drugs to be tested to see if they are influential determinents of biological activity. Even if none of the abstract factors are identified, F/A can be useful in choosing the key columns of data which encompass all independent drug-host interactions. From these key columns of data, one can predict the other columns of data for a new drug. Another asset of F/A is the potentially valuable property of examining the interrelatedness of the biological tests. From this information we can gain a greater insight into the physiological responses and the mechanisms of drug action.

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Structure–Activity Correlations of Antimalarial Compounds. 2. Phenanthreneaminoalkylcarbinol Antimalarials

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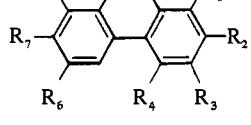
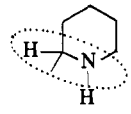
The antimalarial structure-activity relationships in a series of phenanthreneaminoalkylcarbinols have been studied by both the additivity (or Free-Wilson) and multiple parameter analysis methods. Both methods agree on a major finding: whereas the 1-octanol-water partition constants of substituents in the aromatic rings (position 1–8) correlate well with the antimalarial data, the far greater variations in partition coefficients of the aminoalkyl groups do not correlate at all with the biological data. This finding results from a multiple parameter analysis with 54 of 60 analogs for which data were available in 1970 and from additivity analyses with 43 and 28 analogs. In 1971, 47 more analogs were tested, and from a study of 102 of 107 analogs, a separation of polar and partition effects was possible. To obtain these latter results, a redetermination of the partition coefficient for 4-trifluoromethylphenoxyacetic acid was made, and the revised π value for the aromatic CF_3 group is 0.88 log P units.

In support of the increasing emphasis on the development of more effective antimalarial agents, the application of computerized regression analysis to a study of chemical structure-antimalarial activity relationships was begun in 1969 under contract with the Walter Reed Army Institute of Research.[1]

A. **Multiple Parameter Analyses.** Antimalarial test results for 60 phenanthreneaminoalkylcarbinols of structure I were examined in Sept 1970 by the multiple parameter method of analysis.[2] After converting the animal experimental data[3] to estimated ED_{50} values, log $1/C$ values were calculated, where C is the concentration of test drug in moles per kilogram of test animal. These quantitative expressions of antimalarial activity were examined by regression analyses for correlations with various combinations of the following parameters: π_{sum}, π_x, π_y, π_{x+y}, σ_x, σ_y, σ_{x+y} (see Table I footnotes for definitions). In estimating π_{sum} values, the amino side chain was treated as follows. The $-CHOHCH_2N$ moiety was assumed to be constant, and the π values for R or R_2 were used. For the 2-piperidyl group,



I

B = NHR, $N(R)_2$, or 

the encircled moiety was considered to be equivalent to the CH_2N group, and the π value for four cyclohexane methylene groups (4 × 0.42) was used. From this was subtracted 0.13 for the branching at the 2 position of the piperdine ring; thus 1.55 was used for the π contribution due to the 2-piperidyl group, 4.0 and 7.0 for N-butyl$_2$ and N-heptyl$_2$, respectively.[4]

Table I

Compd no.	Log $1/C$[a]	π_{sum}[b]	π_x[c]	π_y[d]	π_{x+y}[e]	σ_x[f]	σ_y[g]	σ_{x+y}[h]	Structure[i]	WR no.[j]
1	4.43	3.85	1.42	0.88	2.30	0.74	0.54	1.28	2,4-DI-CI,6-CF3 2-PIP	154259
2	4.36	6,60	1.72	0.88	2.60	0.62	0.54	1.16	2,3-DI-BR,6-CF3 N-BU2	164123
3	4.35	3.85	0.88	1.42	2.30	0.54	0.74	1.28	3-CF3,5,7-DI-CL 2-PIP	161072
4	4.35	6.58	1.72	0.86	2.58	0.46	0.23	0.69	1,3,6-TRI-BR N-BU2	160430[k]
5	4.29	6.30	1.42	0.88	2.30	0.46	0.54	1.00	1,3-DI-CL,6-CF3 N-BU2	150726
6	4.29	3.68	0.71	1.42	2.13	0.37	0.74	1.11	2,5,7-TRI-CL 2-PIP	157739[k]
7	4.25	3.14	0.88	0.71	1.59	0.54	0.23	0.77	3-CF3,6-CL 2-PIP	149808
8	4.24	6.60	1.72	0.88	2.60	0.78	0.54	1.32	2,4-DI-BR,6-CF3 N-BU2	164122
9	4.22	4.15	1.72	0.88	2.60	0.46	0.54	1.00	1,3-DI-BR,6-CF3 2-PIP	154983
10	4.21	3.85	1.42	0.88	2.30	0.60	0.54	1.14	2,3-DI-CL,6-CF3 2-PIP	148763
11	4.18	6.84	1.42	1.42	2.84	0.60	0.60	1.20	2,3,6,7-TETRA-CL N-BU2	169213[k]
12	4.13	3.27	0.86	0.86	1.72	0.39	0.23	0.62	2,6-DI-BR 2-PIP	149809[k]
13	4.12	3.68	1.42	0.71	2.13	0.46	0.23	0.69	1,3,6-TRI-CL 2-PIP	159216[k]
14	4.12	3.14	0.88	0.71	1.59	0.54	0.37	0.91	3-CF3.7-CL 2-PIP	157319
15	4.11	3.76	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DI-CF3 NH-BU	165543[m]
16	4.10	5.76	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DICF3 N-BU2	143803
17	4.07	3.14	0.71	0.88	1.59	0.37	0.54	0.91	2-CL,6-CF3 2-PIP	131834
18	4.07	5.74	0.86	0.88	1.74	0.39	0.54	0.93	2-BR,6-CF3 N-BU2	136912
19	4.05	3.14	0.71	0.88	1.59	0.37	0.43	0.80	2-CL,5-CF3 2-PIP	149807
20	4.03	3.85	1.42	0.88	2.30	0.46	0.54	1.00	1,3-DI-CL,6-CF3 2-PIP	146459
21	3.98	3.29	0.86	0.88	1.74	0.23	0.54	0.77	3-BR,6-CF3 2-PIP	148749
22	3.97	6.58	1.72	0.86	2.58	0.62	0.23	0.85	2,3,6-TRI-BR N-BU2	159936[k]
23	3.97	4.72	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR N-PR2	158533[l]
24	3.96	3.29	0.86	0.88	1.74	0.39	0.54	0.93	2-BR,6-CF3 2-PIP	149855
25	3.93	3.31	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DI-CF3 2-PIP	122455
26	3.92	4.76	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DI-CF3 N-PR2	145019
27	3.91	3.83	1.42	0.86	2.28	0.60	0.23	0.83	2,3-DI-CL,6-BR 2-PIP	157318[k]
28	3.88	5.59	0.88	0.71	1.59	0.54	0.23	0.77	3-CF3,6-CL N-BU2	131756
29	3.87	5.59	0.71	0.88	1.59	0.23	0.54	0.77	3-CL,6-CF3 N-BU2	102237
30	3.86	3.29	0.88	0.86	1.74	0.54	0.23	0.77	3-CF3,6-BR 2-PIP	153433
31	3.85	3.31	0.88	0.88	1.76	0.43	0.54	0.97	2,6-DI-CF3 2-PIP	136913
32	3.81	3.14	0.71	0.88	1.59	0.23	0.54	0.77	3-CL,6-CF3 2-PIP	138400
33	3.80	5.42	0.71	0.71	1.42	0.23	0.23	0.46	3,6-DI-CL N-BU2	161784[m]
34	3.80	2.71	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DI-CF3 NH-I-PR	165544[m]
35	3.78	4.76	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DI-CF3 NH-HEX	164640[m]
36	3.73	6.72	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR N-AMYL2	151313
37	3.72	6.00	1.12	0.88	2.00	0.18	0.54	0.72	3-I,6-CF3 N-BU2	148762
38	3.72	8.59	0.71	0.88	1.59	0.23	0.54	0.77	3-CL,6-CF3 N-HEPT2	101680
39	3.72	8.59	0.71	0.88	1.59	0.37	0.54	0.91	2-CL,6-CF3 N-HEPT2	125675
40	3.71	3.83	1.42	0.86	2.28	0.46	0.23	0.69	1,3-DL-CL,6-BR 2-PIP	157162[k]
41	3.69	5.59	0.71	0.88	1.59	0.37	0.54	0.91	2-CL,6-CF3 N-BU2	126927
42	3.69	7.88	0.0	0.88	0.88	0.0	0.54	0.54	6-CF3 N-HEPT2	126981
43	3.69	3.68	1.42	0.71	2.13	0.60	0.23	0.83	2,3,6-TRI-CL 2-PIP	157882[k]
44	3.66	3.79	−1.63	1.42	−0.21	0.60	0.60	1.20	2-SO2CH3 6,7-DI-CL N-BU2	167470[n]
45	3.63	5.72	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR N-BU2	151318[l]
46	3.61	3.25	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR NH-T-BU	151314[l]
47	3.55	7.86	0.0	0.86	0.86	0.0	0.23	0.23	6-BR N-HEPT2	33063
48	3.54	3.31	0.88	0.88	1.76	0.43	0.54	0.97	4,6-DI-CF3 2-PIP	144800
49	3.53	9.30	1.42	0.88	2.30	0.46	0.54	1.00	1,3-DI-CL,6-CF3 N-HEPT2	152117
50[p]	3.51	4.15	1.72	0.88	2.60	0.62	0.54	1.16	2,3-DI-BR,6-CF3 2-PIP	158474
51	3.50	2.97	0.71	0.71	1.42	0.23	0.23	0.46	3,6-DI-CL 2-PIP	148748[k]
52	3.50	7.72	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR N-HEX2	151319[l]
53	3.45	5.52	0.0	0.86	0.86	0.0	0.23	0.23	6-BR N-HEPT2-NO	133560
54	3.45	8.72	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR N-HEPT2	150256[l]
55	3.44	2.91	0.0	0.86	0.86	0.0	0.23	0.23	6-BR N-ME-2-PIPERIDYL	157081[m]
56	3.43	3.23	0.86	−1.63	−0.77	0.39	0.72	1.11	2-BR,6-SO2ME N-BU2	160938[n]
57	3.40	2.43	0.88	0.0	0.88	0.54	0.0	0.54	3-CF3 2-PIP	109824
58	3.37	2.43	0.0	0.88	0.88	0.0	0.54	0.54	6-CF3 2-PIP	126980
59	3.32	0.80	−1.63	0.88	−0.75	0.72	0.54	1.26	3-SO2ME,6-CF3 2-PIP	157237
60	3.31	3.27	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR 2-PIP	158966
61	3.29	9.00	1.12	0.88	2.00	0.18	0.54	0.72	3-I,6-CF3 N-HEPT2	149856
62	3.23	4.88	0.0	0.88	0.88	0.0	0.54	0.54	6-CF3 N-BU2	91186
63	3.23	2.41	0.0	0.86	0.86	0.0	0.23	0.23	6-BR 2-PIP	112321
64	3.23	5.72	0.86	0.86	1.72	0.0	0.23	0.23	6,10-DI-BR N-BU2	163321[o]
65[p]	3.22	5.74	0.86	0.88	1.74	0.39	0.54	0.93	4-BR,6-CF3 N-BU2	136914
66	3.22	4.41	0.0	0.86	0.86	0.0	0.23	0.23	6-BR 2-PIP-N-BU	158499[m]
67	3.17	7.36	1.68	1.68	3.36	−0.20	−0.20	−0.40	3,6-DI-T-BU N-BU2	163324[l]
68	3.13	8.74	0.86	0.88	1.74	0.23	0.54	0.77	1-BR,6-CF3 N-HEPT2	123937
69	3.12	7.88	0.88	0.0	0.88	0.54	0.0	0.54	3-CF3 N-HEPT2	105756
70	3.12	8.42	0.71	0.71	1.42	0.23	0.23	0.46	3,6-DI-CL N-HEPT2	125676[k]
71	3.09	7.71	0.71	0.0	0.71	0.37	0.0	0.37	2-CL N-HEPT2	111531[k]
72	3.09	7.71	0.0	0.71	0.71	0.0	0.37	0.37	5-CL N-HEPT2	129390[k]
73	3.08	7.14	0.0	0.14	0.14	0.0	0.06	0.06	6-F N-HEPT2	91185[k]
74	3.06	2.59	0.0	1.04	1.04	0.0	0.35	0.35	6-OCF3 2-PIP	136911[k]
75	3.05	2.93	0.88	0.50	1.38	0.54	−0.17	0.37	3-CF3,6-ME 2-PIP	152110
76	3.01	4.71	0.71	0.0	0.71	0.37	0.0	0.37	2-CL N-BU2	129388[k]

Table I *(Continued)*

Compd no.	Log $1/C^a$	$\pi_{sum}{}^b$	$\pi_x{}^c$	$\pi_y{}^d$	$\pi_{x+y}{}^e$	$\sigma_x{}^f$	$\sigma_y{}^g$	$\sigma_{x+y}{}^h$	Structure[i]	Wr no.[j]
77	2.98	7.69	0.71	−0.02	0.69	0.23	−0.27	−0.04	3-CL,6-OCH3 N-HEPT2	121499[k]
78	2.97	7.71	0.0	0.71	0.71	0.0	0.37	0.37	7-CL N-HEPT2	129394[k]
79	2.92	7.00	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-HEPT2	94197[l]
80	2.88	8.59	0.88	0.71	1.59	0.54	0.23	0.77	3-CF3,6-CL N-HEPT2	131751
81	2.83	2.05	0.0	0.50	0.50	0.0	−0.17	−0.17	6-CH3 2-PIP	150656[k]
82	2.82	4.50	0.50	0.0	0.50	−0.17	0.0	−0.17	10-ME N-BU2	158972[o]
83	2.82	7.71	0.71	0.0	0.71	0.37	0.0	0.37	4-CL N-HEPT2	106941[k]
84	2.78	4.88	0.88	0.0	0.88	0.54	0.0	0.54	3-CF3 N-BU2	90410
85	2.74	4.71	0.0	0.71	0.71	0.0	0.23	0.23	6-CL N-BU2	129391[k]
86	2.74	4.71	0.0	0.71	0.71	0.0	0.37	0.37	5-CL N-BU2	129389[k]
87	2.65	4.71	0.71	0.0	0.71	0.23	0.0	0.23	1-CL N-BU2	100351[k]
88	2.62	8.00	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-OCTYL2	94199[l]
89	2.59	7.71	0.71	0.0	0.71	0.23	0.0	0.23	3-CL N-HEPT2	5999
90	2.59	7.71	0.0	0.71	0.71	0.0	0.23	0.23	6-CL N-HEPT2	129392[k]
91	2.58	7.14	0.14	0.0	0.14	0.06	0.0	0.06	3-F N-HEPT2	88433[k]
92[p]	2.56	8.42	0.71	0.71	1.42	0.37	0.37	0.74	2,5- OR -7-DI-CL N-HEPT2	13555
93	2.56	7.71	0.71	0.0	0.71	0.23	0.0	0.23	1-CL N-HEPT2	106940[k]
94	2.56	2.26	0.71	0.0	0.71	0.37	0.0	0.37	2-CL N-PIP	138705[k]
95	2.54	4.69	0.71	−0.02	0.69	0.23	−0.27	−0.04	3-CL,6-OCH3 N-BU2	122454[k]
96	2.53	6.00	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-HEX2	94407[l]
97	2.49	4.14	0.0	0.14	0.14	0.0	0.06	0.06	6-F N-BU2	91187[k]
98	2.43	4.14	0.14	0.0	0.14	0.06	0.0	0.06	3-F N-BU2	84588[k]
99	2.41	−0.52	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-DI-2VQ	109187
100	2.37	2.40	0.0	0.0	0.0	0.0	0.0	0.0	UNSUB N-ALLYL2	98151
101	2.36	−0.70	0.0	0.0	0.0	0.0	0.0	0.0	UNSUB N(CH2CH2CH2NH2)2	122092
102[p]	2.32	4.71	0.0	0.71	0.71	0.0	0.37	0.37	7-CL N-BU2	130856[k]
103[p]	2.32	4.71	0.0	0.71	0.71	0.0	0.23	0.23	8-CL N-BU2	133561[k]
104	2.30	1.71	0.0	0.0	0.0	0.0	0.0	0.0	UNSUB N-CYHEX,CH2CH2OH	122093
105	2.27	2.04	0.0	0.0	0.0	0.0	0.0	0.0	UNSUB N-CYHEX, CYANOET	120801
106	2.24	−0.94	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-DICYANOET	102251
107	2.20	1.80	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-DIPROPARGYL	90208

[a] C represents the molar concentration (mol of drug/kg of animal) which resulted in 50% cures (see ref 7). [b] π_{sum} = sum of all substituents in positions 1-8 plus the substituents on the amino group. [c] π_x = sum of π values for all substituents in positions 1-4 of the phenanthrene ring. [d] π_y = sum of π values for all substituents in position 5-8 of the phenanthrene ring. [e] π_{x+y} = sum of π values for all substituents in positions 1-8 of the phenanthrene ring. [f] Sum of σ constants for substituents in positions 1-4 of the phenanthrene ring, based upon position 10; hence, a group at position 2 is considered to exert a meta σ effect. [g] Sum of σ constants for groups in positions 5-8, based upon position 9; hence, a group at position 6 is considered as para. [h] Sum of $\sigma_x + \sigma_y$. [i] The following abbreviations have been used: PIP = 2-piperidyl, BU2 = dibutyl, PR2 = dipropyl, I-PR = isopropyl, AMYL2 = diamyl, HEX2 = dihexyl, HEPT2 = diheptyl, T-BU = *tert*-butyl, NO = *N*-oxide, SO2ME = methylsulfonyl, OCTYL2 = dioctyl, DI-2VQ = $(CH_2CH_2COOH)_2$, CYHEX = cyclohexyl, CYANOET = cyanoethyl. [j] Number assigned by Walter Reed Army Institute of Research. [k] Compound prepared by E. A. Nodiff and coworkers, Germantown Labs., Philadelphia, Pa. 19144. [l] Compound prepared by D. W. Henry and coworkers, Stanford Research Institute, Menlo Park, Calif. 94025. [m] Compound prepared by C. C. Cheng and coworkers, Midwest Research Institute, Kansas City, Mo. 64110. [n] Compound prepared by C. L. Stevens and coworkers, Ash-Stevens, Inc., Detroit, Mich. 48202. [o] Compound prepared by D. P. Pearson and coworkers, Vanderbilt University, Nashville, Tenn. 37203. [p] Compound not used in derivation of eq 1-10.

Preliminary trials showed that no better correlations were obtained using F and R values than by using the σ constants.[5] It was also found that no reasonable correlations were obtained using Yamamoto's E_R constants.[6]

Three dissimilar equations were obtained, involving π and/or σ values for aromatic ring substituents, each of which appeared to do a reasonable job of relating physical properties to antimalarial activity. These results pointed out the need for a greater variety of aromatic ring substituents. The aromatic ring substituents (CF_3, I, Br, Cl, F, OCH_3, and, of course, H) were seen to lie essentially on a straight line (covariance correlation coefficient = 0.919) when their σ constants values were plotted against their π substituent values.[7] Thus, either π or σ values for this limited series of substituents would be expected to give similar results in correlation studies.† To escape from this bind, the study of the methylsulfonyl group, as an aromatic substituent, was suggested and three analogs were prepared; in addition, new analogs with *tert*-butyl and methyl groups on the aromatic ring positions had already been prepared, and antimalarial test results for examples of all three additional ring substituents became available and were included in the spring 1971 compilation, which totaled 107 analogs.

With the addition of the methyl sulfone, methyl, and *tert*-butyl groups, the substituents now permit a separation of polar and partition factors (covariance correlation coefficient now less than 0.2). Equations 1-10 resulted from a study of 102 analogs of type I. (Numbers in parentheses are the 95% confidence intervals for the terms above.)

To obtain these results, five out of 107 analogs were withheld from the calculations; the antimalarial activities of these five compounds were poorly predicted by all ten equations. These are compound no. 50, 65, 92, 102, and 103; they do not share any obvious structural features which would explain their lower than predicted activities. Compound 103 is the only example of an 8-substituted compound of type I in the whole series, and substitution of any type at this position may be detrimental to antimalarial activity. The other four compounds do not contain unique structural features, and the variability of biological test data offers the best tentative explanation for those discrepancies. However, 102 out of 107 analogs do fit the best

†A preliminary account of these findings was presented by P. N. Craig before the joint symposium of the American Society for Pharmacology and Experimental Therapeutics, Inc., and the Division of Medicinal Chemistry, American Chemical Society, in Burlington, Vt., on Aug 24, 1971.

	n	R	s‡	
$\log 1/C = 2.699\ (\pm 0.141) + 0.557\ (\pm 0.092)\pi_{x+y}$	102	0.768	0.395	(1)
$\log 1/C = 3.324\ (\pm 0.286) + 0.017\ (\pm 0.053)\pi_{sum}$	102	0.069	0.616	(2)
$\log 1/C = 2.721\ (\pm 0.120) + 1.218\ (\pm 0.173)\sigma_{sum}$	102	0.814	0.359	(3)
$\log 1/C = 2.522\ (\pm 0.105) + 0.327\ (\pm 0.079)\pi_{x+y} + 0.833\ (\pm 0.163)\sigma_{sum}$	102	0.894	0.278	(4)
$\log 1/C = 2.723\ (\pm 0.121) + 1.115\ (\pm 0.331)\sigma_x + 1.315\ (\pm 0.315)\sigma_y$	102	0.815	0.360	(5)
$\log 1/C = 2.666\ (\pm 0.140) + 0.728\ (\pm 0.165)\pi_y + 0.444\ (\pm 0.129)\pi_x$	102	0.783	0.386	(6)
$\log 1/C = 2.588\ (\pm 0.409) + 0.409\ (\pm 0.175)\pi_{sum} - 0.041\ (\pm 0.017)\pi^2_{sum}$	102	0.426	0.561	(7)
	[ideal π_{sum} = 5.05 (4.43-5.76)]			
$\log 1/C = 2.350\ (\pm 0.195) + 0.313\ (\pm 0.079)\pi_{x+y} + 0.134\ (\pm 0.088)\pi_{sum} - 0.015\ (\pm 0.009)\pi^2_{sum} + 0.791\ (\pm 0.157)\sigma_{sum}$	102	0.908	0.263	(8)
	[ideal π_{sum} = 4.42 (3.15-5.22]			
$\log 1/C = 2.335\ (\pm 0.194) + 0.396\ (\pm 0.134)\pi_y + 0.270\ (\pm 0.105)\pi_x + 0.654\ (\pm 0.280)\sigma_x + 0.878\ (\pm 0.269)\sigma_y + 0.137\ (\pm 0.087)\pi_{sum} - 0.015\ (\pm 0.009)\pi^2_{sum}$	102	0.913	0.258	(9)
	[ideal π_{sum} = 4.44 (3.25-5.21)]			
$\log 1/C = 2.511\ (\pm 0.105) + 0.281\ (\pm 0.106)\pi_x + 0.416\ (\pm 0.141)\pi_y + 0.724\ (\pm 0.292)\sigma_x + 0.894\ (\pm 0.286)\sigma_y$	102	0.899	0.275	(10)

equations very well; eq 8 predicts all but six of the 102 compounds used in its derivation to within less than (±) twice the standard deviation. The consistency of these data is a most impressive confirmation of the reliability of the mouse antimalarial test as used by Rane, *et al.*, at the University of Miami.

From eq 1, 3, 5, and 6, it can be seen (from both R and s values) that neither π_{x+y} or σ_{sum} alone nor $(\pi_x + \pi_y)$ or $(\sigma_x + \sigma_y)$ can account satisfactorily for the biological variability in these compounds ($R^2 = <0.70$). Equations 4 and 10, which use both partition and polar factors, do account for 80% of the variability ($R^2 = 0.81$), and when the terms for π_{sum} and π^2_{sum} are added (eq 8 and 9) the improvement in R^2, although small, is justified at greater than the 1% level, as shown by an F test. These equations (8 and 9) involve 4 and 6 independent variables but are acceptable due to the large number of compounds involved (102).[8] Consideration of eq 4 and 8, and 9 and 10, as sets, indicates that the overall partition value for the entire molecule (π_{sum}) indeed plays but a minor role in the antimalarial activity of these compounds. However, the systematic approach employed in this multiple parameter analysis does enable a determination of this role, thanks to the combination of a large number of compounds and a reliable biological test system. The optimal value for π_{sum} of about 4.4π units indicates the desirability of using the 2-piperidyl side chain, since the values for bromine, chlorine, or trifluoromethyl substituents in both aromatic rings require almost 2π units, leaving about 2.5π units for the amino substituents. Thus, the diheptyl and dibutyl substituents (7 and 4π units) would exceed this optimum π_{sum} value, with typical aromatic ring substituents.

In the preliminary work, the published value of $\pi = 1.16$ was used for the aromatic CF_3 π constant.[9] During the course of this work, the value of π (octanol-H_2O) for this important pharmacophoric group was redetermined, and the revised value of 0.88 was used in the derivation of eq 1-10.§

‡n = number of compounds, R = correlation coefficient, s = standard deviation.

§Determined by D. Nikaitani at Pomona College, 1972.

These equations, especially 8, 9, and 10, do a reasonable job of predicting activities for the methyl sulfone, methyl, and *tert*-butyl analogs. The three dissimilar equations obtained earlier from a study of 60 analogs gave conflicting predictions for these analogs; it was not until the data from the methyl sulfone compounds were available that the desired separation of polar and partition effects could be obtained. The importance of avoiding the covariance problem between the π and σ effects was shown by the addition of just one methyl sulfone analog to the original 60 compounds; this gave equations which were very similar to eq 8, 9, and 10.

The predictive use of these equations suggests that only slight improvement in the antimalarial activity of analogs in this series can be anticipated. This would be accomplished by loading the aromatic ring positions with substituents having high positive π and σ values. Since the preparation of such analogs is quite difficult, it probably is not worth trying to increase the antimalarial activity beyond the several highly active analogs already in hand. Instead, the antimalarial potential of one or more of these active analogs should be developed.

B. Additivity Analyses. Concurrently with the earlier phases of this work, additivity (Free-Wilson) analyses were run, using 43 analogs of type I. The matrix employed is presented in Table II. The methodology has been described recently in detail.[10]

This matrix contains six substituents for which only unique examples were tested and three more substituents for which only two examples were tested; hence, the *de novo* substituent constants derived for these groups are not as well defined as those for which many examples were tested. The *de novo* substituent constants found by solution of this matrix are listed in Table III.

The overall statistics of this analysis indicate that the basic concepts, those of additivity and constancy of group effects, are confirmed at better than the 1% level of significance.[11] Study of the ranges of values for the substituent constants of groups at each position shows the greatest ranges at positions 3 and 6.

A second Free-Wilson matrix was solved for the 29 analogs which contain substituents at positions 3, 6, and 9 only. The compounds used in this matrix are identified by the superscript *a* after the WR numbers listed in Table II. The

Table II

	R_1			R_2			R_3						R_4			R_6						B			
Log 1/*C*	H	Cl	BR	H	Cl	CF_3	H	F	Cl	Br	I	CF_3	H	Cl	CF_3	H	F	Cl	BR	CF_3	OCH_3	2-Pip	*N*-Bu_2	*N*-$Hept_2$	WR no.
4.21	1				1				1				1							1		1			148763
4.10	1			1								1	1							1			1		143803[a]
4.07	1				1		1						1							1		1			131834
4.03		1		1					1				1							1		1			146459
3.98	1			1						1			1							1		1			148749[a]
3.93	1			1								1	1							1		1			122455[a]
3.88	1			1								1	1					1					1		131756[a]
3.87	1			1					1				1							1			1		102237[a]
3.85	1					1	1						1							1		1			136913
3.81	1			1					1				1							1		1			138400[a]
3.72	1			1							1		1							1			1		148762[a]
3.72	1			1					1				1							1				1	101680[a]
3.72	1				1		1						1							1				1	125675
3.69	1				1		1						1							1			1		126927
3.69	1			1			1						1							1				1	126981[a]
3.55	1			1			1						1						1					1	33063[a]
3.54	1			1			1								1					1		1			144800
3.50	1			1					1				1					1				1			148748[a]
3.40	1			1								1	1			1						1			109824[a]
3.37	1			1			1						1							1		1			126980[a]
3.23	1			1			1						1							1			1		91186[a]
3.23	1			1			1						1						1			1			112321[a]
3.13			1	1			1						1							1				1	123937
3.12	1			1								1	1			1								1	105756[a]
3.12	1			1					1				1					1						1	125676[a]
3.09	1				1		1						1			1								1	111531
3.08	1			1			1						1				1							1	91185[a]
3.01	1				1		1						1			1							1		129388
2.98	1			1					1				1								1			1	121499[a]
2.92	1			1			1						1			1								1	94197[a]
2.88	1			1								1	1					1						1	131751[a]
2.82	1			1			1							1		1								1	106941
2.78	1			1								1	1			1							1		90410[a]
2.74	1			1			1						1					1					1		129391[a]
2.65		1		1			1						1			1							1		100351
2.59	1			1					1				1			1								1	5999[a]
2.59	1			1			1						1					1						1	129392[a]
2.58	1			1				1					1			1								1	88433[a]
2.56	1				1		1						1			1						1			138705
2.56		1		1			1						1			1								1	106940
2.54	1			1					1				1								1		1		122454[a]
2.49	1			1			1						1				1						1		91187[a]
2.43	1			1				1					1			1							1		84588[a]
n	39	3	1	35	7	1	22	2	10	1	1	7	41	1	1	13	2	6	2	18	2	13	13	17	

[a] Free-Wilson matrix using substituents at positions at 3, 6, and 9 only.

Table III[a]

Position	Group	No. of examples	Substituent constant	Range
R_1	Cl	3	0.130	
R_1	H	39	−0.001	
R_1	Br	1	−0.338	0.468
R_2	Cl	7	0.301	
R_2	CF_3	1	0.292	
R_2	H	35	−0.069	0.370
R_3	CF_3	7	0.384	
R_3	Br	1	0.296	
R_3	Cl	10	0.155	
R_3	I	1	0.129	
R_3	F	2	−0.193	
R_3	H	22	−0.194	0.578
R_4	Cl	1	0.273	
R_4	CF_3	1	0.043	
R_4	H	41	−0.008	0.280
R_6	CF_3	18	0.451	
R_6	Br	2	0.363	
R_6	Cl	6	−0.187	
R_6	F	2	−0.196	
R_6	H	13	−0.477	
R_6	OCH_3	2	−0.570	1.021
B	2-Piperidyl	13	0.037	
B	*N*-Bu_2	13	0.0142	
B	*N*-$Hept_2$	17	−0.056	0.093

[a] For the overall regression, $R^2 = 0.853$, $s = 0.274$, $F = 7.83$ ($F_{24,18} = 2.7$ for 1%).

Table IV[a]

Position	Group	No. of examples	Substituent constant	Range
R_3	CF_3	7	0.330	
R_3	Br	1	0.221	
R_3	I	1	0.076	
R_3	Cl	8	0.066	
R_3	H	10	−0.260	
R_3	F	2	−0.268	0.598
R_6	CF_3	10	0.460	
R_6	Br	2	0.372	
R_6	Cl	6	−0.135	
R_6	F	2	−0.175	
R_6	H	7	−0.447	
R_6	OCH_3	2	−0.526	0.986
B	2-Piperidyl	7	0.058	
B	*N*-$Hept_2$	12	0.014	
B	*N*-Bu_2	10	−0.057	0.115

[a] For the overall regression, $R^2 = 0.778$, $s = 0.330$, $F = 4.66$ ($F_{16,12} = 3.55$ for 1%).

de novo substituent constants from this run are given in Table IV. Again, the overall analysis was significant at the 1% level, confirming the validity of the basic assumptions insofar as this series of compounds is concerned.

The most striking single result from both of the Free-Wilson analyses is that there is no essential difference in the substituent constants for the three types of amino groups studied. (The values all were approximately 0, and the range is not sufficient to show any significant difference.) This is independent confirmation of the same conclusion which was obtained by the multiple parameter analysis approach (see eq 2 where the bulk of π_{sum} is contributed by the values of the dialkyl substituents on the amine nitrogen).

The practical significance of this finding can be seen when one examines the structures listed in Table I. In most cases, two or three different amino groups were studied for each new ring-substituted phenanthrene. Since both of the techniques studied show the essential equivalence of all these amino groups, as far as the animal antimalarial test is concerned, other factors such as pharmaceutical compounding, etc., in retrospect, should have led to the selection of one amino group for preparation in each new ring-substituted phenanthrene rather than preparing two or three analogs.

Table V

Group	R_3 subst const	π	σpara	R_6 subst const
CF_3	0.332	0.88	0.54	0.476
Br	0.223	0.86	0.23	0.388
Cl	0.069	0.71	0.23	−0.118
H	−0.257	0	0	−0.431
F	−0.265	0.14	0.06	−0.159
OCH_3		−0.02	−0.27	−0.510
Range	0.60			0.98

Table VI. Simple Correlation Matrix

	π	σ
R_3 subst const	0.971	0.910
R_6 subst const	0.910	0.885
π	1.00	0.919

The results shown in Tables V and VI offer independent confirmation of the conclusions arrived at from a study of eq 1-10, namely, that the σ and π values of the aromatic ring substituents can account for most of the variation in antimalarial activities for members of this series.

Study of Table V suggests that substitution in the 6 position plays a more important role than in the 3 position. This is shown by comparison of the ranges for the *de novo* substituent constants at these positions; the difference of almost 0.4 log $1/C$ units suggests this is a real effect. This same point arises from a comparison of the coefficients in eq 5, 6, 9, and 10, obtained by the multiple parameter method.

Additional information is gained when the *de novo* substituent constants from the second F-W run are ranked and compared with the π and σ values for these groups (Table V). Obvious correlations exist between these constants, as shown in Table VI.

This study represents the largest number of closely related analogs for which the identical biological test data are known, which has been studied by these two methods of structure-activity correlation. Although Cammarata has shown how the two methods can be interrelated theoretically,[12] there are real differences which exist in these approaches. They give different quantitative results, and, more importantly, they have differing requirements for application. The agreement between the major conclusions arrived at in these studies is impressive confirmation that they both are applicable to this large set of data.

In retrospect, the careful selection of aromatic ring substituents, coupled with the application of either method of structure-activity analysis, applied earlier in the course of this synthetic program, could have led to the same knowledge concerning the structure-activity relationships with the preparation of perhaps one-half of the analogs actually prepared. This point cannot be overemphasized; one should apply these techniques as early as possible in the planning phases of a large synthetic program.

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Compounds Affecting the Central Nervous System. 3.[1] 3β-Phenyltropan-2-ols

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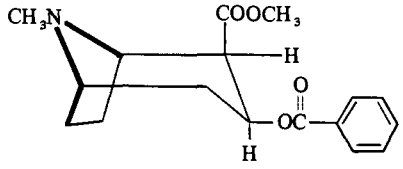
A group of 3β-phenyltropanes bearing both axial and equatorial hydroxyl and acetoxyl groups at C-2 was prepared. The ability of these compounds to prevent and reverse reserpine-induced ptosis in mice and their effects on overt behavior are reported. The modification having a 2β-hydroxyl group appeared to be at least as active as cocaine in the reserpine-induced ptosis screen and a more active stimulant. The optical antipodes of the more interesting compounds were prepared by resolving (±)-3-phenyltropidine. (±)-8a appears to be more active than the active enantiomer (−)-8a but no explanation is apparent. The ethylene bridge of the tropane structure was found necessary for activity.

The structure of cocaine (**1**) has been modified in a continued effort to obtain a variation of this molecule that would be a useful stimulant or antidepressant. This paper concerns that modification wherein a phenyl group is attached directly to the 3β position of the tropane ring and the 2β-carbomethoxy group is replaced by hydroxyl or acetoxyl in either the α or β configuration.



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Shortly after we prepared the compound with the 2α-hydroxyl configuration (**2a**), Lyle, *et al.*,[2] reported the synthesis of the same compound, but without biological data, by a similar procedure. Treatment of this 2α-hydroxy compound **2a** with ethyl chloroformate followed by saponification of the 2α-carbonate **4** afforded the α-hydroxyurethane **5a**. An alternate approach to **5a** was through the 2α-acetate **3a**,[3] prepared in our hands by the Ac_2O–pyridine method.† The acetate **3a** was converted to the urethane **6a** which was saponified to give the α-hydroxyurethane **5a**. The 2-ketourethane **7a**, obtained by Jones oxidation of **5a**, was reduced with $LiAlH_4$ to afford 3β-phenyltropan-2β-ol (**8a**, 30%), 3β-phenyltropan-2α-ol (**2a**, 31%), and a third 3-phenyltropan-2-ol (9%) which we speculate has the 3α-phenyl structure **9a**. The axial 2β-alcohol **8a** had a band in its ir spectrum at 3455 cm^{-1} that persisted even on dilution to a 0.001 *M* concentration, a characteristic of expected intramolecular hydrogen bonding with nitrogen.[4] Acetylation of **8a** with Ac_2O–pyridine afforded the 3β-acetate **10** (Scheme I).

Similarly **2b** was converted to the 2α-acetate **3b**.† Treatment of **3b** with methyl chloroformate afforded the urethane **6b** which was saponified to give **5b**. Jones oxidation followed by $LiAlH_4$ reduction gave equal amounts of the equatorial 2α-alcohol **2b** and the axial 2β-alcohol **8b**. We did not try to isolate the isomer **9b**. The axial 2β-alcohol **8b** had a band in its ir spectrum at 3450 cm^{-1} that persisted even on dilution to a 0.001 *M* concentration.

In order to gain insight into the role which chirality plays in this biological activity, the optical antipodes of **3a** and **8a** were prepared. 3-Phenyltropidine[5] was resolved by means of its bitartrate salt and the resulting enantiomers were hydroborated using Lyle's[2] method to give (+)- and (−)-**2a**. These alcohols were then converted to (+)- and (−)-**3a** and -**8a** by the procedures described above. *trans*-1-Ethyl-4-phenyl-3-piperidinol acetate (**11**), a nonrigid analog of **3a**, was prepared in order to relate rigidity factors with activity.

Biological Results. The compounds reported were evaluated by means of the reserpine-induced eyelid ptosis screen in mice[6] and by observation of overt behavioral changes (see Table I). Cocaine was included in the study for comparative purposes.

In the ptosis prevention test, only compound (±)-**8a** showed activity, being perhaps slightly more active than cocaine. In the ptosis reversal test, compounds (±)-**8a** and (±)-**3a** were quite active; (±)-**2a** and (±)-**8b** were minimally active. It is interesting that conversion of the 2-equatorial hydroxyl of (±)-**2a** to the axial configuration (±)-**8a** resulted in a substantial increase in activity in the ptosis reversal test. Acetylation of this axial isomer [forming (±)-**10**] produced a drop in this activity. In sharp contrast, acetylation of the equatorial isomer (±)-**2a** caused an increase in ptosis reversal activity. Introduction of a *p*-methoxyl group into the aromatic ring of (±)-**3a** lowered its activity [see (±)-**3b**].

The signs of overt stimulation paralleled the results of the ptosis screen, with indications that stimulation lasted as long as 3 hr with (±)-**8a** and (±)-**10**. (±)-**3a** and (±)-**8a** appear to be more stimulative than cocaine.

Study of the optical antipodes of **3a** and **8a** revealed that only one enantiomer of each was active. These active enantiomers [(+)-**3a** and (−)-**8a**] differ in actual sign of optical rotation but belong to the same absolute configurational

†Ellefson[3] reported failure in the preparation of 2α-acetates **3a** and **3b** using Ac_2O; it required ketene. He reported mp 65–75° (petroleum ether) for **3a**, mp 236.5–239° for **3a** HBr salt, and mp 88–92° for **3b**. We found mp 72–74° (pentane) for **3a**, mp 259–261° for **3a** HBr salt, and mp 100–102° (pentane) for **3b**.