pH 7, at 25 °C using 10 nN enzyme. A Cary 118 C spectrophotometer with a 0.05-A scale was used to record the assays. Steady-state velocities (i.e., activity between 3 and 4 min of reaction) were used, since the extent of inhibition is time dependent. The data were fitted to the equation for competitive inhibition using Cleland's program,[20] which computes the standard errors.

The inhibition constants obtained for the new 3-substituted pyrazoles were about tenfold higher than the values for the corresponding 4-substituted pyrazoles, but the 3-substituted derivatives may have been slightly contaminated by the 4-substituted derivatives. Therefore, dissociation constants for the 3-substituted derivatives were determined by difference titration, with the pyrazole compound, of 19 to 27 μN enzyme in the presence of 1 mM NAD^+ in 0.1 M sodium phosphate buffer, pH 7.0, at 25 °C, in one sector (0.438-mm path length) of a double-sector cuvette against a reference cuvette containing enzyme in one sector and NAD^+ and pyrazole in the other sector. Alternatively, or in addition, the pyrazole was titrated with enzyme as in Figure 1. On the basis of an extinction coefficient of 7200 M^{-1} cm^{-1} at 300 nm, the concentration of enzyme–NAD^+–pyrazole complex was calculated, after subtracting 0.25 A_{328} from the A_{300} as a correction for the formation of small amounts of enzyme–NADH complex.[15] The dissociation constant was computed by a linear least-squares fit to the data graphed as a Scatchard plot. Titrations with 3-methylpyrazole and 4-substituted pyrazoles with dissociation constants larger than 1 μM gave dissociation constants approximately the same as the inhibition constants for these compounds.

Irreversible inactivation of 1 mg of enzyme/mL of 0.1 M $Na_4P_2O_7$ buffer adjusted to pH 8 with H_3PO_4 was determined at 25 °C with reagent concentrations ranging from 1 to 100 mM by assaying 10 μL of reaction mixture in 1 mL of a standard assay mixture[16] after various times of reaction, usually over a 24-h period. The effect of 2 mM AMP or 1 mM NAD^+ or 0.2 mM NADH was routinely studied in order to be able to identify reagents that reacted specifically in the presence of NAD^+. In order to determine if the reagent affected the activity of the enzyme in the assay, a control was run. To the assay mixture containing NAD^+ and ethanol was added the same amount of reagent as would be present when the reaction mixture was diluted (100-fold) into the assay mixture. After the assay mixture was stirred, unmodified enzyme in pH 8 buffer was added and the steady-state rate was determined. If the reagent did not strongly inhibit the enzyme, the activity in the control should be the same as the assay of the unmodified enzyme, but, as discussed above, several of the reagents did strongly inhibit activity. Second-order rate constants were calculated on the assumption that the reaction was bimolecular.

Amino acid analyses were performed by the usual methods.[21]

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References and Notes

(1) T.-K. Li and H. Theorell, *Acta Chem. Scand.*, **23**, 892 (1969).
(2) B. V. Plapp, "Biochemical Pharmacology of Ethanol", E. Majchrowicz, Ed., Plenum Press, New York, N.Y., 1975, pp 77–109.
(3) H. Theorell, T. Yonetani, and B. Sjöberg, *Acta Chem. Scand.*, **23**, 255 (1969).
(4) R. Dahlbom, B. R. Tolf, Å. Åkeson, G. Lundquist, and H. Theorell, *Biochem. Biophys. Res. Commun.*, **57**, 549 (1974).
(5) R. Blomstrand and H. Theorell, *Life Sci.*, **9**, 631 (1970).
(6) D. Lester and G. D. Benson, *Science*, **169**, 282 (1970).
(7) M. Reynier, *Agressologie*, 11, 401 (1970).
(8) U. Rydberg, *Biochem. Pharmacol.*, **18**, 2425 (1969).
(9) U. Rydberg and A. Neri, *Acta Pharmacol. Toxicol.*, **31**, 421 (1972).
(10) H. Theorell and T. Yonetani, *Biochem. Z.*, **338**, 537 (1963).
(11) D. C. Sogin and B. V. Plapp, *Biochemistry*, **15**, 1087 (1976).
(12) C.-I. Brändén, H. Jörnvall, H. Eklund, and B. Furugren, *Enzymes, 3rd Ed.*, 11, 103 (1975).
(13) H. Eklund, B. Nordström, E. Zeppezauer, G. Söderlund, I. Ohlsson, T. Boiwe, B.-O. Söderberg, O. Tapia, C.-I. Brändén, and Å. Åkeson, *J. Mol. Biol.*, **102**, 27 (1976).
(14) R. C. Jones, *J. Am. Chem. Soc.*, **71**, 3994 (1949).
(15) S. Taniguchi, H. Theorell, and Å. Åkeson, *Acta Chem. Scand.*, **21**, 1903 (1967).
(16) B. V. Plapp, *J. Biol. Chem.*, **245**, 1727 (1970).
(17) B. R. Baker and J. H. Jordaan, *J. Heterocycl. Chem.*, **2**, 21 (1965).
(18) J. D. Shore and M. J. Gilleland, *J. Biol. Chem.*, **245**, 3422 (1970).
(19) R. Dworschack and B. V. Plapp, *Biochemistry*, **16**, 111 (1977).
(20) W. W. Cleland, *Adv. Enzymol.*, **29**, 1 (1967).
(21) S. Moore and W. H. Stein, *Methods Enzymol.*, **6**, 819 (1963).

Quantitative Structure–Activity Relationships for Biguanides, Carbamimidates, and Bisbiguanides as Inhibitors of *Streptococcus mutans* No. 6715

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Thirty-seven compounds, including 17 biguanides, 6 carbamimidates, and 14 bisbiguanides, were evaluated for potential antiplaque activity by measuring their minimum inhibitory concentrations [MIC (M)] against *Streptococcus mutans* no. 6715. Linear regression analysis was conducted with the log 1/MIC (M) values and log P, π, σ, and MR. The best correlation for the biguanides ($r^2 = 0.92$) was obtained with log P and (log P)^2. When the biguanides were included with the carbamimidates, essentially the same correlation ($r^2 = 0.91$) was obtained with log P and (log P)^2. The best correlation for the bisbiguanides ($r^2 = 0.70$) was also obtained with log P and (log P)^2. Use of an indicator variable (I) for the bisbiguanides allowed all three groups to be included in one equation, which accounted for over 87% of the variance in the data for inhibition of bacterial growth. The results from the classical parabolic model were also compared with those from the recently developed bilinear model.

The organism *Streptococcus mutans* no. 6715 plays a major role in the formation of dental plaque. Dental plaque, in turn, is the primary cause of caries and periodontal disease.[1] One approach for the prevention of these diseases has involved the use of antibacterial agents. Chlorhexidine and its analogues have been shown to be

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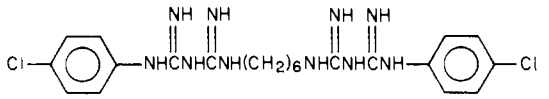
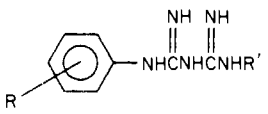


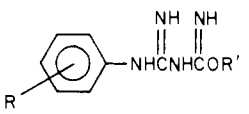
chlorhexidine

some of the most potent in vitro inhibitors of *S. mutans* no. 6715.[2-5]

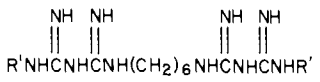
Initial studies by Gjermo et al.[6] had led to the suggestion that both biguanide residues were required for antibacterial activity against *S. mutans* no. 6715. As part of our continuing studies of antibacterial agents as potential dental-plaque inhibitors, we have synthesized and tested a series of biguanides (I),[7] carbamimidates (II),[8] and



I



II



III

bisbiguanides (III).[4,5] A preliminary study with the biguanides (**1-6**, **8**, and **10**) showed that both biguanide residues were not required for antibacterial activity against *S. mutans* no. 6715.[7] The carbamimidates were first obtained as an undesirable product during an attempt to increase the reaction yields of biguanides.[8] Since the biguanides (**1-6**, **8**, and **10**) and carbamimidates (**18** and **19**) previously prepared showed good antibacterial activity, several additional derivatives were prepared (**7**, **9**, 11–17, and **20-23**).

To delineate the structural requirements for optimal antibacterial activity, we have investigated 37 compounds as inhibitors of *S. mutans* no. 6715. The antibacterial activities were measured by determining the minimum molar concentrations of the agents required for total inhibition of bacterial growth. These are recorded as the 1/MIC (M) values in Tables I and II. Tables I and II also list the experimentally determined log P values (octanol–buffer) for certain compounds in each series and calculated log P values for the remaining compounds. The pK_a values listed in Tables I and II were used in correcting the experimental log P values for ionization. Literature values of the σ, π_R, $\pi_{R'}$, and the calculated values for fragment molar refractivity (MR_R) for the biguanides and carbamimidates are also given in Table I, while Table II contains calculated $MR_{R'}$ values in addition to log P and $\pi_{R'}$ values for the bisbiguanides.

Correlation between the logarithm of the reciprocal form of the minimum inhibitory concentration (MIC) and parameters listed in Tables I and II was attempted using Hansch analysis. In the regression equations, 1/MIC (24) represents the data obtained after 24 h of test periods, n represents the number of data points used in the regression equations, r the correlation coefficient, and s the standard deviation. The figures in parentheses are the 95% confidence intervals.

Equations 1–7 in Table III are equations obtained from compounds 1–17 in Table I. These comprise a set of biguanides designated as group I. In the single-parameter equations (eq 1–4 in Table III), the best correlation was obtained with either the partition coefficient (log P) or the fragment molar refractivity ($MR_{R'}$). Log P represents the lipophilic effects of the molecule, and $MR_{R'}$ represents the nonhydrophobic and/or steric effects of the substituent R'.[9,10] The fact that both log P and $MR_{R'}$ gave equal results was not unexpected, because of the high correlation coefficient (r^2 = 0.96, Table IV, A) existing between log P and $MR_{R'}$ for the compounds in Table I. As a result, it is difficult to differentiate these effects in the present set of compounds, although it is more likely that such effects are lipophilic or nonhydrophobic rather than steric. Such high collinearity between log P and $MR_{R'}$ has occurred most often with apolar groups,[9] as was the case of substituents R' in the present set of compounds. It was noted, however, that log P describes the structure–activity relationship better than does $MR_{R'}$ in the present study.

In a single-parameter equation, log P accounted for approximately 73% of the variance in the data: r^2 = 0.73. With the addition of a second parameter, $(\log P)^2$, over 92% of the variance in the data was accounted for (eq 4 in Table III): r^2 is 0.92.

From the two-parameter equation (eq 4 in Table III), the ideal log P was found to be 5.80 (5.28–6.86). The two-parameter eq 4 is statistically significant at the 99.5% level: $F_{1,15}$ = 35.66 for equation 4, and $F_{1,15(\alpha=0.0005)}$ = 10.80.

Electronic effects appeared to have little significance, as judged from the poor correlation between 1/MIC (24) with the electronic parameter, σ. Slightly better results were obtained with $\pi_{R'}$ in all cases (eq 5 and 7 in Table III). However, it is difficult to differentiate the effect of distribution (log P) from the effect of hydrophobic interaction ($\pi_{R'}$) at the site of R' because of the high collinearity (r^2 = 0.97) (Table IV, A) between these two variables. Good correlation was not obtained with π_R (eq 6 in Table III). Although the R' groups might be thought to be involved in the hydrophobic interaction more than the R groups (in Table III, eq 5 has a correlation coefficient of r = 0.87, while eq 6 has a correlation coefficient of r = 0.32), it would require further study to say this definitely, since there was insufficient variation in π_R values in the present set of compounds.

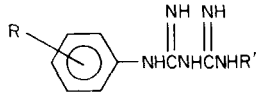
Equations 8 and 9 in Table III are derived from compounds **18-23**. This series of carbamimidates is designated as group II. Like compounds 1–17, log P gave the highest correlation coefficient in the single-parameter equations for 1/MIC (24). Although the clear differentiation between log P and $MR_{R'}$ in this series of compounds was difficult because of high collinearity (Table IV, B) between log P and $MR_{R'}$, log P appears to be a better parameter than $MR_{R'}$, accounting for 4% more variance in the data. Equation 8 is statistically significant at a 97.5% level: $F_{1,4}$ = 12.41, and $F_{1,4(\alpha=0.025)}$ = 12.22. It should be noted that the addition of the $(\log P)^2$ term to the single-parameter equation also improved the correlation.

Similarity of coefficients a and b, as well as the constant c, in groups I and II suggested that these coefficients could be combined, and regression analysis was performed on all 23 compounds. The resulting correlation equations are given in Table III (eq 10 and 11). The overall correlation equations with all 23 compounds are essentially the same as those of either group I or II.

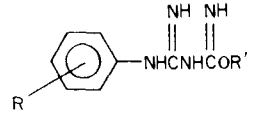
The single-parameter equations accounted for over 70% of the variance of the data, and two-parameter equations accounted for over 90% of the variance of the data (r^2 = 0.91 for eq 10 in Table III). The two-parameter eq 10 showed the ideal value of log P, which is virtually the same as those for groups I and II. Inclusion of an additional parameter such as the electronic parameter, σ, did not improve the quality of the equations already obtained.

The results of regression analysis with compounds **24-37** are in Table III (eq 12 and 13). These comprise a series of bisbiguanides designated as group III. As a single-parameter equation (eq 12 in Table III), log P accounts for 39% of the variance in the data. With the additional

Table I. Physicochemical Parameters of N^1-Aryl-N^5-Akylbiguanides and Alkyl [(4-Chlorophenyl)amino]iminomethylcarbamimidates



1-17

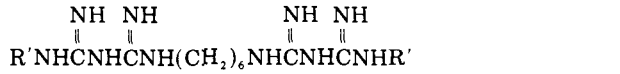


18-23

								log 1/MIC values						
								24 h						
									parabolic		bilinear		48 h:	
no.	R[a]	π_R[b]	σ[b]	R'[c]	$\pi_{R'}$	$MR_{R'}$[b]	log P[d]	obsd	calcd[h]	deviat	calcd[i]	deviat	obsd	pK_a[j]
1	4-Cl	0.70	0.23	Me	0.5	0.565	1.58[e]	3.00	2.36	0.64	2.57	0.43	3.00	10.60 (0.04)
2	4-Cl	0.70	0.23	Et	1.0	1.030	2.14[e]	3.04	3.10	−0.06	3.10	0.06	3.00	10.82 (0.06)
3	4-Cl	0.70	0.23	*i*-Pr	1.3	1.498	2.43[h]	3.04	3.45	−0.41	3.37	0.33	3.00	
4	4-Cl	0.70	0.23	*n*-Pr	1.5	1.496	2.63[e]	3.04	3.67	−0.63	3.56	0.52	3.00	10.78 (0.06)
5	4-Cl	0.70	0.23	Bu	2.0	1.959	3.13[f]	4.00	4.16	−0.16	4.02	0.02	4.00	10.78 (0.04)
6	4-Cl	0.70	0.23	hexyl	3.0	2.875	3.13[f]	5.00	4.88	0.12	4.89	0.12	5.00	
7	4-Cl	0.70	0.23	2-Et-hexyl	3.8	3.802	4.93[f]	5.40	5.22	0.18	5.32	0.09	5.40	
8	4-Cl	0.70	0.23	octyl	4.0	3.799	5.13[g]	5.22	5.17	0.05	5.35	0.13	5.22	
9	4-Cl	0.70	0.23	decyl	5.0	4.723	6.13[g]	5.10	5.31	−0.21	5.22	0.11	5.00	
10	4-Cl	0.70	0.23	dodecyl	6.0	5.647	7.13[g]	5.00	5.01	−0.01	4.88	0.12	4.70	
11	4-CH_3	0.50	−0.17	octyl	4.0	3.799	4.93[g]	5.40	5.22	0.18	5.32	0.09	5.30	
12	4-CH_3	0.50	−0.17	2-Et-hexyl	3.8	3.802	4.73[g]	5.22	5.15	0.07	5.25	0.03	5.22	
13	H	0.00	0.00	octyl	4.0	3.799	4.43[g]	5.22	5.03	0.19	5.09	0.13	5.04	
14	H	0.00	0.00	decyl	5.0	4.723	5.43[g]	5.30	5.32	−0.02	5.36	0.06	5.15	
15	3-CF_3	0.88	0.43	hexyl	3.0	2.875	4.31[g]	5.00	4.98	0.02	5.01	0.01	4.96	
16	3-CF_3	0.88	0.43	octyl	4.0	3.799	5.31[g]	5.30	5.30	0.00	5.37	0.07	5.30	
17	4-CH_3O	−0.02	−0.27	octyl	4.0	3.799	4.41[g]	5.22	5.03	0.20	5.08	0.14	5.00	
18	4-Cl	0.70	0.23	Et	1.0	1.030	2.32[e]	3.70	3.32	0.38	3.27	0.43	3.70	9.36 (0.02)
19	4-Cl	0.70	0.23	*i*-Pr	1.3	1.498	2.64[e]	3.30	3.68	−0.38	3.57	0.27	3.30	9.35 (0.04)
20	4-Cl	0.70	0.23	Bu	2.0	1.959	3.32[f]	4.15	4.32	−0.17	4.20	0.05	4.00	
21	4-Cl	0.70	0.23	hexyl	3.0	2.875	4.32[g]	5.10	4.98	0.12	5.02	0.08	5.00	
22	4-Cl	0.70	0.23	octyl	4.0	3.799	5.32[g]	5.52	5.30	0.22	5.37	0.16	5.30	
23	4-Cl	0.70	0.23	decyl	5.0	4.723	6.32[g]	5.05	5.28	−0.23	5.16	0.11	5.05	

[a] Aryl substituent. [b] Values from C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973). $MR_{R'}$ was multiplied by 0.1. [c] Alkyl substituent. [d] Corrected for ionization. [e] Experimentally determined. [f] Calculated from the experimental value of the salt. [g] Calculated from the experimental value of lower homologue. [h] Log 1/MIC calculated values were obtained from eq 11 of Table III. [i] Log 1/MIC calculated values were obtained from eq 2 of Table V. [j] pK_a values were determined at 10^{-3} M in 3:1 (water–ethanol).

Table II. Physicochemical Parameters of 1,6-Disubstituted Bisbiguanidinohexanes



					log 1/MIC values						
					24 h						
						parabolic		bilinear		48 h:	
no.	R	log P^a	$\pi_{R'}{}^b$	$MR_{R'}{}^b$	obsd	calcd[c]	deviat	calcd[d]	deviat	obsd	$pK_a{}^e$
24	4-ClC_6H_4	4.78[f]	2.67	3.036	5.30	5.33	−0.03	5.40	0.10	5.22	10.78 (0.06)
25	3-$CF_3C_6H_4$	5.12	2.84	2.935	5.52	5.41	0.11	5.42	0.10	5.22	
26	cyclohexyl	4.46	2.51	2.669	5.40	5.23	0.17	5.38	0.02	5.40	
27	adamantyl	6.04	3.30	4.063	5.00	5.56	−0.56	5.42	0.42	5.00	
28	4-$CH_3SC_6H_4$	4.58[g]	2.57	3.805	5.40	5.27	0.13	5.39	0.01	5.40	
29	4-$C_2H_5SC_6H_4$	5.58	3.07	4.267	5.70	5.50	0.20	5.42	0.28	5.70	
30	4-$C_4H_9SC_6H_4$	7.58	4.07	5.191	5.70	5.49	0.21	5.42	0.28	5.52	
31	4-$C_5H_{11}SC_6H_4$	8.58	4.57	5.653	5.52	5.25	0.27	5.42	0.10	5.30	
32	4-$C_3H_7SO_2C_6H_4$	2.10[h]	1.33	2.273	3.70	4.00	−0.30	3.69	0.02	3.70	
33	4-$C_4H_9SO_2C_6H_4$	3.10	1.83	2.735	4.70	4.63	0.07	4.78	0.08	4.52	
34	4-$C_5H_{11}SO_2C_6H_4$	4.10	2.33	3.197	5.52	5.10	0.42	5.32	0.20	5.40	
35	4-$C_6H_{13}SO_2C_6H_4$	5.10	2.83	3.659	5.40	5.41	−0.01	5.42	0.02	5.40	
36	4-$C_3H_7SC_6H_4$	6.58	3.57	4.729	5.30	5.58	−0.28	5.42	0.12	5.22	
37	2-Et-hexyl	7.04	3.80	3.824	5.15	5.56	−0.41	5.42	0.27	5.10	

[a] Calculated based on the value for chlorhexidine:[7] $\log P_{R=H} = \log P_{R=4\text{-}ClC_6H_4}$ (4.78) − $2\pi_{4\text{-}ClC_6H_5}$ (5.34) = −0.56. [b] Values from C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nakaitani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1977), or calculated by usual methods. $MR_{R'}$ was multiplied by 0.1. [c] Log 1/MIC calculated values were obtained from eq 13 of Table III. [d] Log 1/MIC calculated values were obtained from eq 3 of Table V. [e] pK_a values were determined at 10^{-3}, 3:1 water-ethanol. [f] The average difference between the log P of biguanide free bases and their salts was determined to be 2.35 2.35 ± 0.07.[7] This average difference enabled the assignment of a π value of −2.35 for the protonation of the biguanide moiety. Since chlorhexidine is dibasic, the log P of its free base was calculated from the log P of the diacetate salt (0.081) in the following manner: $\log P_{\text{free base}} = 0.081 + 2\ (2.35) = 4.78$. [g] Log $P = 2[C_6H_5\ (1.96) + SCH_3\ (0.61)] - 0.56 = 4.58$. [h] Log $P = 2[C_6H_5\ (1.96) + SO_2CH_3\ (-1.63) + C_2H_5\ (1.00)] - 0.56 = 2.10$.

Table III. Results of Regression Analysis of the Antibacterial Activity of Alkyl [(4-Chlorophenyl)amino]iminomethylcarbamimidates, N^1-Aryl-N^5-alkylbiguanides, and 1,6-Disubstituted Bisbiguanidinohexanes Using Log P, π_R, $MR_{R'}$, and σ

equation	n	s	r
1. log 1/MIC (24) = 0.552 (±0.187) log P + 2.251 (±0.846)	17	0.520	0.852
2. log 1/MIC (24) = 0.590 (±0.181) $MR_{R'}$ + 2.744 (±0.626)	17	0.482	0.874
3. log 1/MIC (24) = −1.449 (±2.503) σ + 4.835 (±0.616)	17	0.945	0.304
4. log 1/MIC (24) = 1.943 (±0.528) log P − 0.167 (±0.062) (log P)^2 − 0.291 (±1.059) ideal log P = 5.803 (5.279–6.855)	17	0.293	0.958
5. log 1/MIC (24) = 0.542 (±0.167) $\pi_{R'}$ + 2.837 (±0.603)	17	0.484	0.873
6. log 1/MIC (24) = −1.036 (±1.713) π_R + 5.211 (±1.096)	17	0.941	0.316
7. log 1/MIC (24) = 1.534 (±0.375) $\pi_{R'}$ − 0.162 (±0.059) $\pi_{R'}{}^2$ + 1.691 (±0.539) ideal $\pi_{R'}$ = 4.732 (4.219–5.762)	17	0.270	0.965
8. log 1/MIC (24) = 0.489 (±0.385) log P + 2.500 (±1.652)	6	0.488	0.870
9. log 1/MIC (24) = 2.126 (±2.700) log P − 0.192 (±0.314) (log P)^2 − 0.600 (±5.267) ideal log P = 5.55 (±∞)	6	0.374	0.945
10. log 1/MIC (24) = 0.536 (±0.148) log P + 2.316 (±0.658)	23	0.490	0.855
11. log 1/MIC (24) = 1.966 (±0.470) log P − 0.171 (±0.055) (log P)^2 − 0.322 (±0.935) ideal log P = 5.75 (5.31–6.56)	23	0.286	0.955
12. log 1/MIC (24) = 0.185 (±0.146) log P + 4.251 (±0.819)	14	0.422	0.621
13. log 1/MIC (24) = 1.038 (±0.563) log P − 0.079 (±0.051) (log P)^2 + 2.173 (±1.474) ideal log P = 6.56 (5.82–8.97)	14	0.307	0.837
14. log 1/MIC (24) = 0.401 (±0.111) log P + 2.967 (±0.547)	37	0.542	0.778
15. log 1/MIC (24) = 1.542 (±0.341) log P − 0.120 (±0.035) (log P)^2 + 0.562 (±0.788) ideal log P = 6.45 (5.98–7.23)	37	0.353	0.915
16. log 1/MIC (24) = 1.559 (±0.308) log P − 0.125 (±0.032) (log P)^2 + 0.343 (±0.234) I + 0.483 (±0.713) ideal log P = 6.24 (5.84–6.84)	37	0.318	0.934

term (log P)^2 (eq 13 in Table III), lipophilicity accounts for 70% of the variance in the data. The ideal log P value obtained from eq 13 in Table III is 6.56 (5.82–8.97). $MR_{R'}$ gave a poorer correlation in group III than in groups I and II, accounting for only 45% of the variance in the data with $MR_{R'}$ and $MR^2_{R'}$ in the equation. This suggests that the interaction involved in the antibacterial action of the compounds in these groups is hydrophobic in nature rather than polar. Differentiation between the effects of log P and π_R is again impossible because of the high collinearity between these two variables.

A summary of the coefficients a and b and the constant c of the equations of the type log 1/MIC = a (log P)^2 + b log P + c obtained in this study is given in Table V.

In a study reviewing the parabolic relationships between lipophilic character and biological activities, Hansch and Clayton[11] summarized the ranges of the values of a, b, and c for the 100 equations of interest. For convenience in analysis, they divided equations into four groups, based on the range of their log P values: group A was for log P_0 values less than 1.5; group B for log P_0 values between 1.5 and 3.0; group C was for log P_0 values between 3.0 and 5.0;

Table IV. Squared Correlation Matrix Showing the Degree of Collinearity (r^2) between the Variables Used in Correlation Analysis

	MR_R'	π_R'	π_R	σ
A. N^1-Aryl-N^5-alkylbiguanides				
log P	0.964	0.965	0.021	0.015
MR_R'		0.997	0.105	0.074
π_R'			0.108	0.070
π_R				0.620
B. Alkyl [(4-Chlorophenyl)amino]iminomethylcarbamimidates				
log P			0.996	1.000
MR_R'				0.995
C. Alkyl [(4-Chlorophenyl)amino]iminomethylcarbamimidates and N^1-Aryl-N^5-alkylbiguanides				
log P	0.964	0.965	0.021	0.015
MR_R'		0.997	0.105	0.074
π_R'			0.108	0.070
π_R				0.620
D. Alkyl [(4-Chlorophenyl)amino]iminomethylcarbamimidates, N^1-Aryl-N^5-alkylbiguanides, and 1,6-Disubstituted Bisbiguanidinohexanes				
log P	0.87	0.73	0.10	0.06
MR_R'		0.85	0.12	0.11
π_R'			0.01	0.03
π_R				0.55

and group D was for log P_0 values greater than 5.0. They discovered that, while the ranges of the coefficient b of log P within each group vary from group to group, the range of the coefficient a of the $(\log P)^2$ term within each group is essentially constant, varying only from −0.50 to −0.10 for all groups, and the constant of regression c varied significantly among groups.

Since the log P_0 values in this study are over 5, all of our groups (I–III) may be included into group D, and their coefficients may be compared with those of group D. In group D, the coefficient a ranged from −0.24 to −0.06, the coefficient b from 0.80 to 2.45, and the constant c from −3.47 to 1.37. From the 100 equations, 57 were derived from data involving bacterial systems, and it appeared that the coefficient of log P in the equation most often fell between 0.50 and 1.50.[11] From Table V, it is seen that the coefficient of $(\log P)^2$ lies between −0.08 and −0.19, log P between 1.04 and 2.13, and the constant c ranged between −0.60 and +2.17. The coefficients a and b fit into the range of the group D, indicating good agreement of this study with the previous studies. Although the coefficient b is slightly higher than the usual range of 0.50 to 1.50, there are examples having the value of the coefficient b well over 2.00. (See eq 70 and 99 in ref 11.) The large confidence intervals for the constant c in the present study make comparison with literature examples difficult.

It is noted that the coefficients of $(\log P)^2$ and log P in the bisbiguanides are about half of those in the biguanides and carbamimidates and that the constant c of bisbiguanides (group III) is more than one logarithm unit higher than in the biguanides and carbamimidates. This might suggest a difference in their intrinsic activity. An indicator variable (I)[12] assigned the value of 1.0 for the group III compounds and 0.0 for the compounds in groups I and II was used, in an effort to compensate for the difference, if any, in their intrinsic activity. The results are given in eq 14–16 in Table III. Equation 16 in Table III accounts for 87% of the variance in the data for inhibition of bacterial activity. Equation 15 is statistically significant at the 99.5% level, $F_{1,34} = 48.41$ and $F_{1,30(\alpha=0.005)} = 9.18$, and eq 16 at the 99% level, $F_{1,33} = 8.87$ and $F_{1,33(\alpha=0.01)} = 7.56$. The

Table V. Constants for Equations Derived by Regression Analysis by Bilinear and by Parabolic Models

no.	group	a	b	c	d	log $(\beta P + 1)$	n	s	r	F^a
			bilinear model: log 1/MIC (24) = a log $(\beta P + 1)$ + b log P + dI + c							
1	I	−1.285 (±0.33)	0.964 (±0.13)	0.994 (±0.48)		−4.842	17	0.227	0.977	$F_{2,13} = 32.73$
2	I + II	−1.310 (±0.30)	0.941 (±0.12)	1.085 (±0.41)		−4.907	23	0.228	0.973	$F_{2,19} = 39.04$
3	III	−1.273 (±0.47)	1.270 (±0.41)	1.042 (±1.26)		−3.459	14	0.225	0.925	$F_{2,10} = 16.15$
4	I + II + III	−1.089 (±0.20)	0.984 (±0.13)	1.060 (±0.44)	0.334 (±0.19)	−4.396	37	0.257	0.959	$F_{2,32} = 58.51$
			parabolic model: log 1/MIC (24) = a $(\log P)^2$ + b log P + dI + c							
5	I	−0.167 (±0.06)	1.943 (±0.53)	−0.291 (±1.06)			17	0.293	0.958	$F_{1,14} = 33.28$
6	I + II	−0.171 (±0.06)	1.966 (±0.47)	−0.322 (±0.94)			23	0.286	0.955	$F_{1,20} = 41.74$
7	III	−0.079 (±0.05)	1.038 (±0.56)	2.173 (±1.47)			14	0.307	0.837	$F_{1,11} = 11.56$
8	I + II + III	−0.125 (±0.03)	1.559 (±0.31)	0.483 (±0.71)	0.343 (±0.23)		37	0.318	0.934	$F_{1,33} = 8.87$

[a] $F_{2,10(\alpha=0.005)} = 9.43$; $F_{2,13(\alpha=0.005)} = 8.19$; $F_{2,19(\alpha=0.005)} = 7.09$; $F_{2,30(\alpha=0.005)} = 6.36$; $F_{1,11(\alpha=0.01)} = 9.65$; $F_{1,14(\alpha=0.005)} = 11.06$; $F_{1,20(\alpha=0.005)} = 9.94$; $F_{1,30(\alpha=0.01)} = 7.56$.

Table VI. Physical Data for the N^1-Aryl-N^3-cyanoguanidines

arylamine	react. temp, °C	react. time (h)	% yield	mp (solvent),[a] °C	formula	anal.[b]
4-$ClC_6H_4NH_2$·HCl	25	12	79.9	202–203 (A) [lit.[c] 204–205]	$C_8H_7ClN_4$	
4-$CH_3C_6H_4NH_2$·HCl	25	23	39.2	219–220 (A) [lit.[c] 211.5–212.5]	$C_9H_{10}N_4$	
$C_6H_5NH_2$·HCl	60	5	43.75	196–197 (B) [lit.[c] 198–199]	$C_8H_8N_4$	
3-$CF_3C_6H_4NH_2$·HCl	25	20.5	63.85	216–217 (A)	$C_9H_7F_3N_4$	C, H, N
4-$CH_3OC_6H_4NH_2$·HCl	60	8	68.2	190–192 (C) [lit.[c] 192]	$C_9H_{10}N_4O$	

[a] Recrystallization solvents: A = absolute ethanol; B = ethanol–water (1:1); C = 95% ethanol. [b] Within ±0.4% of theoretical value. [c] F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 729 (1946).

derivation is based on the assumption that all of the members of the groups I–III have the same mechanism of action on *S. mutans* no. 6715. The fact that similar equations can be obtained with $\pi_{R'}$ might suggest that only one biguanide group in the bisbiguanides is interacting with the receptor sites. If this is true, the likelihood of receptor interaction for a bisbiguanide molecule is twice that for a biguanide or carbamimidate. The coefficient of the indicator variable may simply reflect this statistical preference. Thus, one may expect the coefficient of the indicator variable, I, to be 0.3; if there is only one R′ group in group III, the chance that R′ will act on the receptor sites is half that of the bisbiguanides. Thus, 2/MIC rather than 1/MIC should be used in such cases:

$$\log 2/\mathrm{MIC} = \log 1/\mathrm{MIC} + \log 2 = \log 1/\mathrm{MIC} + 0.3$$

The coefficients of the indicator variable are in agreement with this value within their confidence intervals.

Tables I and II include the calculated log 1/MIC (24) values. For biguanides and carbamimidates, they were derived from eq 11 in Table III. For the bisbiguanides, they were derived from eq 13 in Table III.

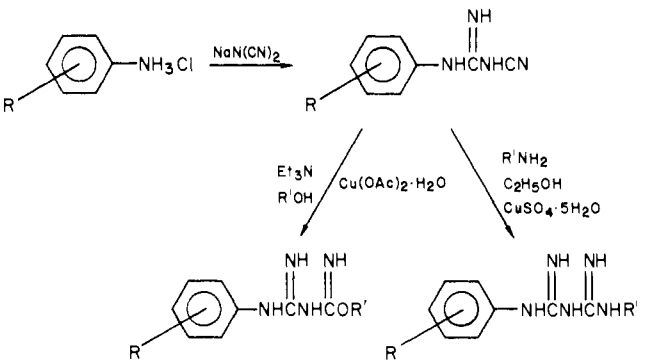
Recently, Kubinyi[13,14] developed a bilinear model[15] for the parabolic dependence of biological activity on hydrophobic character and compared it with the classic parabolic model. In this model, $-a \log (\beta P + 1) + b \log P + C$ replaces $-a (\log P)^2 + b \log P + C$. By comparing the standard deviations, correlation coefficients, F values, and the residuals resulting from the parabolic and from the bilinear models, Kubinyi suggested that the latter often gave more significant correlations than the former, if there are enough data points and if the log P values vary over a wide range.

Since we obtained parabolic relationships in the present study, it was interesting to compare these equations with the bilinear equations. Table V is the summary of the equations derived from the bilinear model analysis.[15] Equations obtained from the parabolic model are also included in the table for comparison. In all cases, the bilinear equations in the present study gave a smaller standard deviation(s) and larger correlation coefficients (r) than the corresponding equations from the parabolic model and are significant above the 99.5% level as judged by F tests. Equations obtained from the carbamimidates (group II) are not included for comparison because of the small number of the data points involved.

Tables I and II also include the calculated log 1/MIC (24) values from bilinear equations which correspond to the values obtained from the parabolic equations.

In summary, we have found a parabolic relationship between the antibacterial activity of the biguanides, carbamimidates, and bisbiguanides against *S. mutans* no. 6715 and the lipophilicity of these molecules. Both the data obtained after a 24-h test period and that obtained after a 48-h test period gave essentially the same results. The results suggest that all three groups may act by the same mechanism on the inhibition of bacterial activity of *S. mutans* no. 6715. The optimum log P value is 5.6–6.6 and the optimum $\pi_{R'}$ is 3.4–4.7 for all three groups. Further studies are needed to separate the effects of distribution from hydrophobic interaction in the mechanism of action of these compounds. $MR_{R'}$ gave a much poorer correlation in group III, while log P or $\pi_{R'}$ gave equally good correlations with all three groups. Thus, hydrophobic character rather than nonhydrophobic character due to dispersion interaction appears to be the physicochemical parameter most closely associated with the observed antibacterial activity.

Scheme I



Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. NMR (Varian Associates Model T-60 spectrometer) and IR (Perkin-Elmer Model 700 spectrometer) spectral data were in accord with assigned structures. Spectra of all compounds were recorded at 253 nm using a Beckman DB-G spectrophotometer. An Orion Research Ionanalizer Model 801 digital pH meter with a full range Corning combination electrode was used for pK_a determinations.

Compounds **28–36** were obtained as a gift from Sterling Winthrop Research Institute. Compound **24** was received from Ayerst Laboratories, Inc., and compound **37** was obtained from Reed and Carnrick. Compounds **1–6**, **8**, **10**, **18**, and **19** were prepared as previously described.[5,7,8,16]

Synthesis. The synthetic approach involved the method of Curd and Rose,[17] as outlined in Scheme I.

***N*^{1}-Aryl-*N*^{3}-cyanoguanidines.** Arylamine hydrochlorides (0.162 mol) and sodium dicyanamide (15.14 g, 0.17 mol) were dissolved in water (175 mL) and stirred. The reaction mixture was then filtered. The tan residue was crystallized, yielding white needles. Details are given in Table VI.

***N*^{1}-Aryl-*N*^{5}-alkylbiguanides (7, 9, and 11–17).** The N^1-aryl-N^3-cyanoguanidine (0.05 mol), the appropriate alkylamine (0.20 mol), ethanol (80 mL), and copper sulfate pentahydrate (6.25 g, 0.025 mol) in water (30 mL) were refluxed with stirring for 16 h. A semisolid precipitate of the copper–biguanide complex

Table VII. Physical Data for the N^1-Aryl-N^5-alkylbiguanides

compd	R	R'	mp (solvent),[a]	% yield	formula	anal.[b]
7	4-Cl	2-Et-hexyl	125–126 (A)	54.2	$C_{16}H_{26}ClN_5 \cdot C_2H_4O_2$	C, H, N
9	4-Cl	decyl	183–185 (A)	12.3	$C_{18}H_{30}ClN_5 \cdot HCl$	C, H, N
11	4-CH_3	octyl	185–186 (A)	64.2	$C_{17}H_{29}N_5 \cdot HCl$	C, H, N
12	4-CH_3	2-Et-hexyl	193.5–195 (A)	33.2	$C_{17}H_{29}N_5 \cdot HCl \cdot 0.5H_2O$	C, H, N
13	H	ocyl	158–159 (B)	43.9	$C_{16}H_{27}N_5 \cdot HCl \cdot 0.25H_2O$	C, H, N
14	H	decyl	167–168 (A)	39.7	$C_{18}H_{31}N_5 \cdot HCl$	C, H, N
15	3-CF_3	hexyl	194 (A)	44.2	$C_{15}H_{22}F_3 \cdot HCl$	C, H, N
16	3-CF_3	octyl	195–196 (A)	38.2	$C_{17}H_{26}F_3 \cdot HCl$	C, H, N
17	4-CH_3O	octyl	178–179 (B)	37.6	$C_{17}H_{29}N_5O \cdot HCl$	C, H, N

[a] Recrystallization solvents: A = methanol; B = ethanol. [b] Within ±0.4% of theoretical values.

Table VIII. Physical Data for Alkyl [(4-Chlorophenyl)amino]iminomethylcarbamimidates

compd	R	mp (solvent),[a] °C	% yield	formula[b]	anal.[c]
20	butyl	158–159	48.9	$C_{14}H_{21}ClN_4O_3$	C, H, N
21	hexyl	159	25.2	$C_{16}H_{25}ClN_4O_3$	C, H, N
22	octyl	145–146	27	$C_{18}H_{29}ClN_4O_3$	C, H, N
23	decyl	140–142	32	$C_{20}H_{33}ClN_4O_3$	C, H, N

[a] Recrystallization solvent was ethyl acetate. [b] Acetate salt. [c] Within ±0.4% of theoretical values.

formed upon the addition of water (250 mL) to the purple solution. The copper complex was destroyed upon addition of either acetic acid (15 g, 0.25 mol) or 10 N HCl (10 mL) and $Na_2S \cdot 9H_2O$ (20 g, 0.08 mol) in water (50 mL). The resulting copper sulfide was removed by vacuum filtration. The filtrate was evaporated in vacuo to ca. one third of its original volume. The filtrate was adjusted to pH 8, using concentrated NH_4OH, and allowed to stand at 4 °C. An oil separated with standing. Treatment of this oil with ether produced a waxy solid. This solid was successively triturated with water (2 × 10 mL), acetone (2 × 10 mL), and ethyl acetate (3 × 10 mL), resulting in a white powder. Crystallization from methanol or ethanol gave the desired product. Details are given in Table VII.

Alkyl [(4-Chlorophenyl)amino]iminomethylcarbamimidates 20–23. N^1-4-Chlorophenyl-N^3-cyanoguanidine (4.86 g, 0.025 mol), $Cu(OAc)_2 \cdot H_2O$ (2.5 g, 0.0125 mol), triethylamine (10 mL), and alcohol (100 mL) were heated at 75–80 °C for 12 h. The purple reaction mixture was evaporated in vacuo to yield a semisolid. Water (100 mL) was added and the remaining alcohol was removed by azeotropic distillation. An additional 100 mL of water was then added, and the insoluble copper complex was destroyed with glacial acetic acid (25 mL). Gaseous H_2S was bubbled through the mixture, and the resulting copper sulfide was removed by filtration. The filtrate was adjusted to pH 7 with concentrated NH_4OH and allowed to stand at 4 °C for 12 h. The crystals that formed were recrystallized from ethyl acetate. Details are given in Table VIII.

Antibacterial Activity. To 8.75 mL of sterile trypticase soy broth, 0.1 mL of an ethanolic solution of the acetate or hydrochloride salt of the test compound and 1.0 mL of a 50% sterile sucrose solution were added. The media were inoculated with 0.15 mL of a 24-h culture of *S. mutans* no. 6715, a pure strain of plaque-forming bacteria isolated and made available by the National Institute of Dental Research. This mixture was incubated under anaerobic conditions (BBL-Gaspak, BBL, Division of Bioquest, Cockeyville, Md.) at 37 °C. Bacterial growth was determined after 24 and 48 h spectrophotometrically, using a Coleman Jr. spectrophotometer. Once the range for 100 and 0% inhibition was established for each compound, a series of dilutions was made and each dilution was run in sets of five. The set of tubes containing the smallest amount of drug for which %T readings were above 60%T after 24 h was considered the MIC of that particular agent. Repeated determinations gave the same MIC values.

Partition Coefficients. The experimental partition coefficients for compounds 1, 2, 4, and 24 were previously reported.[7] Compounds 18 and 19 were partitioned between a 0.05 M phosphate buffer (pH 11.5) saturated with octanol and octanol saturated with phosphate buffer. Usually, 50–150-mL portions of octanol and buffer were used. In partitioning these compounds, gentle shaking for 90 min was carried out at room temperature (25 ± 5 °C). The volume ratio of these two phases and the amount of sample were chosen so that the absorbance of the sample from the buffered layer after partitioning had a value between 0.2 and 0.9, using a 1-cm cell and buffer solution as a blank. By working at a fixed pH and knowing the pK_a for these compounds, the partition coefficient (P) of the free base could be determined, using the following equation, wherein α = degree of ionization.[18]

$$P = \frac{C_{\text{octanol}}}{C_{\text{buffer}}(1 - \alpha)}$$

Determination of pK_a. The pK_a values of compounds 1, 2, 4, 5, and 24 were previously reported.[7] The pK_a values of compounds 18 and 19 were determined in duplicate by potentiometric titration. A water-jacketed 200-mL beaker connected to a circulating water bath held the temperature of the titration vessel at 25 °C. Nitrogen was bubbled through the solution to be titrated, and the buret (10 mL) was fitted with a soda lime drying tube to exclude atmospheric carbon dioxide. At least 15 aliquots (0.25 mL) of carbonate-free 0.02 N KOH were added to 100 mL of a 10^{-3} M solution of the carbamimidate in deionized distilled water–ethanol (3:1). For each addition of titrant, the pH was measured and the pK_a was calculated, using the method of Albert and Serjeant.[19]

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References and Notes

(1) I. L. Shklairin "Streptococcus Mutans and Dental Caries" Proceedings of a Round Table Discussion, May 10, 1973, National Institute of Dental Research, 1974, pp 7–13.
(2) P. Gjermo and G. Rolla, *Scand. J. Dent. Res.*, **78**, 464 (1970).
(3) H. Loe, *J. Periodont. Res.*, **8**, Suppl 12, 93 (1973).
(4) V. D. Warner, D. B. Mirth, S. S. Turesky, and I. Glickman, *J. Pharm. Sci.*, **62**, 1189 (1973).
(5) V. D. Warner, D. B. Mirth, S. S. Turesky, and I. Glickman, *J. Med. Chem.*, **16**, 732 (1973).
(6) P. Gjermo, K. L. Baastad, and G. Rolla, *J. Periodont. Res.*, **5**, 102 (1970).
(7) V. D. Warner, D. M. Lynch, and R. S. Ajemian, *J. Pharm. Sci.*, **65**, 1070 (1976).
(8) V. D. Warner and D. M. Lynch, *J. Dent. Res.*, **56**, 94 (1977).
(9) M. Yoshimoto and C. Hansch, *J. Med. Chem.*, **19**, 71 (1976).
(10) V. D. Warner, J. D. Musto, J. N. Sane, K. H. Kim, and G. L. Grunewald, *J. Med. Chem.*, **20**, 92 (1977).
(11) C. Hansch and J. M. Clayton, *J. Pharm. Sci.*, **62**, 1 (1973).

(12) C. Daniel and F. S. Wood, "Fitting Equations to Data", Wiley-Interscience, New York, N.Y., 1971, pp 55, 169, and 203.
(13) H. Kubinyi, *J. Med. Chem.*, **20**, 625 (1977).
(14) H. Kubinyi, *Arzneim-Forsch*, **26**, 1991 (1976).
(15) Further discussion on the bilinear model will be published elsewhere: K. H. Kim, C. Hansch, J. Y. Fukunaga, E. E. Steller, P. Y. C. Jow, P. N. Craig, and J. Page, submitted for publication.
(16) V. D. Warner, D. M. Lynch, C. A. Meszoely, and W. G. Dykstra, Jr., *J. Pharm. Sci.*, **66**, 418 (1977).
(17) F. H. S. Curd and F. L. Rose, *J. Chem. Soc.*, 4422 (1956).
(18) A. F. Yapel, *Adv. Chem. Ser.*, **No. 114**, 189 (1972).
(19) A. Albert and E. P. Serjeant, in "Determination of Ionization and Stability Constants", Butler and Tanner Ltd., London, England, 1962.

Quantitative Structure–Activity Relationships in 1-Aryl-2-(alkylamino)ethanol Antimalarials[1]

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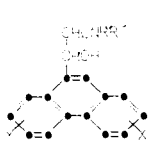
A quantitative structure–activity relationship has been formulated for 646 antimalarials acting against *P. berghei* in mice. The equation developed has 14 terms, 9 of which are indicator variables. The correlation coefficient for the QSAR is 0.898 and the standard deviation is 0.309. The antimalarials are all arylcarbinols of the type X-ArCHOHCH$_2$NR$_1$R$_2$. Sixty different aryl structures, including a variety of heterocycles, are contained in the study. The most important determinate of activity is found to be the electron-withdrawing ability of the substituents X; the hydrophobic character of X and R play less important roles. Suggestions for more potent analogues are made and the level of activity of about 100 additional analogues is also considered.

The use of quinine in the treatment of malaria constitutes one of the oldest successful examples of chemotherapy. Its replacement by synthetic drugs is a most interesting chapter in modern chemotherapy.[2]

Prior to World War II, pamaquine, quinacrine, and chloroquine were developed in Germany. The war stimulated a huge increase in research for synthetic antimalarials which has been documented by Wiselogle and Coatney;[3] this work yielded, among others, amodiaquine, primaquine, and chlorguanide. The impetus of this research was also responsible for the somewhat later development of pyrimethamine and chloroproguanide.

During the later 1940s it began to become clear that various strains of malaria were more or less resistant to many of the known drugs. Drug resistance has been confirmed in South America, Southeast Asia, Central Africa, and New Guinea. All human malaria parasites have shown drug resistance. During the period of the Vietnam war, renewed interest in drug development came about as a result of developing resistance to known drugs, resistance of mosquitoes to residual insecticides, and the inability to use insecticides under some conditions. The Walter Reed Army Institute has taken the leading role in the current effort to find more effective antimalarial drugs.

The extensive history of malaria chemotherapy has been well reviewed by Thompson and Werbel[2a] and Pinder.[2b] Our concern in this report is with compounds of types I–III



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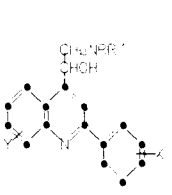
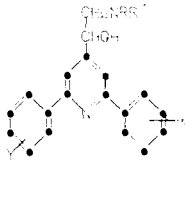


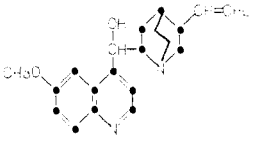
II



III

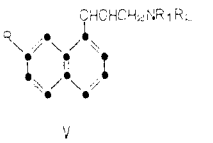
and a number of closely related congeners (see Table II).

We considered analogues of type I in a preliminary analysis[4] of the structure–activity relationship of phenanthrene carbinols. These compounds can be regarded as analogues of quinine, IV. Early efforts were made by



IV

Rabe,[5,6] Kaufmann,[7] Karrer,[8] and Ruzicka[9,10] to make quinoline analogues of quinine by replacing the quinuclidine unit with simpler structures. None of these early efforts were successful in a chemotherapeutic sense. King[11] and his co-workers produced the first quite active synthetic derivatives of type V.



V

Up to this time, chemists had not been able to break away from the conservative idea that there was something magical about the quinoline ring which was essential for antimalarial activity. May and Mosettig[12] broke out of this restricting view by showing that analogues of I were active against malaria. It was soon shown that even the simple aromatic rings such as naphthalene, benzene, and pyridine could be turned into arylcarbinols with antimalarial activity. The limits have never been reached on the kind of aromatic ring which will serve as the base for an aminocarbinol-type antimalarial.

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