The changes in blood pressure, carotid blood flow, heart rate, and contractile force for each compound are reported in Tables I and II. The changes in blood pressure for standard drugs in the test system are reported in Table IV.

The cardiovascular changes were analyzed to determine the predominant cardiovascular effect(s) caused by a compound at a given dose level. With certain guanidines the predominant cardiovascular effect(s) were dissimilar at different dose levels. Moreover, dose-response effects for a given compound were not always apparent for all dose levels.

The changes in systemic blood pressure, carotid blood flow, heart rate, and myocardial contractile force were analyzed to determine if the predominant cardiovascular effect was vasodilation or vasoconstriction with or without concurrent cardiac stimulation. Systemic blood pressure is the resultant of total peripheral resistance (determined primarily by the degree of vasoconstriction and vasodilation) and cardiac output (heart rate times stroke volume). Although cardiac output was not measured directly, similar directional changes in heart rate and myocardial contractile force were considered to be indicative of a corresponding change in cardiac output.

Pure vasoconstrictor effects were directly indicated at threshold doses by decreases in carotid artery blood flow. At higher doses pure vasoconstrictor compounds may continue to cause decreased carotid blood flow, even in the face of increased mean arterial blood pressure. Since blood flow through a vascular bed is dependent both on the mean arterial blood pressure and the caliber of blood vessels in the bed, no change in blood flow in the presence of increased mean arterial blood pressure is direct evidence of vasoconstriction. Slight increases in blood flow through a vascular bed may occur with a pure vasoconstrictor when the systemic blood pressure rise overrides local constrictor effects. In this regard, the potent vasoconstrictive effect of many of the aromatic guanidines on the vascular bed supplied by the carotid artery was emphasized by the fact that in only a few cases did carotid artery blood flow increase or not change concurrently with increased mean arterial blood pressure.

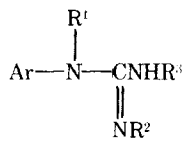
At higher dose levels many of the aromatic guanidines evoking pure vasoconstriction at lower doses caused increases in mean arterial blood pressure associated with signs of increased cardiac output, i.e., tachycardia and increased myocardial contractile force. Since blood flow was often simultaneously decreased, it is apparent that the increases in blood pressure in these cases were due both to generalized vasoconstriction and increased cardiac output. With some of the aromatic guanidines, no signs of increased cardiac output occurred over the entire dose range tested; in these cases the pressor effects were due entirely to vasoconstriction.

Minimally effective doses of certain aromatic guanidines (di- and trisubstituted) often caused both vasoconstriction and cardiac stimulation, the pressor effects at these dose levels being the result, therefore, of both generalized vasoconstriction and increased cardiac output. With other di- and trisubstituted compounds cardiovascular stimulatory effects were absent, sometimes being replaced by evidence of cardiovascular depressant (vasodilation, cardiac depression) actions. Vasodilation was indicated by increased blood flow in the face of a decrease or no change in blood pressure. Cardiac depression was indicated by decreased heart rate and/or myocardial contractile force.

**Effects of Standard Adrenergic Vasoconstrictor Drugs.** Table IV presents mean increases in mean arterial blood pressure in the anesthetized dog following the intravenous administration in 0.9% saline solution of various doses of standard adrenergic vasoconstrictor drugs (isoproterenol causes only decreases in mean arterial blood pressure in this preparation). The number of tests is shown in parentheses in the table.

Epinephrine and norepinephrine caused cardiac stimula-

**Table II**

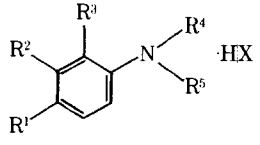


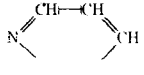
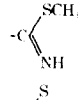
| No. | Ar | $R^1$ | $R^2$ | $R^3$ | Recrystn solvent[a] | Salt | Mp, °C | Method | Yield, % | Formula | Analyses[b] | Dose, mg/kg iv | Blood pressure increase[c] | Change in carotid blood flow[d] | Change in heart rate[e] | Change in contractile force[f] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **40** | $C_6H_5$ | $CH_3$ | H | H | A | HCl | 219–220[g] | 1 | 60 | $C_8H_{12}ClN_3$ | | 0.1 | 1 (2) | − (2) | + (2) | + (2) |
| | | | | | | | | | | | | 1.0 | 2 (1) | − (1) | 0 (1) | + (1) |
| | | | | | | | | | | | | 8.0 | 4 (1) | − (1) | 0 (1) | + (1) |
| **41** | $C_6H_5$ | $C_2H_5$ | H | H | B | HCl | 182–184[h] | 1 | 40 | $C_9H_{14}ClN_3$ | | 1.0 | 2 (2) | − (2) | 0 (2) | + (1) |
| | | | | | | | | | | | | 4.0 | 2 (2) | − (2) | − (2) | + (1) |
| | | | | | | | | | | | | 8.0 | 2 (2) | 0 (2) | + (2) | + (1) |
| **42** | $C_6H_5$ | $(CH_3)_2CH$ | H | H | C | HCl | 215–216 | 1 | 35 | $C_{10}H_{16}ClN_3$ | C, H, N | 2.0 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 8.0 | 0 (1) | − (1) | − (1) | − (1) |
| **43** | $C_6H_5$ | $CH_2 + CHCH_2$ | H | H | A | $HNO_3$ | 141–143 | 1 | 45 | $C_{10}H_{14}N_4O_3$ | C, H, N | 1.0 | 0 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | | | | 8.0 | 0 (1) | − (1) | − (1) | − (1) |
| **44** | 4-$HOC_6H_4$ | $CH_3$ | H | H | D | HCl | 232–234 | 1 | 56 | $C_8H_{12}ClN_3O$ | C, H, N | 0.1 | 1 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | | | | 1.0 | 4 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | | | | 2.0 | 4 (1) | − (1) | − (1) | + (1) |
| **45** | 3,4-$(HO)_2C_6H_3$ | $CH_3$ | H | H | A | HCl | 215–218 | 11 | 80 | $C_8H_{12}ClN_3O_2$ | C, H, N, Cl | 0.001 | 1 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 0.01 | 1 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 0.1 | 3 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | | | | 1.0 | 5 (1) | − (1) | + (1) | + (1) |
| **46** | 3,4-$(C_6H_5CH_2O)_2$-$C_6H_3$ | $CH_3$ | H | H | A | HCl | 207–209 | 1 | 44 | $C_{22}H_{24}ClN_3O_2$ | C, H, N, Cl | 0.1 | 1 (1) | 0 (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 1.0 | 0 (1) | + (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 4.0 | 1 (1) | − (1) | − (1) | − (1) |
| **47** | 3,4-$(Cl)_2C_6H_3$ | H | H | $(CH_3)_2CH$ | C | Base | 102–104 | 4 | 65 | $C_{10}H_{13}N_3Cl_2$ | C, H, N, Cl | 1.0 | 2 (1) | 0 (1) | + (1) | + (1) |
| | | | | | | | | | | | | 5.0 | 3 (1) | − (1) | 0 (1) | + (1) |
| **48** | 4-$HOC_6H_4$ | H | H | $(CH_3)_2CH$ | E | HI | 166–168 | 4 | 31 | $C_{10}H_{16}IN_3O$ | C, H, N, I | 5.0 | 0 (1) | + (1) | − (1) | − (1) |
| | | | | | | | | | | | | 9.0 | 1 (1) | − (1) | − (1) | − (1) |
| **49** | 3,4-$(HO)_2C_6H_3$ | H | H | $CH_3$ | F | HCl | 185–188 | 11 | 74 | $C_8H_{12}ClN_3O_2$ | C, H, N, Cl | 0.1 | 3 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | | | | 0.3 | 5 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | | | | 1.0 | 5 (1) | − (1) | + (1) | + (1) |
| **50** | 3,4-$(HO)_2C_6H_3$ | H | H | $(CH_3)_2CH$ | F | HCl | 221–223 | 11 | 73 | $C_{10}H_{16}ClN_3O$ | C, H, N, Cl | 0.01 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 0.04 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 0.1 | 1 (2) | + (2) | 0 (2) | 0 (2) |
| | | | | | | | | | | | | 2.0 | 0 (1) | + (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 4.0 | 2 (1) | + (1) | − (1) | 0 (1) |
| **51** | 3,4-$(C_6H_5CH_2O)_2$-$C_6H_3$ | H | H | $CH_3$ | E | HCl | 157–159 | 4 | 65 | $C_{22}H_{24}ClN_3O_2$ | C, H, N, Cl | 0.1 | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 1.0 | 1 (1) | + (1) | 0 (1) | 0 (1) |
| **52** | 3,4-$(C_6H_5CH_2O)_2$-$C_6H_3$ | H | H | $(CH_3)_2CH$ | G | Base | 128–131 | 4 | 70 | $C_{24}H_{27}N_3O_2$ | C, H, N | 0.1 | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 1.0 | 2 (1) | − (1) | − (1) | 0 (1) |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | $C_6H_5$ | $CH_3$ | H | $CH_3$ | E | HI | 148–150 | 4 | 52 | $C_9H_{14}IN_3$ | C, H, N, I | 1.0 | 2 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | | | | 2.0 | 1 (1) | + (1) | + (1) | + (1) |
| | | | | | | | | | | | | 8.0 | 2 (1) | + (1) | + (1) | + (1) |
| 54 | 3,4-$(C_6H_5CH_2O)_2$-$C_6H_3$ | H | $(CH_3)_2OH$ | $(CH_3)_2CH$ | J | Base | 72–74 | 8 | 70 | $C_{27}H_{33}N_3O_2$ | C, H, N | | | | | |
| 55 | 3,4-$(HO)_2C_6H_3$ | H | $(CH_3)_2CH$ | $(CH_3)_2CH$ | F | HCl | 191–194 | 11 | 68 | $C_{13}H_{22}ClN_3O_2$ | C, H, N, Cl | 1.0 | *i* (1) | + (1) | + (1) | + (1) |
| | | | | | | | | | | | | 2.0 | *i* (1) | + (1) | + (1) | + (1) |
| 56 | | $C_6H_4$-$CH_2CH_2$ | H | H | H | HCl | 276–278 | 1 | 61 | $C_9H_{12}ClN_3$ | C, H, N, Cl | 0.5 | 0 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | | | | 1.0 | 1 (1) | 0 (1) | + (1) | + (1) |
| | | | | | | | | | | | | 2.0 | *i* (1) | − (1) | 0 (1) | + (1) |
| | | | | | | | | | | | | 8.0 | 0 (1) | + (1) | + (1) | + (1) |
| 57 | | $C_6H_4$-$CH_2$-$CH_2CH_2$ | H | H | H | HCl | 152–156 | 1 | 40 | $C_{10}H_{14}ClN_3$ | C, H, N | 1.0 | 3 (1) | − (1) | 0 (1) | + (1) |
| | | | | | | | | | | | | 2.0 | 4 (1) | − (1) | + (1) | + (1) |
| | | | | | | | | | | | | 4.0 | 4 (1) | + (1) | + (1) | + (1) |
| 58 | | $C_6H_4$-$CH_2CH$-$(CH_3)$ | H | H | H | HCl | 200–204 | 1 | 38 | $C_{10}H_{14}ClN_3$ | C, H, N | 1.0 | 0 (1) | − (1) | 0 (1) | + (1) |
| | | | | | | | | | | | | 2.0 | 1 (1) | − (1) | 0 (1) | + (1) |
| | | | | | | | | | | | | 4.0 | 2 (1) | 0 (1) | − (1) | + (1) |
| | | | | | | | | | | | | 8.0 | 2 (1) | + (1) | − (1) | + (1) |
| 59 | | 4-$CH_3C_6H_3$-$CH_2CH(CH_3)$ | H | H | A | HCl | 229–231 dec | 1 | 53 | $C_{11}H_{16}ClN_3$ | C, H, N, Cl | 0.1 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 0.5 | 1 (1) | + (1) | 0 (1) | |
| | | | | | | | | | | | | 2.0 | 2 (2) | 0 (2) | 0 (2) | + (2) |
| | | | | | | | | | | | | 4.0 | 3 (2) | + (2) | + (2) | + (2) |
| 60 | 3-$ClC_6H_4$ | H | | $CH_2CH_2$ | I | Base | 107–109[j] | 9 | 17 | $C_9H_{10}ClN_3$ | C, H, N, Cl | 0.01 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 0.1 | 1 (1) | − (1) | 0 (1) | 0 (1) |
| 61 | 2-Cl-4-$CH_3C_6H_3$ | H | | $CH_2CH_2$ | I | Base | 154–156[k] | 9 | 49 | $C_{10}H_{11}ClN_3$ | | 0.01 | *d* (2) | − (1) | − (2) | − (1) |
| | | | | | | | | | | | | 0.1 | *d* (2) | − (1) | − (2) | − (1) |
| | | | | | | | | | | | | 1.0 | 3 (1) | − (1) | − (1) | − (1) |
| 62 | | $C_6H_4$-$CH_2CH_2$ | | $CH_2CH_2$ | D | HI | 321–324 | | 42 | $C_{11}H_{14}IN_3$ | C, H, N, I | 0.01 | 0 (2) | − (1) | 0 (2) | 0 (1) |
| | | | | | | | | | | | | 0.1 | 0 (3) | − (2) | + (2) | 0 (2) |
| | | | | | | | | | | | | 1.0 | 0 (3) | − (2) | 0 (3) | + (3) |
| | | | | | | | | | | | | 4.0 | 0[d] (2) | − (1) | − (1) | + (2) |
| 63 | 3,4-$(HO)_2C_6H_3$ | H | H | $NH_2C$-(=NH) | A | $HNO_3$ | 172–175 | 11 | 70 | $C_8H_{12}N_6O_5$ | C, H, N | 0.001 | 0 (1) | − (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 0.01 | 1 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | | | | 0.1 | 4 (1) | − (1) | − (1) | + (1) |
| | | | | | | | | | | | | 1.0 | 5 (1) | − (1) | + (1) | + (1) |
| 64 | 3,4-$(C_6H_5CH_2O)_2$-$C_6H_3$ | H | H | $NH_2C$-(=NH) | C | HCl | 195–197 | 10 | 50 | $C_{22}H_{24}Cl$-$N_5O_2$ | C, H, N, Cl | 0.01 | 0 (1) | + (1) | − (1) | 0 (1) |
| | | | | | | | | | | | | 0.1 | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| | | | | | | | | | | | | 1.0 | 1 (1) | − (1) | − (1) | − (1) |
| | | | | | | | | | | | | 2.0 | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| 65 | $C_6H_5$ | H | H | $NH_2C$-(=NH) | D | HCl | 244–247[l] | 10 | 60 | $C_8H_{11}N_5$ | | 0.1 | 3 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | | | | 1.0 | 4 (1) | − (1) | − (1) | 0 (1) |
| | | | | | | | | | | | | 2.0 | 3 (1) | − (1) | − (1) | + (1) |

[a] A, *i*-PrOH; B, *n*-PrOH; C, EtOH; D, $H_2O$; E, acetone-$(Et)_2O$; F, *i*-PrOH–cyclohexane; G, benzene; H, MeOH-$H_2O$; J, hexane. [b] Analytical results were within ±0.4% of the theoretical values. [c] See footnote *c*, Table I. [d] See footnote *d*, Table I. [e] See footnote *e*, Table I. [f] See footnote *f*, Table I. [g] C. E. Brawn, *J. Am. Chem. Soc.*, 55, 1280-1284 (1933), mp 218-219°. [h] M. Bianchi and F. Barzaghi, *Boll. Chim. Farm.*, 103, 490–498 (1964); *Chem. Abstr.*, 61, 15996*f* (1964), mp 185°. [i] Decrease in blood pressure. [j] H. Hageman and J. A. Riddel, U.S. Rubber, German Patent 1,142,723 (Jan 24, 1963), no melting point reported. [k] Reference 8, mp 150-151°. [l] J. Cohn, *J. Prakt. Chem.*, 84 (2), 396 (1900), mp 237°.

Table III. Intermediates




| No. | X | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Mp, °C | Formula | Solvent[a] | Method | Analyses[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **66** | Cl | $CH_3SO_2NH$ | H | H | H | H | 223–225[c] | $C_7H_{11}ClN_2O_2S$ | A | 2 | |
| **67** | Cl | H | $CH_3SO_2NH$ | H | H | H | 235–238 dec | $C_7H_{11}ClN_2O_2S$ | B | 2 | |
| **68** | Cl | $CH_3SO_2NH$ | HO | H | H | H | 229–234 dec | $C_7H_{11}ClN_2O_3S$ | C | 3 | C, H, N, Cl |
| **69** | Cl | Cl | HO | H | H | H | 170–200 dec | $C_6H_5ClNO$ | A | 3 | |
| **70** | *d* | $HOCH_2$ | HO | H | H | H | 140–143[e] | $C_7H_9NO_2$ | D | 3 | |
| **71** | Cl | $C_5H_6CH_2O$ | $C_6H_5CH_2O$ | H | H | H | 202–203 dec[f] | $C_{20}H_{20}ClNO_2$ | C | 3 | |
| **72** | Cl | $C_6H_5CH_2O$ | $C_6H_5CH_2O$ | H | $CH_3$ | H | 167–170 | $C_{21}H_{22}ClNO_2$ | B | | |
| **73** | *d* | $C_6H_5CH_2O$ | $C_6H_5CH_2O$ | H |  | H | 170–174 | $C_{21}H_{20}N_2O_2S$ | D | 7 | |
| **74** | I | $C_6H_5CH_2O$ | $C_6H_5CH_2O$ | H |  | H | 125–128 | $C_{22}H_{23}IN_2O_2S$ | B | 5 | C, H, I, N |
| **75** | *d* | HO |  | | H | H | 139–141[g] | $C_9H_8N_2O$ | E | 3 | |
| **76** | *d* | Cl | Cl | H |  | H | 205–206[h] | $C_7H_6Cl_2N_2S$ | F | 6 | H, N, S; C[k] |
| **77** | I | Cl | Cl | H |  | H | 168–171 | $C_8H_9Cl_2IN_2S$ | G | 5 | C, H, N |
| **78** | | HO | H | H |  | H | 214–217 | $C_7H_8N_2OS$ | C | 7 | |
| **79** | I | HO | H | H |  | H | 177–181 | $C_8H_{11}IN_2OS$ | A | 5 | |
| **80** | *d* | H | H | H |  | $CH_3$ | 106–108[i] | $C_8H_{10}N_2S$ | C | 6 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **81** | I | H | H | H |  | $CH_3$ | 180–183 dec | $C_9H_{13}IN_2S$ | C | 5 | |
| **82** | *d* | H | H |  |  | | 161–163 | $C_9H_{10}N_2S$ | B | 6 | C, H, N |
| **83** | I | H | H |  |  | | 165–170 | $C_{10}H_{13}IN_2S$ | H | 5 | |
| **84** | | $CH_3$ | Cl | H |  | H | 170–172 | $C_8H_9ClN_2S$ | C | 6 | C, H, N, Cl |
| **85** | | H | Cl | H |  | H | 139–141[j] | $C_7H_7ClN_2S$ | C | 6 | |

[a] A, EtOH–$Et_2O$; B, *i*-PrOH; C, EtOH; D, EtOAc; E, benzene, F, 2-butanone; G, MeOH–$Et_2O$; H, EtOH–*i*-PrOH. [b] Analytical results were within ±0.4% of theoretical values. [c] G. T. Morgan and J. A. Pichard, *J. Chem. Soc.*, **97**, 61 (1910), mp 223°. [d] The compound is not an addition salt. [e] E. Keleczenyl-Dumersnil, *Bull. Chim. Soc. Fr.*, 815–816 (1955), mp 141°. [f] I. E. Balaban, *J. Chem. Soc.*, 1092 (1929), mp 197°. [g] S. Huenig and K. H. Fritsch, *Justus Liebigs Ann. Chem.*, **609**, 143–146 (1957), mp 141–142°. [h] I. B. Douglass and F. B. Davis, *J. Am. Chem. Soc.*, **56**, 719 (1934), mp 203–204°. [i] W. Gebhardt, *Ber.*, **17**, 2094 (1884), mp 107°. [j] G. M. Dyson, H. J. George, and R. T. Hunter, *J. Chem. Soc.*, **125**, 3042 (1925), mp 140°. [k] C: 38.53.

tion (increased heart rate and myocardial contractile force) at minimally effective doses and higher. At minimally effective doses epinephrine often did not increase mean arterial blood pressure; this was less often the case with norepinephrine. These findings are compatible with the known pharmacological effects of epinephrine and norepinephrine. Both of these catecholamines exert potent β-adrenergic stimulant effects on the heart. On vascular beds norepinephrine is predominantly an α-adrenergic stimulant causing primarily vasoconstriction, the net result being most often an increase in mean arterial blood pressure. In contrast, the effect of epinephrine on vascular beds is mixed with some beds constricted via α-adrenergic mechanisms and others dilated via β-adrenergic effects. The net effect on blood pressure of intravenously administered epinephrine in the anesthetized dog varies with the dosage. At low dose levels (as was observed in this study) the vasodilator effects of epinephrine may predominante and a decrease or no change in mean arterial blood pressure may be observed despite simultaneously occurring cardiac stimulation and increased cardiac output. With high doses of epinephrine vasoconstrictor effects dominate and increased mean arterial blood pressure is observed.

Phenylephrine, a powerful α-receptor stimulant with little effect on the β receptors of the heart, caused marked increases in mean blood pressure; however, cardiac stimulation was only observed following the two highest doses tested. Naphazoline, a pure adrenergic vasoconstrictor on vascular beds, caused pressor effects unassociated with cardiac stimulation until the highest dose of 1.0 mg/kg was administered.

All four standard drugs caused only decreases in carotid artery blood flow, even in the face of increased mean arterial blood pressure.

The aromatic guanidines of greatest interest as potential therapeutic agents, i.e., those that were pure vasoconstrictors and did not cause cardiac stimulation at minimally effective pressor doses, were more similar to phenylephrine and naphazoline than to epinephrine and norepinephrine in their patterns of vascular vs. cardiac effects. Of the aromatic guanidines which exerted this pattern of action, the one of most interest was 3,4-dihydroxyphenylguanidine; this compound did not cause cardiac stimulation at lower therapeutically relevant doses and its pure vasoconstrictor action appears to be mediated, at least in part, by a direct action on α-adrenergic receptors.

**Investigation of Vasoconstrictor Mechanism of Action.** Preliminary adrenergic mechanism of action studies using the 3,4-dihydroxy-substituted phenylguanidine analogs of norepinephrine and epinephrine (compounds **21** and **49**) were performed on isolated strips of rabbit jejunum. One end of a jejunal segment, about 4–6 cm in length, was tied to an anchoring rod and immersed in an isolated organ bath of Tyrodes solution which was aerated with 95% $O_2$–5% $CO_2$ and maintained at 37.5°. The other end of the segment was connected by means of a thread to an isotonic transducer which was connected to a strip-chart recorder for recording longitudinal muscle activity.

Stimulation of α- and β-adrenergic receptor sites in fresh segments of isolated rabbit jejunum produces relaxation of tone and rhythmical activity.[9] In vitro cold storage of jejunal segments at 6–8° for 48–72 hr produces a selective impairment or loss of α-receptor activity.

The two catecholamine analogs, **21** and **49**, had $1/1000$ and $1/650$ the potency of norepinephrine in causing relaxation of the fresh jejunal segment. Compounds **21** and **49**, at a dose equipotent to norepinephrine, were without effect on the stored jejunal preparation, whereas the effect of norepinephrine was partially reduced. This finding suggests that

Table IV. Blood Pressure Increase of Standard Drugs

| Test drug | Dose, mg/kg 0.0005 | 0.001 | 0.002 | 0.004 | 0.01 | 0.1 | 1 |
|---|---|---|---|---|---|---|---|
| Epinephrine | 20 (10)[a] | 26 (21) | 44 (11) | 63 (4) | | | |
| Norepinephrine | 26 (25) | 36 (26) | | | | | |
| Phenylephrine | | 13 (1) | | | 46 (3) | 105 (1) | 140 (1) |
| Naphazoline | | 23 (1) | | | 46 (1) | 63 (1) | 58 (1) |

[a] The value is reported in mmHg and is an average of the number of trials reported in parentheses.

Table V. Blood Pressure Effects in Reserpinized Dogs

| Test compd | Dose, mg/kg iv 0.001 | 0.004 | 0.008 | 0.016 | 0.032 | 0.1 | 0.9 |
|---|---|---|---|---|---|---|---|
| 21 | 10[a] | 15 | 30 | 55 | 68 | | |
| 6 | | | | | | 10 | 10 |

[a] The value is reported in mmHg increase in blood pressure.

compounds 21 and 49 act on $\alpha$ receptors in the intestine. The action of norepinephrine is not completely abolished by cold storage since it acts on both $\alpha$- and $\beta$-intestinal receptors.[9]

The response of fresh jejunal segments to equipotent doses of norepinephrine and compounds 21 and 49 was antagonized to an equal degree by the $\alpha$-receptor antagonist, phentolamine. These results also suggest that the two guanidine analogs of epinephrine and norepinephrine exert $\alpha$-adrenergic effects on the isolated rabbit jejunum similar to but less potent than norepinephrine.

Dichlorophenylguanidine (6), while exhibiting the property of jejunal relaxation, was toxic to both fresh and stored segments; repeated washings failed to reestablish the integrity of the strip. The effect of 6 on the rabbit jejunum therefore appears to be nonspecific and qualitatively different than the effects of the dihydroxy analogs. This result is compatible with the finding in the reserpinized dog that 6 acts by an indirect adrenergic mechanism, while 21 exerts at least part of its action by direct action on $\alpha$-adrenergic receptors.

A study to determine whether 3,4-dihydroxyphenylguanidine (21) and 3,4-dichlorophenylguanidine (6) act by direct or indirect adrenergic mechanisms was performed in a reserpinized (reserpine, 0.2 mg/kg ip on each of the 2 days just preceding the day of the experiment) dog. On the day of the experiment this dog was anesthetized and prepared for determination of cardiovascular effects as described above. Reserpinization was shown by potentiation of the pressor responses to intravenous epinephrine and norepinephrine, and antagonism of the pressor response to tyramine, an agent which acts entirely by indirect adrenergic mechanisms. Table V shows the increases in mean arterial blood pressure (mmHg) after single intravenous injections of various doses of compounds 21 and 6.

Since both compounds 21 and 6 were similar in pressor effect in the nonreserpinized dog (see Table I), the reduction of the pressor response caused by dichlorophenylguanidine (6) in the reserpinized dog suggests that this compound acts primarily by indirect adrenergic mechanisms. On the other hand, 21 continues to exhibit pressor activity in the reserpinized dog suggesting that this compound exerts at least part of its pressor effect by direct $\alpha$-adrenergic stimulation.

**Structure–Activity Relationships.** Phenylguanidine (1), the parent compound of the series, was moderately active in raising blood pressure. At threshold dosage it caused vasoconstriction not associated with cardiac stimulation, while at higher dosages the pressor response occurred concomitantly with both vasoconstriction and cardiac stimulation. Following the originally postulated relationship to the $\beta$-phenylethylamine series, hydroxyl substitution of the phenyl ring leads to enhanced pressor action. The monosubstituted hydroxy derivatives, 19 and 20, were moderately strong vasoconstrictors at lower doses, with the 4-hydroxy derivative 20 producing increased heart rate and contractile force at higher doses. The 3,4-dihydroxy derivative 21 was one of the most selective and potent vasoconstrictor agent of the series and produced only slight effect upon heart rate and contractile force at the highest dose tested. This compound is most structurally analogous to norepinephrine in the catecholamine series. Compound 49, a methyl derivative of 21 with the methyl group in the 3 position of the guanidine moiety, is structurally analogous to epinephrine of the catecholamine series. 49 was equipotent as a vasoconstrictor to 21 and was found to cause cardiac stimulation, a finding consistent with its structural similarity to epinephrine. Compound 45, a positional isomer of 49 with the methyl group in the 1 position on the guanidine nucleus, was similar to 21 in pressor activity, heart rate, and contractile force changes. 50, the isopropyl derivative of 21 substituted with this group in the 3 position on the guanidine nucleus, exhibited only slight cardiovascular action. 50 is structurally analogous to isoproterenol of the catecholamine series but did not exhibit its $\beta$-adrenergic stimulant activity. 55, a diisopropyl derivative of 21 with isopropyl groups in the 2,3 position on the guanidine nucleus, caused decrease in blood pressure with increased heart rate and contractile force. The other hydroxyl derivatives with potent vasoconstrictor action were 22–26 and 37. 24, 25, and 37 were 4-hydroxy derivatives with groups bioisosteric to a hydroxyl group in the 3 position.[10-12] These compounds were more potent as vasoconstrictor agents than 4-hydroxyphenylguanidine (20), while the nonhydroxylated analogs 27 and 36 of compounds 25 and 37 were less active than phenylguanidine. Compound 63, 1-(3,4-dihydroxyphenyl) biguanide, was a potent vasoconstrictor agent while the parent compound, 1-phenylbiguanide (65), was only moderately active.

Chlorination of the benzene nucleus in the 3 or/and 4 position, 3, 4, 6, 8–11, 13, and 22, was nearly as effective in increasing vasoconstrictor potency as hydroxylation. Chlorination in the 2 position, 2, 5, and 7, resulted in decreased pressor response in relation to 1. The most potent vasoconstrictor agent of the chlorinated derivatives was 3,4-dichlorophenylguanidine (6), which was as active as 21. Substitution of this compound with an isopropyl group in the 3 position of the guanidine moiety greatly reduced the vasoconstrictor activity as did similar isopropyl substitution in 21, the 3,4-dihydroxy analog.

Simultaneous substitution of the benzene ring by halogens and methyl groups, 9–12, enhanced vasoconstrictor potency compared to 1, especially when substitution was in

the 3,4 positions. The same effect was observed by simultaneous substitution of halogen and hydroxy groups, **22** and **26**.

Substitution of methyl, **17** and **18**, and methoxy groups, **13–16**, on the benzene ring of **1** had little or no effect upon blood pressure. Acetyl substitution, **29** and **30**, was also without effect on blood pressure. Methanesulfonamido substitution in the absence of hydroxyl substitution, **27** and **28**, reduced cardiovascular action. 1-Naphthylguanidine (**32**) and its 5,6,7,8-tetrahydro derivative, **33**, were similar in blood pressure action to **1**. Heterocyclic aromatic guanidines, **34–36**, **38**, and **39**, were less active than **1**.

Alkyl substitution in the 1 position of the guanidine moiety, **40–46**, had no effect or decreased vasoconstrictor potency from the parent compounds. There was a tendency for contractile force to increase which was most pronounced with **40**, **41**, **44**, and **45**. 1-Indoline- and 1-(1,2,3,4-tetrahydroquinoline)carboxamidines, **56–59** and **62**, can also be included in the group of 1,1-disubstituted guanidines. These materials also exhibited only weak cardiovascular action.

Alkyl substitution in the 3 position of the guanidine moiety, **47–52**, generally decreased cardiovascular potency from the parent compound except in the case of methyl substitution, **49**, where almost no change was observed in vasoconstrictor potency and increased effects on both heart rate and contractile force were observed. Alkyl substitution in the 2 and 3 positions of the guanidine nucleus, **55**, appeared to reverse the cardiovascular effects from the parent compound, **21**, causing vasodilation, increased carotid blood flow, heart rate, and contractile force. The 2-anilino-2-imidazolines, **60** and **61**, which can be regarded as 1,2,3-trisubstituted guanidines, showed decreased potency from the parent compounds. **53**, a 1,1,3-trisubstituted guanidine, had reduced vasoconstrictor action with decreased effect on heart rate and contractile force when compared with **1**.

In summary, the main structure–activity relationships of the aromatic guanidine series are that hydroxylation and/or chlorination enhanced vasoconstrictor potency when substitution occurs in the 3 and/or 4 positions of a phenyl ring. This potency is decreased when substitution takes place in the 2 position. Bioisosteric hydroxyl substitution in the 3 position increases vasoconstrictor potency significantly only when hydroxylation occurs in the 4 position. Alkyl substitution on the guanidine nitrogens generally reduces potency except for methyl substitution which has little or no effect upon vasoconstrictor potency but causes increases in heart rate and contractile force. The effect of the series on carotid flow is generally a decrease since the materials are mainly vasoconstrictors. The effects on heart rate are in general to give slightly decreased rate or no change in the rate up to moderate dose. At higher doses heart rate is increased. The effect of the series on contractile force is variable with a tendency toward increases at higher doses for certain compounds.

In conclusion, aromatic guanidines have $\alpha$-adrenergic stimulant effects that are qualitatively similar to the $\beta$-phenylethylamine series, but even at higher dosage give only weak or no $\beta$-adrenergic effects. Preliminary mechanism of action study indicates that the 3,4-dihydroxy-substituted compounds **21** and **49** are $\alpha$-adrenergic stimulants that act partially by a direct mechanism.

## Experimental Section

**Chemistry.** All melting points were obtained in a Mel-Temp apparatus and are reported uncorrected. Satisfactory ir spectra were recorded for all new compounds using a Perkin-Elmer Model 21 spectrophotometer. All elemental analytical results for the compounds were within ±0.4% of theoretical values. The pertinent physical and analytical data for all compounds prepared were reported in Tables I–III.

**Method 1. Mono- and 1,1-Disubstituted Aromatic Guanidines.** A mixture of the appropriate aromatic amine mineral acid salt (or the aromatic amine with 1 molar equiv of the appropriate mineral acid), aqueous 50% hydrogen cyanamide solution (American Cyanamide Company), and ethyl alcohol was heated at reflux for 20 hr. The molar ratio of aromatic amine salt, hydrogen cyanamide, and ethyl alcohol was 1.0:1.5:15, respectively. The reaction mixture cooled at 0° for 20 hr. The precipitated product was collected on a filter and recrystallized several times from the appropriate solvent. If the procuct did not precipitate from the reaction mixture, the reaction solvents were evaporated and the residue was recrystallized from the appropriate solvent. If a solid guanidine salt was not obtained by the procedure described above, the residue obtained after evaporation of solvents was mixed with water and the mixture was extracted several times with ether. The aqueous layer was evaporated to nearly dryness and the residue was mixed with aqueous 25% sodium hydroxide solution. The free base was extracted with benzene. This solution was evaporated and the residue was recrystallized from an appropriate solvent.

**Method 2. Primary Aromatic Amines 66 and 67.** A mixture of 0.1 mol of the nitromethanesulfonanilide, 250 ml of ethyl alcohol, and 0.5 g of 10% palladium on charcoal was shaken 4 hr under an initial hydrogen pressure of 50 psi. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure.

**Method 3. Primary Aromatic Amines 68–71 and 75.** A mixture of 0.1 mol of the corresponding substituted nitrobenzene, 250 ml of ethyl alcohol, and 0.05 g of platinum dioxide was agitated for 2 hr under an initial hydrogen pressure of 50 psi. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was recrystallized from the solvent described in Table III.

**3,4-Dibenzyloxy-*N*-methylaniline Hydrochloride (72).** In a flask equipped with a thermometer and a Vigreux column (15 × 1.5 cm) were placed 38.2 g (0.125 mol) of **71** and 40.4 g (0.38 mol) of trimethyl orthoformate. A solution of 1.2 g of concentrated sulfuric acid in 10 g of trimethyl orthoformate was added to the stirred reaction mixture. The reaction mixture was stirred and heated in an oil bath at an initial temperature of 115°. The bath temperature was gradually increased to 150° while collecting 10 ml of methyl alcohol. The reaction mixture was cooled and evaporated under reduced pressure to a thick brown residue. A mixture of 100 ml of aqueous 10% hydrochloric acid and 10 ml of ethyl alcohol was added to the residue and the mixture was heated at reflux for 2.5 hr. The mixture was cooled and made basic with aqueous 10 *N* sodium hydroxide. The mixture was extracted with benzene. The extract was dried over $MgSO_4$ and filtered. Hydrogen chloride was added to the filtrate and the precipitated solid was collected on a filter. This solid was recrystallized from isopropyl alcohol.

**Method 4. 1,3-Di- and 1,1,3-Trisubstituted Aromatic Guanidines.** A mixture of 1-aryl-2-methyl-2-thiopseudourea hydriodide, the appropriate aliphatic amine, and ethyl alcohol in a molar ratio of 1.0:1.1:15 was heated at reflux for 20 hr. The evolved methyl mercaptan was trapped in aqueous 25% sodium hydroxide solution. The reaction products were isolated and purified as described in method 1.

**Method 5. 1-Aryl-2-methyl-2-thiopseudourea Hydriodides.** To a stirred solution of 0.1 mol of the appropriate aromatic amine in 150 ml of ethyl alcohol was added 0.3 mol of methyl iodide. The mixture was heated to reflux for 1 hr, cooled to ambient temperature (25°), and diluted with 300 ml of ether. The mixture was cooled at 0° for 16 hr. The precipitated solid was collected by filtration and recrystallized from the appropriate solvent.

**Method 6. Aromatic Thioureas 76, 80, 82, 84, and 85.** A mixture of 0.1 mol of aromatic amine hydrochloride, 0.6 ml of potassium thiocyanate, and 100 ml of water was heated in an evaporating dish on a steam bath until dry. The residue was triturated with water and filtered. The solid was purified by crystallization from the appropriate solvent.

**Method 7. Aromatic Thioureas 73 and 78.** To a stirred solution of 0.1 mol of aromatic amine in 200 ml of benzene was added 0.1 mol of benzoyl isothiocyanate.[13] The mixture was heated at reflux for 1 hr. The reaction mixture was cooled at 5° for 12 hr and filtered. The collected solid was added to 800 ml of 10% aqueous sodium hydroxide and the solution was heated at reflux for 1 hr. Glacial acetic acid was added until the pH was 6.0. The mixture was cooled to 0° for 16 hr. The precipitated solid was collected and recrystallized from the appropriate solvent.

**Method 8. 1,2,3-Trisubstituted Aromatic Guanidines.** Di-

isopropylcarbodiimide (0.1 mol) in 30 ml of benzene was added to a stirred solution of the aromatic amine hydrochloride (0.1 mol) in 100 ml of ethyl alcohol. The mixture was heated at reflux for 1 hr. Products were isolated and purified as described in method 1.

**Method 9. 2-Anilino-2-imidazolines.** A mixture of the aromatic thiourea (0.1 mol) and 20 ml of ethylenediamine was stirred and heated at 135° for 2.5 hr. The reaction mixture was cooled and mixed with 100 ml of water. The mixture was acidified to pH 2 by the addition of concentrated hydrochloric acid and was cooled in an ice bath. The mixture was filtered and the filtrate was adjusted to pH 8.0 by addition of aqueous 25% sodium hydroxide solution. The mixture was extracted twice with 50-ml portions of ether. The aqueous layer was made basic (pH 11–12) with aqueous 25% sodium hydroxide solution. The mixture was cooled to 0° and the precipitated solid was collected on a filter. The products were purified by recrystallization from aqueous methanol.

**2-(1-Indolino)-2-imidazoline (62).** Compound **83** (0.1 mol) was heated to 65° with 20 ml of ethylenediamine for 4 hr. The product was isolated as described in method 9.

**Method 10. Aromatic Biguanides.** The aromatic amine hydrochloride, dicyandiamide, and isopropyl alcohol in a molar ratio of 1.0:1.5:15 were heated to reflux for 20 hr. The products were isolated and purified using the procedures described in method 1.

**Method 11. 3,4-Dihydroxyphenylguanidines and Biguanides.** A mixture of 0.1 mol of the 3,4-dibenzyloxyphenylguanidine or biguanide hydrochloride, 250 ml of ethyl alcohol, and 0.5 g of 5% palladium on charcoal was shaken under an initial hydrogen pressure of 50 psi. After 4 hr of agitation the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was recrystallized from the solvents described in Tables I and II. Compound **63** was obtained from the reaction mixture by filtration to remove the catalyst and evaporation of the filtrate to a viscous residue. The residue was dissolved in 100 ml of water and a solution of 17.0 g of silver nitrate in 100 ml of water was added. After stirring for 10 min in the absence of light, the reaction mixture was filtered to remove the precipitated silver chloride. The filtrate was evaporated under reduced pressure. The residue was recrystallized from isopropyl alcohol.

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# Synthesis of a Bifunctional Coordination Complex of Osmium with Curariform Activity

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Based on the known curariform action of tris(bipyridyl)iron(II) sulfate and other complex ions, two series of bifunctional ligands designed to hold transition metal ions at approximately the same distance apart as the interquaternary ammonium distance in the potent neuromuscular blocking agents were synthesized. In the first series two 1,10-phenanthrolines ($R_1$) were joined at the 2 position to form four compounds: $R_1CO\text{-}c\text{-}N(CH_2CH_2)_2N\text{-}COR_1$, $R_1CONH\text{-}1,2\text{-}C_6H_{10}\text{-}NHCOR_1$, $R_1CONH\text{-}1,2\text{-}C_6H_4\text{-}NHCOR_1$, and $R_1CON(CH_3)(CH_2)_2N(CH_3)COR_1$. In the second series two terpyridines ($R_2$) were joined by different chains to give $R_2(CH_2)_2CH{=}CH(CH_2)_2R_2$, $R_2CH_2C(CH_3)(OH)(CH_2)_2C(CH_3)(OH)CH_2R_2$, $R_2CH_2C(CH_3)(OH)C(CH_3)(OH)CH_2R_2$, and $R_2CH_2(OH)\text{-}1,4\text{-}C_6H_{10}\text{-}(OH)CH_2R_2$. Three other ligands in which the terpyridines were joined by 5-, 6-, and 7-methylene groups were also made. The ligands were converted to nickel(II) complexes and the coordination of each nickel ion was completed by adding terpyridine. These were assayed by the intravenous mouse $LD_{50}$ method. The most potent ligand, the dihydroxy compound $R_2CH_2(OH)\text{-}1,4\text{-}C_6H_{10}\text{-}(OH)CH_2R_2$, was then converted to the bis(pyridinebipyridine)diosmium(II) coordinated complex and assayed by the iv mouse $LD_{50}$ method and by the $ED_{50}$ isolated guinea-pig diaphragm method. By the iv mouse $LD_{50}$ method, it was about twice as potent as *d*-tubocurarine and by the isolated diaphragm method, it was 16 times more potent. The compound has been called dihydroxyosmarine tetrachloride or DHO for short. The term "transarine" ions is proposed for transition metal coordination complexes having curariform action. The position of the transarine ions is discussed in the classification of cholinergic ligands, in structure–action relationships, and in relation to some current ideas on receptor mechanisms.

The initial observations of the curariform action of a transition metal complex were made by Beccari in 1938[1-3] who noted that the doubly charged coordination complex of ferrous iron and three 2,2′-bipyridyls caused paralysis and death by failure of ventilation in rabbits. He estimated the minimum lethal subcutaneous dose to be about 35 mg/kg. The compound was not found anywhere in the brain. He also noted that the complex cations showed high chemical stability and were excreted in the urine.

Following Beccari's reports the biological activity of a series of related transition metal complexes was further investigated by Dwyer et al.[4-7] The substances they studied consisted of chelates formed by uniting a variety of ligands to a central ion of one of the transition elements. The most active ligands found were 2,2′-bipyridyl, 1,10-phenanthroline, and 2,2′,2″-terpyridyl. Ions of iron, nickel, cobalt, ruthenium, and osmium functioned adequately as the central element of the complexes. All the complexes of the above ions and ligands they tested caused characteristic reversible curariform paralysis of isolated rat diaphragm and of mice upon intraperitoneal injection. Only positively charged complexes were active and on the isolated dia-