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Antibacterial Action of Some Aromatic Amines, Amidines, Amidoximes, Guanidines and Diguanydes

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The discovery of therapeutic activity in a new type of compound is a noteworthy development in chemotherapy. Such activity may be of a minor order but it can be developed by the art of the organic chemist. Discoveries of this kind often depend upon some accidental observation; it is a laborious task to search systematically, using experimental infections in animals, for specific therapeutic activity in new types of compounds. As however the vital processes of all organisms are fundamentally similar, it seems possible that by choice of a suitable organism which could be easily handled one might be able to uncover unsuspected biological activity in new types of compounds without excessive labour. For this purpose a carefully chosen group of bacterial species seems worthy of consideration.

During the war a long series of aromatic bases was prepared in connexion with investigations into the chemotherapy of virus diseases (Andrewes, King & van den Ende, 1943) and of typhus (Andrewes, King, van den Ende & Walker, 1944; Andrewes, King & Walker, 1946). As these substances were still available it was deemed worth investigating whether any possessed pronounced biological activity as revealed by bacteriostatic action on a range of bacteria *in vitro*. Such indeed proved to be the case. *p*-Methylsulphonylbenzamidinium and *p*-methylsulphonylbenzylamine were found to be outstandingly active against certain obligate anaerobic bacteria. These observations were followed up and the results have been fully reported (Fuller, Tonkin & Walker, 1945; Evans, Fuller & Walker, 1944, 1945). The present communication records the results of bacteriostatic tests on a number of aromatic amines, amidines, amidoximes, guanidines and diguanides which have not hitherto been recorded.

METHODS

The methods used were similar to those previously described (Fuller, 1942). Inhibitory concentrations are recorded as mg./100 ml. (parts/100,000). The sign > means that the drug was inactive at the highest concentration tested. The tests were carried out in 200 μ l. of medium contained in tubes 40 $\times$ 5 mm. (internal) which were afterwards sealed with sealing wax. For the tests with *Clostridium welchii* the broth was first boiled, reduced with 0.1% of thiolacetic acid and neutralized; 4 mm. tubes were used and these were loosely covered with glass caps and incubated in the anaerobe jar. The implant was 10 μ l. of a 1:1000 dilution of an overnight culture of *Streptococcus pyogenes* or *Cl. welchii* and of a 1:10,000 dilution of the other organisms.

The effect of proteins on the activity was determined by testing the drugs against *Strep. pyogenes* in broth and in horse blood instead of in 50% serum broth as previously.

Cultures. The main tests were carried out with the following cultures: *Strep. pyogenes*, group A, type 3, 'Richards' (mouse virulent); *Staphylococcus aureus*, 'Paler'; *Cl. welchii*, 'Roshier'; *Escherichia coli*, '88'; *Proteus vulgaris*, 'Hunt'.

RESULTS

Table 1 summarizes the results obtained on a series of aromatic amidines.

It will be noticed that the aromatic amidines with few exceptions are not highly bacteriostatic. The relatively high activity of the nitro-compounds is probably due to a specific effect of the nitro-group. Of the compounds recorded in Table 1 it seems that *p*-ethoxybenzamidinium (12), and *p*-sulphonamido-phenylacetamidinium (21), might be worth while examining on other organisms including the Protozoa. The *o*-aminophenol grouping in (18) on which Ehrlich laid considerable stress has no eutherapeutic effect in this series.

Table 1. Inhibitory concentrations in mg./100 ml. of derivatives of benzamidine

	In blood <i>Strep.</i> <i>pyogenes</i>	In broth				
		<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>	<i>Proteus</i> <i>vulgaris</i>
1. Benzamidine	150	30	1000	200	750	1000
2. Benzamidine, <i>m</i> -Cl	30	50	500	8	500	500
3. Benzamidine, <i>p</i> -Cl	30	25	200	10	200	400
4. Benzamidine, <i>p</i> -Br	100	10	250	5	100	500
5. Benzamidine, <i>m</i> -NO ₂	2	5	40	5	50	75
6. Benzamidine, <i>p</i> -NO ₂	1	3	25	3	15	20
7. Benzamidine, <i>m</i> -NH ₂	120	50	500	500	400	1000
8. Benzamidine, <i>p</i> -NH ₂	100	20	150	75	200	1000
9. Benzamidine, <i>p</i> -Me	100	15	400	25	750	300
10. Benzamidine, <i>p</i> -OH	60	20	100	200	200	>1000
11. Benzamidine, <i>p</i> -OMe	50	7	150	10	250	500
12. Benzamidine, <i>p</i> -OEt	15	1	15	0.5	75	100
13. Benzamidine, 4:5-CH ₂ O ₂	100	7	200	7	500	500
14. Benzamidine, <i>p</i> -CONH ₂	10	5	400	100	500	>1000
15. Benzamidine, <i>m</i> -SO ₂ NH ₂	250	50	>1000	1000	1000	>1000
16. Benzamidine, <i>p</i> -SO ₂ NH ₂	5	1.5	500	7	1500	1200
17. Benzamidine, <i>p</i> -CH ₂ SO ₂ NH ₂	50	25	600	500	1000	>1000
18. Benzamidine, 3-NH ₂ , 4-OH	50	35	300	150	500	>1000
19. Phenylacetamidine	75	100	750	150	500	1500
20. Phenylacetamidine, <i>p</i> -NO ₂	30	15	75	2	20	300
21. Phenylacetamidine, <i>p</i> -SO ₂ NH ₂	4	0.5	150	3	1000	>1000
22. α -Phenylbutyramidine	60	100	200	50	200	500

Table 2. Inhibitory concentrations of derivatives of *p*-sulphonamidobenzamidine

	In blood (mg./100 ml.)	In broth (mg./100 ml.)				
	<i>Strep.</i> <i>pyogenes</i>	<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>	<i>Proteus</i> <i>vulgaris</i>
(a) Substitution in the sulphonamide group						
16. —SO ₂ NH ₂	5	1.5	500	7	1500	1200
23. —SO ₂ NHMe	5	1.5	500	10	1000	>2000
24. —SO ₂ NHBu ^α	50	10	300	600	200	500
25. —SO ₂ NMe ₂	150	100	350	20	1000	>1000
26. —SO ₂ NEt ₂	150	75	200	—	300	500
27. —SO ₂ NHC(:NH)NH ₂	150	120	700	—	1000	>1000
28. —SO ₂ NHCH ₂ C(:NH)NH ₂	35	20	500	—	1000	>1000
29. —SO ₂ N(CH ₂ CH ₂ OH) ₂	200	100	>1000	>1000	1000	>1000
30. —SO ₂ N. CH ₂ .CH ₂ .CH ₂ .CH ₂ .CH ₂	100	100	200	750	500	750
31. —SO ₂ N. CH ₂ .CH ₂ .CH ₂ .O.CH ₂ .CH ₂	250	150	1000	—	1000	>1000
32. —SO ₂ NHPh	15	5	50	20	50	200
33. —SO ₂ NHC ₆ H ₄ C(:NH)NH ₂	>200	100	1000	1000	1000	>1000
34. —SO ₂ NHC ₆ H ₄ .SO ₂ NH ₂	150	200	>1000	500	1000	1000
35. —SO ₂ NHC ₆ H ₄ .SO ₂ NMe ₂	>50	>50	>50	>50	>50	>50
36. —SO ₂ NH. C.N.CH.CH.CH	250	80	1000	—	1000	>1000
37. —SO ₂ .NHC N.CH.CH.S	>100	60	>200	20	>200	>200
38. —SO ₂ NH.C.N.CMe:CH.CMe:N	>200	150	>200	>200	>200	>200
39. —SO ₂ NHOEt	50	50	350	15	400	1000
40. —SO ₂ NHOPr ^α	150	50	120	20	250	500
41. —SO ₂ NHOBu ^α	100	20	>200	15	>200	>200
(b) Substitution in the amidine group						
42. —C(:NH)NHMe	200	100	>1000	500	1000	>1000
43. —C(:NMe)NHMe	200	500	>2000	1200	2000	>2000
44. —C(:NH)NH.NH ₂	100	10	500	20	200	>500

The effect of substituents in the sulphonamide group and in the amidine group of *p*-sulphonamidobenzamidine, a drug which has some action on experimental typhus and a pronounced action on some bacteria is recorded in Table 2.

A survey of Table 2 shows that as a rule substitution in the sulphonamide or the amidine group reduces the bacteriostatic activity. Hydrocarbon radicals, however, increase the activity against staphylococci and the Gram-negative bacteria; e.g. the phenyl (32), diethyl (25), butyl (24), propoxy (40), and pentamethylene (30) derivatives are all more active than the parent compound. Introduction of polar groups, e.g. the conversion of a sulphonamido- (16) to a sulphaguanidino- (27) derivative, seriously lowers the activity against streptococci. In the case of the amidrazone (44), there is some enhancement of activity possibly due to a specific effect of the hydrazine grouping.

Table 3 records the results of tests on a few benzamidoximes. Comparison with the corresponding amidines in Table 1 shows that conversion to the amidoxime has an unfavourable effect, although *p*-

sulphonamidobenzamidoxime is equal if not superior to *p*-sulphonamidobenzamidine in experimental typhus in mice. This superiority or equivalence is not shown to the bacteria here examined.

In Table 4 are recorded the results of the effect of substitution in the sulphonamido- or the amidoxime-group of *p*-sulphonamidobenzamidoxime.

These compounds on the whole are very weakly bacteriostatic and also sparingly soluble.

In Table 5 are given the results of tests on a series of guanidines. These compounds were specially prepared (King & Tonkin, 1946) when it was found that *p*-tolylguanidine had a marked bacteriostatic activity and also a weak true causal prophylactic activity against a sporozoite-induced infection of *Plasmodium gallinaceum* in the chick.

It will be observed that the marked anti-bacterial action of *p*-tolylguanidine is also found in *p*-ethylphenylguanidine, in *p*-anisylguanidine and in *p*-phenetylguanidine. Of these compounds *p*-anisylguanidine proved to possess the most active true causal prophylactic effect against bird malaria (King & Tonkin, 1946). There is little difference in

Table 3. Inhibitory concentrations of derivatives of benzamidoxime

	In blood (mg./100 ml.)	In broth (mg./100 ml.)				
		<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>	<i>Proteus</i> <i>vulgaris</i>
45. Benzamidoxime	>200	250	2000	1000	1000	1500
46. Benzamidoxime, <i>p</i> -Cl	>100	50	800	40	200	500
47. Benzamidoxime, <i>p</i> -Br	>200	20	500	20	500	500
48. Benzamidoxime, 4:5-CH ₂ O ₂	>200	200	500	250	500	>1000
49. Benzamidoxime, <i>p</i> -SO ₂ NH ₂	>200	50	>1000	700	1000	2000

Table 4. Inhibitory concentrations of derivatives of *p*-sulphonamidobenzamidoxime

	In blood (mg./100 ml.)	In broth (mg./100 ml.)				
		<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>	<i>Proteus</i> <i>vulgaris</i>
		(a) Substitution in the sulphonamide group				
49. —SO ₂ NH ₂ (unsubstituted)	>200	50	>1000	700	1000	2000
50. —SO ₂ NEt ₂	>200	100	400	150	500	>500
51. —SO ₂ N(CH ₂ .CH ₂ OH) ₂	>200	600	>1000	>1000	>1000	>1000
52. —SO ₂ N[CH ₂ .CH ₂ .CH ₂ .CH ₂ .CH ₂ .CH ₂]	>50	100	>100	>100	>100	>100
53. —SO ₂ N[CH ₂ .CH ₂ .CH ₂ .O.CH ₂ .CH ₂]	>200	1000	>1000	500	1000	>1000
54. —SO ₂ NH.C ₆ H ₄ .SO ₂ NMe ₂	>100	150	>500	—	>500	>500
55. —SO ₂ NH.C[CH ₂ .CH ₂ .CH ₂ .CH ₂ .CH ₂ .S]	150	75	>500	500	>500	>500
56. —SO ₂ NHOH	>200	>800	>800	800	>800	>800
57. —SO ₂ NHOMe	300	250	250	50	200	500
58. —SO ₂ NHOEt	200	150	750	50	600	>1000
59. —SO ₂ NHOPr ^α	>200	120	500	50	600	>1000
60. —SO ₂ NHOBu ^α	150	400	250	20	>400	>400
(b) Substitution in the amidoxime group						
61. —C(:N.OMe).NH ₂	500	250	1500	500	1000	>2000
62. —C(:N.OEt).NH ₂	>200	150	700	15	>700	>700
63. —C(:NOPr ^α).NH ₂	>200	>500	500	100	>500	>500
64. —C(:NOMe)NHOMe	>200	350	1000	800	800	>1000
65. —C(:N.OEt)NHOEt	>200	200	800	150	>800	>800

activity between the amidines of Table 1 and the guanidines of Table 5, except that the *p*-sulphono-amido-derivative (85) is much less active against streptococci than is the corresponding amidine (16), and that *p*-tolylguanidine (72) is much more active than *p*-tolylamidine (9).

butyl (93) derivative when the H of the amino group is substituted.

The result of diguanide formation is shown in Table 7.

It will be noticed that the pronounced bacteriostatic effect associated with the *p*-anisyl and *p*-tolyl

Table 5. *Inhibitory concentrations of guanidines*

	In blood (mg./100 ml.)	In broth (mg./100 ml.)				
		<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>	<i>Proteus</i> <i>vulgaris</i>
66. Phenylguanidine	150	100	400	100	500	500
67. Phenylguanidine, <i>m</i> -Cl	100	20	120	100	200	200
68. Phenylguanidine, <i>p</i> -Cl	20	20	100	20	200	300
69. Phenylguanidine, <i>p</i> -Br	10	10	75	50	250	400
70. Phenylguanidine, <i>o</i> -Me	200	100	200	50	500	1000
71. Phenylguanidine, <i>m</i> -Me	20	100	150	150	200	500
72. Phenylguanidine, <i>p</i> -Me	5	0.5	10	0.5	—	300
73. Phenylguanidine, 3:6-Me ₂	100	100	100	70	100	200
74. Phenylguanidine, 4:5-Me ₂	50	50	50	20	50	150
75. Phenylguanidine, 4:6-Me ₂	50	50	150	50	200	1000
76. Phenylguanidine, <i>p</i> -Et	1	0.5	5	0.7	70	200
77. Phenylguanidine, <i>p</i> -OH	100	30	100	50	500	2000
78. Phenylguanidine, <i>o</i> -OMe	100	200	500	500	500	—
79. Phenylguanidine, <i>p</i> -OMe	5	0.5	30	5	200	1000
80. Phenylguanidine, <i>p</i> -OEt	3	1	20	2	100	500
81. Phenylguanidine, 4:5-CH ₃ O ₂	50	1.5	50	1.5	200	800
82. Phenylguanidine, 4:5(OMe) ₂	20	100	200	100	500	>2000
83. Phenylguanidine, <i>p</i> -COMe	50	5	50	5	200	500
84. Phenylguanidine, <i>p</i> -SO ₃ OH	>250	>500	>500	>500	>500	>500
85. Phenylguanidine, <i>p</i> -SO ₃ NH ₂	50	30	100	150	1000	>1000
86. α -Naphthylguanidine	100	20	100	50	75	150
87. β -Naphthylguanidine	60	15	50	50	50	100
88. Benzylguanidine	20	60	50	200	100	200

Table 6. *Inhibitory concentrations of derivatives (RX) of p-tolylguanidine (72) and of p-anisylguanidine (79) substituted in the guanidine group*

		In blood (mg./100 ml.)	In broth (mg./100 ml.)				
R	X		<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>	<i>Proteus</i> <i>vulgaris</i>
72.	<i>p</i> -Tolyl—NHC(:NH)NH ₂	5	0.5	10	0.5	—	300
89.	<i>p</i> -Tolyl—N.Me.C(:NH)NH ₂	100	100	500	100	100	2000
90.	<i>p</i> -Tolyl—N.Et.C(:NH)NH ₂	200	50	200	150	100	800
91.	<i>p</i> -Tolyl—NH.C(:NMe)NH ₂	200	150	500	50	500	1000
92.	<i>p</i> -Tolyl—NH.C(:NEt)NH ₂	200	50	500	50	500	600
93.	<i>p</i> -Tolyl—NH.C(:NBu ^a)NH ₂	100	20	100	3	100	300
94.	<i>p</i> -Tolyl—NH.C(:NH)NMe ₂	500	500	1000	500	1000	>2000
95.	<i>p</i> -Tolyl—NH.C(:NH)NEt ₂	300	500	2000	200	800	2000
79.	<i>p</i> -Anisyl—NH.C(:NH)NH ₂	5	0.5	30	5	200	—
96.	<i>p</i> -Anisyl—NMe.C(:NH).NH ₂	150	50	500	200	200	1000
97.	<i>p</i> -Anisyl—NEt.C(:NH)NH ₂	100	200	200	200	100	500
98.	<i>p</i> -Anisyl—NH.C(:NMe)NH ₂	150	150	300	150	700	2000
99.	<i>p</i> -Anisyl—NH.C(:NEt)NH ₂	300	200	1000	100	500	1000
100.	<i>p</i> -Anisyl—NH.C(:NBu ^a)NH ₂	100	50	200	10	200	300
101.	<i>p</i> -Anisyl—NH.C(:NH)NHPr ^b	—	50	600	100	500	1000
102.	<i>p</i> -Anisyl—NH.C(:NH)NEt ₂	200	800	2000	200	1000	>2000
103.	<i>p</i> -Anisyl—NH.C(:NMe)NHMe	500	500	2000	500	1500	>2000
104.	<i>p</i> -Anisyl—NMe.C(:NMe)NHMe	2000	500	1000	500	1000	1000

Table 6 shows that substitution in the guanidine group both in the case of *p*-tolyl- and *p*-anisyl-guanidine leads to diminished bacteriostatic activity. There is, however, an increase in activity, especially against *Cl. welchii*, from the methyl (91) to the

and homologous groups observed in the guanidines is lost here and that in general the diguanides are not markedly bacteriostatic.

When the N¹ nitrogen atom of the diguanides is alkylated (Table 8), there is no pronounced change

Table 7. *Inhibitory concentrations of diguanides*

	In blood (mg./100 ml.)	In broth (mg./100 ml.)				
		<i>Strep.</i> <i>pyogenes</i>	<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>
105. Phenyldiguanide	30	5	400	100	1000	>1000
106. Phenyldiguanide, <i>m</i> -Cl	100	20	60	50	100	200
107. Phenyldiguanide, <i>p</i> -Cl	70	50	50	30	100	100
108. Phenyldiguanide, <i>p</i> -Br	30	20	30	30	75	50
109. Phenyldiguanide, <i>o</i> -Me	200	200	500	100	500	1000
110. Phenyldiguanide, <i>m</i> -Me	200	100	100	70	200	500
111. Phenyldiguanide, <i>p</i> -Me	100	200	100	70	200	500
112. Phenyldiguanide, 3:6-Me ₂	200	100	100	70	200	500
113. Phenyldiguanide, 4:5-Me ₂	100	50	50	8	100	200
114. Phenyldiguanide, 4:6-Me ₂	200	100	100	100	200	500
115. Phenyldiguanide, <i>p</i> -Et	100	50	30	4	50	120
116. Phenyldiguanide, <i>p</i> -OH	100	100	200	300	500	1500
117. Phenyldiguanide, <i>o</i> -OMe	200	500	500	200	500	2000
118. Phenyldiguanide, <i>p</i> -OMe	100	100	200	100	500	1500
119. Phenyldiguanide, <i>p</i> -OEt	100	10	50	100	200	500
120. Phenyldiguanide, 4:5-CH ₃ O ₂	100	75	120	70	400	1000
121. Phenyldiguanide, <i>p</i> -COMe	200	100	200	100	200	700
122. α -Naphthyldiguanide	50	10	75	50	30	120
123. β -Naphthyldiguanide	50	10	50	20	50	100
124. Benzyl diguanide	50	70	50	100	100	500

Table 8. *Inhibitory concentrations of various substituted diguanides*

	In blood (mg./100 ml.)	In broth (mg./100 ml.)				
		<i>Strep.</i> <i>pyogenes</i>	<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>
125. <i>N</i> ¹ -Methyltolylidiguanide	80	20	50	150	250	1500
126. <i>N</i> ¹ -Ethyltolylidiguanide	100	40	50	250	100	500
127. <i>N</i> ¹ -Methyl <i>p</i> -methoxyphenylidiguanide	200	30	200	1000	500	2000
128. <i>N</i> ¹ -Ethyl <i>p</i> -ethoxyphenylidiguanide	100	120	50	500	150	800
129. <i>p</i> -Chlorophenyl- <i>N</i> ¹ -methyl- <i>N</i> ⁵ -isopropylidiguanide	15	5	20	10	25	70

Table 9. *Inhibitory concentrations of aniline and derivatives*

	In blood (mg./100 ml.)	In broth (mg./100 ml.)				
		<i>Strep.</i> <i>pyogenes</i>	<i>Staph.</i> <i>aureus</i>	<i>Cl.</i> <i>welchii</i>	<i>Esch.</i> <i>coli</i>	<i>Proteus</i> <i>vulgaris</i>
130. Aniline	>200	150	500	200	600	600
131. Aniline, <i>m</i> -Cl	200	75	200	10	200	150
132. Aniline, <i>p</i> -Cl	—	100	200	10	200	150
133. Aniline, <i>p</i> -Br	>100	50	100	50	100	75
134. Aniline, <i>p</i> -NO ₂	75	7	100	100	100	100
135. Aniline, <i>m</i> -NH ₂	100	35	200	20	>1000	1000
136. Aniline, <i>p</i> -NH ₂	50	1.5	25	20	100	20
137. Aniline, <i>p</i> -NHCOMe	>200	100	>1000	—	>1000	>1000
138. Aniline, <i>p</i> -Me	>200	1.5	200	200	400	500
139. Aniline, <i>p</i> -Et	200	30	300	500	200	400
140. Aniline, <i>p</i> -OH	>50	1.5	5	200	20	5
141. Aniline, <i>o</i> -OMe	500	100	200	100	500	500
142. Aniline, <i>p</i> -OMe	200	20	100	200	100	1000
143. Aniline, <i>p</i> -OEt	200	3	200	500	300	500
144. Aniline, <i>p</i> -SO ₂ NH ₂	4	—	10*	—	4*	7*
145. Aniline, <i>p</i> -COOH	1000	1000	1000	1500	750	1500
146. Benzylamine	20	100	600	—	200	700

* In synthetic medium.

in bacteriostatic properties but if the terminal N⁵ nitrogen atom is alkylated as in *p*-chlorophenyl-N⁵-methyl-N⁵-isopropyldiguanide (M4430) (for which I am indebted to Imperial Chemical Industries (Pharm.), Ltd.) there is a distinct enhancement of bacteriostatic properties. It is significant that this substance is closely related to paludrine and like paludrine has pronounced antimalarial properties (Curd & Rose, 1946).

Finally, in Table 9, are summarized the effects of substitution in the nucleus of a series of anilines. As might be anticipated, *p*-phenylenediamine and *p*-aminophenol, substances readily oxidized to imines, are markedly active but *m*-phenylenediamine is not. *p*-Aminobenzoic acid is relatively harmless whilst sulphanilamide is uniformly of marked activity.

Most of the substances were also tested against *Pseudomonas aeruginosa* which was inhibited on an average by about three-quarters of the concentration necessary for *Proteus vulgaris*. A few were tested against *Eberthella typhosa* which was inhibited at approximately the concentration required for *Esch. coli* and against *Shigella paradysenteriae* Flexner W which needed approximately three-quarters of that value.

DISCUSSION

Most of the compounds are moderately active against streptococci, less so against *Cl. welchii*, and weakly active against staphylococci and the Gram-negative bacteria. This is the common pattern of activity for simple bases. *p*-Sulphonamidobenzamidine (16) is very similar in activity to the German drug 'Marfanil' (*p*-sulphonamidobenzylamine), and like it has a strong basic group separated from the benzene ring by a carbon atom. The insertion of a second carbon atom to give *p*-sulphonamidophenylacetamidine (21) results in even greater potency. The corresponding compound in the Marfanil series (β -*p*-sulphonamidophenylethylamine) was shown by Lawrence (1945) to be inactive, and Fuller, Tonkin & Walker (1945) found that β -*p*-methylsulphonylphenylethylamine was very much weaker than *p*-methylsulphonylbenzylamine. The activity of the

amidines persists through a greater change of constitution than does that of the amines.

In general, substitution, particularly by polar groups, lowers activity, which means that there are few outstanding drugs in the present series. However, alkyl and phenyl substitution in *p*-sulphonamidobenzamidine and -amidoxime raises the activity against *Esch. coli* and *Proteus vulgaris* (24, 26, 32, 50); and *p*-methyl, -ethyl or -ethoxyl cause a general increase in the activity in the guanidine and aniline series (12, 72, 76, 80, 138, 143). *Para* substitution, particularly of a sulphonamide or a carbamide group often raises the activity against streptococci specifically (14, 16, 21, 49, 144), while *meta* substitution lowers it (2, 7, 15).

Although the first substituent may lower the activity, higher homologues may be more active than the first member. For example, there is always an increase in activity from *p*-OH to *p*-OC₂H₅ (10, 11, 12; 77, 79, 80; 116, 118, 119). Similarly, as the series of O-ethers of *p*-sulphonamidobenzamidoxime is ascended (56-60), the activity against *Cl. welchii* increases. Changes in constitution affect the activity against streptococci and *Cl. welchii* more than that against other bacteria (e.g. 16, 17). The staphylococci are very similar to the Gram-negative bacteria in their response to changes in constitution.

The activity of most of the drugs is decreased in blood. In general those groups which lead to an increase of activity also show a more serious interference by blood.

SUMMARY

1. The bacteriostatic activities of a number of derivatives of benzamidine, phenylguanidine, phenyldiguanide and benzamidoxime are recorded.
2. Substitution in these compounds generally leads to lowering of activity, but a methyl, ethyl, methoxyl, ethoxyl or sulphonamide group in the *para* position greatly increases the potency against streptococci.

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