#### Phenanthreneaminoalkylcarbinol Antimalarials

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

Paul N. Craig\*

Craig Chemical Consulting Services, Inc., Ambler, Pennsylvania 19002

#### and Corwin H. Hansch

Department of Chemistry, Pomona College, Claremont, California 91711. Received November 27, 1972

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 l-octanol-water partition constants of substituents in the aromatic rings (position 1-8) correlate well with the antimalarial data, the far greater variations in partiion 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  $\pi$  value for the aromatic CF<sub>3</sub> 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.<sup>1</sup>

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.<sup>2</sup> After converting the animal experimental data<sup>3</sup> to estimated ED<sub>50</sub> 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:  $\pi_{sum}$ ,  $\pi_x$ ,  $\pi_y$ ,  $\pi_{x+y}$ ,  $\sigma_x$ ,  $\sigma_y$ ,  $\sigma_{x+y}$  (see Table I footnotes for definitions). In estimating  $\pi_{sum}$  values, the amino side chain was treated as follows. The -CHOHCH<sub>2</sub>N moiety was assumed to be constant, and the  $\pi$  values for R or R<sub>2</sub> were used. For the 2-piperidyl group,



the encircled moiety was considered to be equivalent to the CH<sub>2</sub>N group, and the  $\pi$  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  $\pi$  contribution due to the 2-piperidyl group, 4.0 and 7.0 for N-butyl<sub>2</sub> and Nheptyl<sub>2</sub>, respectively.<sup>4</sup>

Tabla	
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nb.   Log  /C*   max   max   max   max   max   max   max     1   44.3   4.36   6.40   1.72   0.88   2.00   0.44   1.16   2.3D18R,GCT3 NBU2   164123     3   4.35   6.35   0.58   0.44   0.25   0.54   0.17   1.273,7.D1C.2PTP   164123     4   4.43   6.60   1.73   0.66   0.33   0.67   1.573,7.D1C.2PTP   167739K     6   4.23   6.60   1.72   0.88   2.60   0.73   0.573,7.D1C.2PTP   167739K     7   4.25   1.41   0.88   0.71   1.579,0.64   1.33   1.47,0.18,0.273,7.D1C.12717   167334     8   4.24   6.60   0.73   0.54   0.23   0.673   1.37,67174.672,0.2717   167334     11   4.16   6.34   0.172   0.39   0.23   0.662   1.35,717474.721   169334     12   4.13   0.76   0.88   0.14   0.03	Compd										
1   4.43   3.84   1.42   0.88   2.00   0.62   0.64   1.18   2.4D4BR,CC3 N=012   1644.23     3   4.33   3.85   0.88   1.42   2.30   0.64   0.74   0.84   0.20   0.67   0.84   2.3D4BR,CC3 N=012   1604.30     4   4.33   5.85   0.46   0.23   0.77   0.84   1.30   0.64   0.14   1.25D4LC4,CC3 N=012   1604.30     7   4.23   5.44   0.64   0.023   0.77   3.675.3C4/23 P=11   1697.26     9   4.21   5.14   0.88   0.71   0.58   0.60   0.54   1.32   2.4D4BR,C73 P=11   1699.26     9   4.21   3.48   0.47   0.88   0.71   0.13   0.14   2.3D4BR,C73 P=11   1699.26     12   4.13   1.42   3.68   0.71   2.13   0.46   0.23   0.67   1.35   0.74   0.84   0.23   0.67   1.35   0.74   0.84   0.74 </td <td>no.</td> <td><math>\log 1/C^a</math></td> <td><math>\pi_{sum}^{b}</math></td> <td><math>\pi_x^c</math></td> <td><math>\pi_y^d</math></td> <td><math>\pi_{x+y}^{e}</math></td> <td><math>\sigma_{x}^{f}</math></td> <td><math>\sigma_y^g</math></td> <td><math>\sigma_{x+y}^{h}</math></td> <td>Structure<sup>i</sup></td> <td>WR no.<sup>j</sup></td>	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 <sup>i</sup>	WR no. <sup>j</sup>
2   4:36   6:60   1:72   0:88   2:50   0:62   0:54   1:16   2:50*/10*K, CF3*NEU2   164132     4   4:33   6:38   1:42   0:86   2:38   0:46   0:23   0:69   1:36*CF3*NEU2   150*278   160430     7   4:25   5:14   0:88   2:38   0:46   0:23   0:67   1:57*16*CF3*NEU2   160430     8   4:24   6:06   1:72   0:88   2:60   0:78   0:54   0:32   2:4D*18*K, CF3 NEU2   164122     9   4:22   4:15   1:72   0:88   2:60   0:78   0:54   0:52   2:4D*18*K, CF3 NEU2   164122     9   4:22   4:16   1:44   0:84   0:71   1:59   0:54   0:37   0:62   2:4D*18*K, CF3 NEU2   169213*     11   4:13   3:44   0:84   0:37   0:43   0:37   0:43   0:38   1:47   0:39   2:40*17   1:30*12     12   4:16   3:54	1	4 4 3	3.85	1.4.2	0.88	2 30	0.74	0.54	1 28	2 4-DI-CI 6-CF3 2-PIP	154259
3   4.35   3.82   0.68   1.42   2.30   0.54   0.74   1.28   3.267.5.20.7CL 2.PP   16072     4   4.35   6.58   1.42   0.88   2.30   0.46   0.23   0.67   1.35.7TB/LEX   150739     7   4.23   5.64   0.17   1.42   0.88   2.00   0.46   0.54   1.00   1.35.7TB/LCL 2.PP   157739     7   4.24   6.60   1.27   0.88   2.60   0.46   0.54   1.32   2.40.19R, ACT3 APR   164923     9   4.22   4.15   1.42   0.48   2.00   0.46   0.54   1.01   1.30-BR, CT3 APR   1649218     11   4.18   6.84   1.42   1.48   0.48   0.71   1.13   0.46   0.37   0.57   1.35.75.02.278   1.47   1.43   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44   1.44	2	4.36	6.60	1 72	0.88	2.50	0.74	0.54	1 16	2 3-DI-BR 6-CF3 N-BU2	164123
4   435   6.58   1.72   0.86   2.58   0.64   0.02   1.36/CHLOR NAU2   150/26     6   4.29   3.68   0.71   1.42   2.13   0.64   0.54   1.10   1.3D/CLACCT 3NEU2   150/26     7   4.33   3.14   0.86   0.71   1.52   0.72   0.71   1.11   2.57/THECL 2PTP   157/39F     7   4.33   1.14   1.8   0.84   1.42   0.88   2.60   0.64   0.54   1.11   2.57/THECL 2PTP   154983     10   4.21   3.34   1.42   0.88   1.26   0.66   0.54   1.12   2.16/THER ACL NEU   165/317     11   4.18   6.44   1.42   3.44   0.88   0.75   0.54   0.91   3.6D/CT3 NEU2   163/37     12   4.13   3.67   0.54   0.91   3.6D/CT3 NEU2   163/37     13   14   1.85   0.71   0.88   1.76   0.54   0.92   0.86/CT3 NEU2 <td>3</td> <td>4.35</td> <td>3,85</td> <td>0.88</td> <td>1.42</td> <td>2.30</td> <td>0.54</td> <td>0.74</td> <td>1.10</td> <td>3-CF3.5 7-DI-CL 2-PIP</td> <td>161072</td>	3	4.35	3,85	0.88	1.42	2.30	0.54	0.74	1.10	3-CF3.5 7-DI-CL 2-PIP	161072
s   4:29   6:30   1:42   0:88   2:30   0:46   0:34   1:30   1:50/10.2.6CT 3:NEU2   1:57739*     7   4:25   3:14   0:88   0:71   1:59   0:54   0:23   0:77   3CT;6,6CL 2:PTP   1:490.02   1:641223     9   4:24   1:84   1:42   0:88   2:00   0:60   0:54   1:14   1:250.01   1:641223     9   4:22   1:86   1:44   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:44   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:42   1:43   1:44   1:44   1:44   1:44   1:44   1:44   1:44   1:44   1:44   1:44   1:44   1:44   1:43   1:44   1:43   1:46   1:44   1:43   1:45   1:43   1:45   1:44	4	4.35	6.58	1 72	0.86	2.58	0.46	0.23	0.69	1 3 6-TRI-BR N-BU2	160430k
6   4.29   1.68   0.71   1.42   2.13   0.37   0.74   0.23   0.77   0.76   0.88   0.77   0.74   0.88   0.77   0.54   0.03   0.27   0.77   1.71   0.88   1.76   0.24   0.25   0.77   1.71   0.88   1.76   0.24   0.24   0.27   0.77   1.71   0.88   1.76   0.24   0.	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
7 4.25 3.14 0.88 0.71 1.59 0.54 0.23 0.77 5/73 <t< td=""><td>6</td><td>4.29</td><td>3.68</td><td>0.71</td><td>1.42</td><td>2.13</td><td>0.37</td><td>0.74</td><td>1.11</td><td>2.5.7-TRI-CL 2-PIP</td><td>157739k</td></t<>	6	4.29	3.68	0.71	1.42	2.13	0.37	0.74	1.11	2.5.7-TRI-CL 2-PIP	157739k
8   4.24   6.60   1.72   0.88   2.60   0.64   1.32   2.40   1.80   1.36   1.30   1.36   1.36   1.30   1.36   1.36   1.36   1.36   1.36   1.36   1.36   1.36   1.36   1.36   1.37   1.36   1.37   1.36   1.36   1.37   1.36   1.37   1.36   1.36   1.37   1.36   1.37   1.36   1.37   1.36   1.37   1.36   1.37   1.36   1.37   1.36   1.37   1.36   1.36   1.37   1.37   1.36   1.36   1.37   1.37   1.36   1.37   1.37   1.36   1.37   1.37   1.	7	4.25	3.14	0.88	0.71	1.59	0.54	0.23	0.77	3-CF3.6-CL 2-PIP	149808
9   4.22   4.15   1.72   0.88   2.60   0.64   0.54   1.10   1.3D-IRR.GCT3 2.PIP   154983     11   4.18   6.54   1.14   2.3D-IRG.GCT3 2.PIP   148763     12   4.13   3.27   0.80   0.56   1.30   0.26   1.26   1.25   0.44   0.23   0.62   2.60 ILR.PT   113484     14   4.12   3.14   0.88   0.88   1.76   0.54   0.54   1.08   3.60 ICT3 NH2U   165343"     15   4.11   3.76   0.88   0.88   1.76   0.54   0.54   0.91   2.CL_6.CT3 N-BU2   143834     16   4.10   5.76   0.88   1.76   0.54   0.91   2.CL_5.CT3 N-BU2   14384     18   4.07   5.74   0.86   0.88   1.76   0.44   0.03   2.2L_5.CT3 N-BU2   14383     19   4.03   3.14   0.71   0.88   1.76   0.44   0.39   2.2L_5.CT3 N-BU2   1438925	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
10   4.21   3.85   1.42   1.42   2.84   0.66   0.64   1.14   2.30,CT_ECTRACL NBU2   148763     12   4.13   3.27   0.86   0.86   1.72   0.59   0.23   0.62   2.6.01-RR 24P   145604     13   4.12   3.66   1.43   0.71   0.86   0.81   0.71   0.81   0.81   0.71   0.81	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
11 4.18 6.64 1.42 2.84 0.60 0.60 1.20 2.3,6,7,12TRA-CL NBU2 169213*   12 4.13 3.27 0.58 0.86 0.71 2.13 0.46 0.33 0.09 1.3,6,TRKCL 2-PTP 159216*   14 4.12 3.16 0.58 0.71 0.54 0.54 0.54 1.05 3.62 0.71 1.57 <td>10</td> <td>4.21</td> <td>3.85</td> <td>1.42</td> <td>0.88</td> <td>2.30</td> <td>0.60</td> <td>0.54</td> <td>1.14</td> <td>2,3-DI-CL,6-CF3 2-PIP</td> <td>148763</td>	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 <i>k</i>
13 4.12 3.64 0.42 0.71 2.13 0.46 0.23 0.69 1.3,6-TRL(CL_2PIP 1592164   15 4.11 3.76 0.88 0.77 0.54 0.34 1.08 3.6-DLCT3 NFBU2 1653439   16 4.07 5.74 0.86 0.88 1.76 0.54 0.91 3.6-DLCT3 NFBU2 143893   17 4.07 5.74 0.86 0.88 1.79 0.53 0.64 0.93 2.9R, G-CT3 NFBU2 136912   19 4.03 3.85 1.42 0.88 2.30 0.46 0.54 1.00 1.3DLCL, G-CT3 2PIP 149807   21 3.93 0.56 0.88 1.74 0.32 0.34 0.03 2.3,6-TR+BR N-RU2 1599364   23 3.31 0.86 0.88 1.74 0.39 0.34 0.93 2.2,6-CT3 N-PL 149835   24 3.66 3.29 0.66 0.88 1.76 0.34 0.93 2.2,6-CT3 N-PL2 149353   25 3.33 0.88 0.88 1.76 0.34<	12	4.13	3.27	0.86	0.86	1.72	0.39	0.23	0.62	2,6-DI-BR 2-PIP	149809 <sup>k</sup>
14 4.12 3.14 0.88 0.88 1.76 0.54 0.37 0.91 3-CF3.7CL 2-PP 15719   15 4.10 5.76 0.88 0.88 1.76 0.54 0.54 1.08 3-DCT3 NHAU 1655437   17 4.00 3.14 0.71 0.88 1.59 0.37 0.43 0.91 2-CL_5CT3 2-PIP 149807   18 4.05 3.14 0.71 0.88 1.59 0.37 0.43 0.80 2-CL_5CT3 2-PIP 149807   20 4.03 3.85 1.42 0.88 1.74 0.32 0.54 0.77 3-BC-CF3 2-PIP 149807   21 3.95 6.32.9 0.66 0.88 1.74 0.39 0.54 0.53 3-6CF3 2-PIP 149837   22 3.93 3.31 0.86 0.88 1.76 0.54 0.54 1.08 3-6DFCT3 2-PIP 149835   25 3.93 3.31 0.88 0.88 1.76 0.54 0.54 0.64 0.52 3-6DFCT3 2-PIP 149435   26 </td <td>13</td> <td>4.12</td> <td>3.68</td> <td>1.42</td> <td>0.71</td> <td>2.13</td> <td>0.46</td> <td>0.23</td> <td>0.69</td> <td>1,3,6-TRI-CL 2-PIP</td> <td>159216<sup>k</sup></td>	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 <sup>k</sup>
	14	4.12	3.14	0.88	0.71	1.59	0.54	0.37	0.91	3-CF3.7-CL 2-PIP	157319
16   4.10   5.76   0.88   0.76   0.54   1.08   3.6DCF3 3-MU2   143833     17   4.07   3.14   0.31   0.54   0.35   0.31   2.54   CF3 3-MU2   131834     18   4.03   5.74   0.56   0.35   0.35   0.31   2.56   CF3 3-MU2   131834     21   3.98   3.29   0.46   0.88   1.74   0.32   0.54   0.07   3.56   CF3 3-MP1   146459     21   3.95   0.56   0.88   1.74   0.32   0.54   0.77   3.56 DCT3 3-MP1   149749     23   3.97   4.72   0.66   0.88   1.76   0.54   0.54   0.05   3.56 DCT3 3-MP1   124855     26   3.92   4.76   0.88   0.88   1.76   0.54   0.54   0.68   3.6DCT3 3-MP1   12383     27   3.31   3.83   1.42   0.86   0.23   0.23   0.24CT3 3-MP1   123183     313<	15	4.11	3.76	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DI-CF3 NH-BU	16554 <i>3m</i>
$  \begin{array}{ccccccccccccccccccccccccccccccccccc$	16	4.10	5.76	0.88	0.88	1.76	0.54	0.54	1.08	3,6-DICF3 N-BU2	143803
18   4.07   5.74   0.88   1.74   0.39   0.54   0.93   248.6-57.3 PHP   149000     20   4.03   3.85   1.42   0.88   2.50   0.46   0.54   1.00   1.51PCL.6-CT3 PHP   149000     21   3.39   3.42   0.86   0.88   2.53   0.64   0.54   1.00   1.51PCL.6-CT3 PHP   149000     21   3.397   4.42   0.86   0.88   1.72   0.23   0.24   3.64   3.64   3.64   3.64   3.64   3.64   3.64   3.64   3.64   3.64   3.64   1.64   1.68   3.66DCT3 PHP   149855     26   3.92   4.76   0.88   0.88   1.76   0.54   0.23   0.77   3.62DCT3 PHP   12450     27   3.91   3.83   1.42   0.88   1.76   0.44   0.54   0.77   3.62CT3.6BR 2.PHP   153433     31   3.85   3.31   0.88   0.88   1.76   0.44 <t< td=""><td>17</td><td>4.07</td><td>3.14</td><td>0.71</td><td>0.88</td><td>1.59</td><td>0.37</td><td>0.54</td><td>0.91</td><td>2-CL,6-CF3 2-PIP</td><td>131834</td></t<>	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
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	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
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	21	3.98	3.29	0.86	0.88	1.74	0.23	0.54	0.77	3-BR,6-CF3 2-PIP	148/49
24 3.9 1 1/2 0.23 0.46 3.6-DJCRN+TRZ 120335   25 3.93 3.31 0.86 0.88 1.76 0.39 0.34 1.08 3.6-DJCT3 PJP 129455   26 3.92 4.76 0.88 0.88 1.76 0.34 0.34 1.08 3.6-DJCT3 NPL2 145057   27 3.91 3.83 1.42 0.86 2.28 0.60 0.23 0.83 2.3-DJCLC,BR ZPIP 157118   28 3.88 5.59 0.88 0.86 1.74 0.54 0.23 0.77 3-CC3-CLB SPLP 13913   30 3.86 3.29 0.88 0.88 1.76 0.44 0.54 0.97 2.6-DLC3 NPLP 13913   31 3.80 5.42 0.71 0.71 0.71 0.72 0.54 0.64 1.08 3.6-DLC3 NPLP 139403   33 3.80 5.42 0.71 0.88 1.59 0.23 0.54 0.46 3.6-DLC3 NPLP 139403   33 3.80 2.72 6.59	22	3.97	6.58	1.72	0.86	2.58	0.62	0.23	0.85	2,3,6-1 KI-BK N-BU2	159530*
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	23	3.97	4.72	0.86	0.86	1.72	0.23	0.23	0.46	3,0-DI-BK N-PK2	138333
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	24	3.96	3.29	0.86	0.88	1.74	0.39	0.54	0.93	2-BR, 6-CF 3 2-PIP	149833
20   3.9.2   4.7.6   0.38   0.38   1.7.6   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.34   0.35 <t< td=""><td>25</td><td>3.93</td><td>3.31</td><td>0.88</td><td>0.88</td><td>1.76</td><td>0.54</td><td>0.54</td><td>1.08</td><td>3,0-DI-CF3 2-PIP</td><td>122433</td></t<>	25	3.93	3.31	0.88	0.88	1.76	0.54	0.54	1.08	3,0-DI-CF3 2-PIP	122433
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	20	3.92	4./0	0.88	0.88	1.70	0.54	0.34	1.08	3,0-DI-CF 3 N-FK2	143019 157319k
20   3.86   0.33   0.81   0.39   0.11   1.39   0.43   0.44   0.45   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.47   3.46   0.46   0.47   3.46   0.47   3.46   0	27	2.91	5.85	1.42	0.00	2.20	0.60	0.25	0.83	2,5-DI-CL,0-BK 2-FIF	131756
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	20	2.00	5.59	0.00	0.71	1.59	0.34	0.25	0.77	3-CL 6-CE2 N-BU2	102237
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	29	3.07	2.39	0.71	0.00	1.39	0.23	0.34	0.77	3-CE3 6-BP 2-DID	153433
31   3.63   3.64   0.71   3.67   0.77   3.67   5.77   5	21	3.80	3.29	0.00	0.80	1.74	0.34	0.23	0.77	2 6-DLCE3 2-PIP	136913
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	22	2.05	3.31	0.88	0.00	1.70	0.73	0.54	0.77	3-CL 6-CF3 2-PIP	138400
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	32	3.80	5 4 2	0.71	0.00	1.39	0.23	0.34	0.46	3 6-DI-CL N-BU2	161784m
35   3.78   4.76   0.80   1.76   0.54   1.08   3.6 DLCT3 NH-HEX   144400     36   3.73   6.72   0.86   0.86   1.72   0.23   0.23   0.46   3.6 DLB NH-HEX   144400     37   3.72   6.00   1.12   0.88   0.20   0.18   0.54   0.77   3.16 C-T3 NHLPT2   125675     38   3.72   8.59   0.71   0.88   1.59   0.37   0.54   0.91   2.CL, 6-CT3 N-HLPT2   125675     40   3.71   3.83   1.42   0.86   2.28   0.46   0.91   2.CL, C-F3 N-HLPT2   125675     41   3.66   5.9   0.71   0.88   0.89   0.80   0.80   0.83   2.36 C-T3 N-HLPT2   125675     42   3.69   0.68   1.42   0.60   0.50   0.23   0.623   0.623   0.83   2.36 C-T3 N-HEY12   125782/L     43   3.65   5.72   0.86   0.86   1.72   0.23	33	3.80	271	0.71	0.71	1.76	0.23	0.23	1.08	3 6-DI-CF3 NH-I-PR	165544m
363.736.730.000.000.000.000.010.020.020.020.020.020.020.020.010.020.010.020.010.020.010.020.010.020.010.020.010.020.010.020.010.020.010.020.010.020.010.020.0	35	3.78	476	0.88	0.88	1.76	0.54	0.54	1.00	3 6-DI-CF3 NH-HEX	164640m
37 $5.72$ $6.60$ $1.12$ $0.88$ $2.00$ $0.18$ $0.54$ $0.72$ $31,6-F3$ $3102$ $148762$ 38 $3.72$ $8.59$ $0.71$ $0.88$ $1.59$ $0.23$ $0.54$ $0.77$ $3-CL,6-CF3$ $N+EPT2$ $10680$ 39 $3.72$ $8.59$ $0.71$ $0.88$ $1.59$ $0.37$ $0.54$ $0.91$ $2-CL,6-CF3$ $N+EPT2$ $10560$ 40 $3.71$ $3.83$ $1.42$ $0.86$ $2.28$ $0.46$ $0.23$ $0.69$ $1.3-DL-CL,6+R$ $2-PIP$ $157162x^{1}$ 41 $3.69$ $5.8$ $1.42$ $0.88$ $0.88$ $0.0$ $0.54$ $0.54$ $0.54$ $0.571-CL-P1P$ $157862x^{1}$ 43 $3.69$ $3.68$ $1.42$ $-0.21$ $0.60$ $0.23$ $0.83$ $2.35-CR1-CL-2P1P$ $157862x^{1}$ 44 $3.66$ $3.79$ $-1.63$ $1.42$ $-0.21$ $0.60$ $0.23$ $0.23$ $0.46$ $3.6-DL-BR$ $N=U2$ $151318^{1}$ 45 $3.63$ $5.72$ $0.86$ $0.86$ $1.72$ $0.23$ $0.23$ $0.46$ $3.6-DL-BR$ $N=U2$ $151318^{1}$ 46 $3.61$ $3.25$ $0.86$ $0.86$ $0.72$ $0.23$ $0.23$ $0.46$ $3.6-DL-BR$ $N=U2$ $15318^{1}$ 47 $3.53$ $3.30$ $1.42$ $0.88$ $2.30$ $0.46$ $0.54$ $1.00$ $1.3DLCL.6-CF3$ $N=HPT2$ $15308^{1}$ 48 $3.54$ $3.51$ $4.15$ $1.72$	36	3 73	6.72	0.86	0.00	1.72	0.23	0.23	0.46	3.6-DI-BR N-AMYL2	151313
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	37	3 72	6.00	1 12	0.88	2.00	0.18	0.54	0.72	3-L 6-CF3 N-BU2	148762
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	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-CF3N-HEPT2	125675
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	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 <sup>k</sup>
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	41	3.69	5.59	0.71	0.88	1.59	0.37	0.54	0.91	2-CL,6-CF3 N-BU2	126927
43 $3.69$ $3.68$ $1.42$ $0.71$ $2.13$ $0.60$ $0.23$ $0.83$ $2.3,6TRI-CL 2-PIP$ $157882k$ 44 $3.66$ $3.72$ $0.86$ $0.86$ $1.72$ $0.23$ $0.23$ $0.46$ $3,6D1-BR N=BU2$ $167170n^2$ 45 $3.63$ $5.72$ $0.86$ $0.86$ $1.72$ $0.23$ $0.23$ $0.46$ $3,6D1-BR N=H2U2$ $151318^1$ 46 $3.61$ $3.25$ $0.86$ $0.86$ $1.72$ $0.23$ $0.23$ $0.46$ $3,6D1-BR N=H2T2$ $33063$ 48 $3.54$ $3.31$ $0.88$ $0.88$ $1.76$ $0.43$ $0.54$ $0.97$ $4,6D1-CF3.2PIP$ $144800$ 49 $3.53$ $9.30$ $1.42$ $0.88$ $2.30$ $0.46$ $0.54$ $1.100$ $1,3D1-CL,6-CF3$ $NHEPT2$ $152117$ 50° $3.51$ $4.15$ $1.72$ $0.88$ $2.60$ $0.62$ $0.54$ $1.16$ $3,6D1-BR N=HEY2$ $158474$ 51 $3.50$ $2.97$ $0.71$ $0.71$ $1.42$ $0.23$ $0.23$ $0.46$ $3,6D1-BR N=HEY2$ $153350$ 53 $3.45$ $5.52$ $0.0$ $0.86$ $0.60$ $0.23$ $0.23$ $0.23$ $6.6T3$ $2.91P$ $148748k$ $52$ $3.52$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $0.23$ $6.6T3$ $NHEY2$ $153350$ $53$ $3.44$ $2.91$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $6.6T3$ $2.91P$	42	3.69	7.88	0.0	0.88	0.88	0.0	0.54	0.54	6-CF3 N-HEPT2	126981
44 $3.66$ $3.79$ $-1.63$ $1.42$ $-0.21$ $0.60$ $0.60$ $1.20$ $2.502CH3 6,7-D1CL N-BU2$ $167470n$ 45 $3.63$ $5.72$ $0.86$ $0.86$ $0.72$ $0.23$ $0.23$ $0.46$ $3,6-D1-BR N-BU2$ $151318^1$ 46 $3.61$ $3.25$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $0.46$ $3,6-D1-BR N-BU2$ $151318^1$ 47 $3.55$ $7.86$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $6-BR N-BU2$ $33063$ 48 $3.54$ $3.31$ $0.88$ $0.88$ $1.76$ $0.43$ $0.54$ $0.97$ $4,6-D1-CF 3-2PIP$ $158474$ 50 $3.51$ $4.15$ $1.72$ $0.88$ $2.60$ $0.62$ $0.54$ $1.16$ $2.3D1-B6, 6-CF 3.2PIP$ $158474$ 51 $3.50$ $2.97$ $0.71$ $0.71$ $1.42$ $0.23$ $0.23$ $0.24$ $3,6-D1-BR N-HEY2$ $151318^1$ 53 $3.45$ $5.52$ $0.0$ $0.86$ $0.86$ $0.23$ $0.23$ $0.23$ $0.24$ $6-DF 3-2PIP$ $158474$ 54 $3.45$ $8.72$ $0.86$ $0.86$ $1.72$ $0.23$ $0.23$ $0.23$ $0.46$ $3,6-D1-BR N-HEY2$ $151318^1$ 53 $3.44$ $2.91$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.23$ $0.25$ $0.54$ $0.54$ <th< td=""><td>43</td><td>3.69</td><td>3.68</td><td>1.42</td><td>0.71</td><td>2.13</td><td>0.60</td><td>0.23</td><td>0.83</td><td>2,3,6-TRI-CL 2-PIP</td><td>157882<sup>k</sup></td></th<>	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 <sup>k</sup>
453.635.720.860.861.720.230.230.463.6-D1-BR N-BU2151314'463.613.250.860.860.0230.230.240.463.6-D1-BR N-HT-BU151314'473.557.860.00.860.860.00.230.230.236-BR N-HEPT233063483.543.310.880.881.760.430.541.001.3-D1-CL,6-CF3 N-HEPT215211750°3.514.151.720.882.600.620.541.162.3-D1-BR,6-CF3 2-PIP158474513.502.970.710.711.420.230.230.463.6-D1-L2 PIP188474513.502.970.710.711.420.230.230.463.6-D1-BR N-HEX2151319'533.455.520.00.860.860.00.230.230.463.6-D1-BR N-HEX2151319'533.442.910.00.860.860.00.230.230.246-BR N-HEPT2-NO133260543.458.720.860.860.00.230.230.246-BR N-HEPT2150236'553.442.910.00.860.860.00.230.230.246-BR N-HEPT2150236'553.433.230.86-1.63-0.770.390.721.112-BR,6-SO2ME N-BU2160938"56 <th< td=""><td>44</td><td>3.66</td><td>3.79</td><td>-1.63</td><td>1.42</td><td>-0.21</td><td>0.60</td><td>0.60</td><td>1.20</td><td>2-SO2CH3 6,7-DI-CL N-BU2</td><td>167470<sup>n</sup></td></th<>	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 <sup>n</sup>
463.613.250.860.861.720.230.230.230.463.6-D1-BR NH-T-BU151314473.557.860.00.860.860.00.230.236-BR N-HEPT233063483.543.310.880.881.760.430.540.974.6-D1-CF3 2-PIP144800493.539.301.420.882.300.460.541.101.3-D1-CL,6-CF3 N-HEPT2152117503.514.151.720.882.600.620.541.162.3-D1-BR,6-CF3 2-PIP188474513.502.970.710.711.420.230.230.463,6-D1-BR,0-CF3 2-PIP188474523.507.720.860.861.720.230.230.463,6-D1-BRN-HEPT21502567533.442.910.00.860.860.00.230.230.463,6-D1-BR N-HEPT21502567553.442.910.00.860.860.00.230.230.463,6-D1-BR N-HEPT21502567563.433.230.86-1.63-0.770.390.721.112-BR,6-SO2ME N-B22160938n573.402.430.880.00.540.540.540.540.540.540.54593.320.80-1.630.880.540.00.543,6-D1-BR 2-PIP126980593	45	3.63	5.72	0.86	0.86	1.72	0.23	0.23	0.46	3,6-DI-BR N-BU2	1513184
473.557.860.00.860.00.230.230.230.246-BR N-HEP123306.3483.543.510.880.881.760.430.540.974,6-DLCF3 2-PIP144800493.539.301.420.882.600.620.541.001,3-DI-CL,6-CF3 N-HEPT2152117503.514.151.720.882.600.620.541.162,3-DL-BR,6-CF3 2-PIP148748/513.502.970.710.711.420.230.230.463,6-DL-BR N-HEX2151319'533.455.520.00.860.860.00.230.236-BR N-HEPT2-NO133560543.458.720.860.860.00.230.236-BR N-HEPT2150236'553.442.910.00.860.860.00.230.236-BR N-ME-2-PIPERIDYL150938''563.433.230.86-1.63-0.770.390.721.112-BR,6-S02ME N-BU21609338''573.402.430.880.00.840.540.546-CF3 2-PIP109824583.372.430.00.880.840.00.543-C51 2-PIP150936''593.320.80-1.630.750.720.541.263-S02ME,6-CF3 2-PIP157237'603.235.740.860.861.720.230.23<	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
483.543.310.880.881.760.430.540.974,6-D1-CF3 2-PIP144800493.539.301.420.882.300.460.541.001.3D1-CL,6-CF3 N-HEPT215211750°3.514.151.720.882.600.620.541.162,3-D1-BR,6-CF3 2-PIP158474513.502.970.710.711.420.230.230.463,6-D1-BR N-HEX21513191533.455.520.00.860.860.00.230.236-BR N-HEPT2-NO133560543.458.720.860.861.720.230.230.463,6-D1-BR N-HEPT21502561553.442.910.00.860.860.00.230.230.463,6-D1-BR N-HEPT21502561563.433.230.86-1.63-0.770.390.721.112-BR,6-SO2ME N-BU2160938n573.402.430.880.00.540.540.546-CF3 2-PIP109824583.372.430.00.880.840.00.541.263-SO2ME,6-CF3 2-PIP157237603.313.270.860.861.720.230.230.463,6-D1-BR N-HEPT2149836613.299.001.120.880.000.540.540.546-CF3 N-BU291186633.232.410.00.86<	47	3.55	7.86	0.0	0.86	0.86	0.0	0.23	0.23	6-BR N-HEP12	33063
493.539.301.420.882.300.460.541.001.5-D1-L, 6-L-5, N-HEP1213211750°3.514.151.720.882.600.620.541.162.3D1-BR, 6-CF3 2-PIP158474513.502.970.710.711.420.230.230.463,6-D1-RL 2-PIP148748k523.507.720.860.861.720.230.230.463,6-D1-BR N-HEX2151319 <sup>1</sup> 533.455.520.00.860.860.00.230.230.463,6-D1-BR N-HEPT2150256 <sup>1</sup> 543.458.720.860.860.1720.230.230.463,6-D1-BR N-HEPT2150256 <sup>1</sup> 553.442.910.00.860.860.00.230.230.236-BR N-HEPT2150256 <sup>1</sup> 553.442.910.00.860.860.00.230.230.230.230.24DBR/SO2ME N-BU2160938 <sup>n</sup> 563.433.230.860.880.540.00.543-CF3 2-PIP126866593.320.80-1.630.880.540.00.543-CF3 2-PIP158966613.299.001.120.880.000.540.540.6CF3 N-BU291186633.232.410.00.860.860.0230.236-BR 2-PIP112321643.232.440.0	48	3.54	3.31	0.88	0.88	1.76	0.43	0.54	0.97	4,6-DI-CF 3 2-PIP	144800
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	49 p	3.53	9.30	1.42	0.88	2.30	0.46	0.54	1.00	1,3-DI-CL, $0$ -CF $3$ N-HEP $12$	152117
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	50	3.51	4.15	1.72	0.88	2.60	0.62	0.34	1.10	2,5-DI-BK,0-CI-5,2-FIF	148748k
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	51	3.50	2.97	0.71	0.71	1.42	0.23	0.23	0.46	2 C DI DD N HEY?	1513101
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	52	3.50	5.52	0.00	0.00	1.72	0.23	0.23	0.40	6-BR N-HFPT2-NO	133560
545.45.720.600.860.1720.0230.236.606.68N-ME-2-PIPERIDYL157081m563.433.230.86 $-1.63$ $-0.77$ 0.390.721.112-BR,6-SO2ME N-BU2160938n573.402.430.880.00.880.540.00.543-CF32-PIP109824583.372.430.00.880.700.541.263-CF32-PIP126980593.320.80 $-1.63$ 0.88 $-0.75$ 0.720.541.263-SO2ME,6-CF32-PIP157237603.313.270.860.861.720.230.230.463,6-DI-BR2-PIP158966613.299.001.120.882.000.180.540.723-I,6-CF3N-HEPT2149856623.232.410.00.860.860.00.230.236-BR2-PIP112321643.235.720.860.861.720.00.230.236-BR2-PIP112321653.225.740.860.861.720.00.230.236-BR2-PIP113221643.225.740.860.881.740.390.540.934-BR,6-CF3N-BU2163324'653.138.740.860.881.740.230.236-BR2-PIP-N-BU158499m67<	55	2.45	077	0.0	0.00	1 7 7	0.0	0.23	0.25	3 6-DL-BR N-HEPT?	1502561
333.442.910.000.000.000.000.721.112.BR, 6-SO2ME N-BU210938n573.402.430.880.00.880.540.00.543-CF3 2-PIP109824583.372.430.00.880.880.00.540.546-CF3 2-PIP126980593.320.80-1.630.88-0.750.720.541.263-SO2ME,6-CF3 2-PIP158966613.299.001.120.882.000.180.540.723-1,6-CF3 N-HEPT2149856623.234.880.00.880.880.00.540.546-CF3 N-HEPT2149856633.232.410.00.860.860.00.230.236-BR 2-PIP112321643.235.720.860.861.720.00.230.236-BR 2-PIP112321653.225.740.860.860.00.230.236-BR 2-PIPN-BU15849914663.224.410.00.860.860.00.230.236-BR 2-PIPN-BU15849914663.138.740.860.881.740.230.540.771-BR,6-CF3 N-HEV2136914683.138.740.860.881.740.230.540.771-BR,6-CF3 N-HEV2136914683.138.740.860.880.770.86-DI-CL N-HEV72<	55	3.43	0.72	0.00	0.80	0.86	0.25	0.23	0.40	6-BR N-ME-2-PIPERIDYL	157081m
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	56	3 4 3	3 23	0.0	-163	-0.77	0.39	0.72	1.11	2-BR.6-SO2ME N-BU2	160938 <sup>n</sup>
583.372.430.00.880.080.000.540.546-CF3 2-PIP126980593.320.80 $-1.63$ 0.88 $-0.75$ 0.720.541.263-SO2ME,6-CF3 2-PIP157237603.313.270.860.861.720.230.230.463,6-DI-BR 2-PIP158966613.299.001.120.882.000.180.540.546-CF3 N-HEPT2149856623.234.880.00.880.880.00.540.546-CF3 N-BU291186633.232.410.00.860.860.00.230.236-BR 2-PIP112321643.235.720.860.861.720.00.230.236-BR 2-PIP163321°65P3.225.740.860.861.720.00.230.236-BR 2-PIP-N-BU158499m673.177.361.681.683.36 $-0.20$ $-0.40$ 3,6-DI-T-BU N-BU2163324'683.138.740.860.881.740.230.230.540.771-BR,6-CF3 N-HEPT2123937693.127.880.880.00.880.540.00.543,6-DI-CL N-HEPT2123937713.097.710.710.00.370.375-CL N-HEPT2123937733.087.140.00.710.370.00.372-CL N	57	3 40	2.43	0.88	0.0	0.88	0.54	0.0	0.54	3-CF3 2-PIP	109824
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	58	3.37	2.43	0.0	0.88	0.88	0.0	0.54	0.54	6-CF3 2-PIP	126980
603.313.270.860.861.720.230.230.463,6-DI-BR 2-PIP158966613.299.001.120.882.000.180.540.723-I,6-CF 3 N-HEPT2149856623.234.880.00.880.880.00.540.546-CF 3 N-BU291186633.232.410.00.860.861.720.00.230.236-BR 2-PIP112321643.235.720.860.861.720.00.230.236-BR 2-PIP112321643.235.720.860.861.740.390.540.934-BR,6-CF 3 N-BU2163321065P3.225.740.860.881.740.390.540.934-BR,6-CF 3 N-BU2136914663.224.410.00.860.860.00.230.230.236-BR 2-PIP-N-BU158499m673.177.361.681.683.36 $-0.20$ $-0.40$ 3,6-DI-T-BU N-BU2163324 <sup>1</sup> 683.138.740.860.880.740.230.540.771-BR,6-CF 3 N-HEPT2123937693.127.880.880.00.880.540.00.543,6-DI-CL N-HEPT2125676k713.097.710.710.00.710.370.00.372-CL N-HEPT2125676k733.087.140.00.71<	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
$62$ $3.23$ $4.88$ $0.0$ $0.88$ $0.88$ $0.0$ $0.54$ $0.54$ $6-CF3$ $N-BU2$ $91186$ $63$ $3.23$ $2.41$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $6-BR$ $2-PIP$ $112321$ $64$ $3.23$ $5.72$ $0.86$ $0.86$ $1.72$ $0.0$ $0.23$ $0.23$ $6-BR$ $2-PIP$ $112321$ $64$ $3.23$ $5.72$ $0.86$ $0.86$ $1.72$ $0.0$ $0.23$ $0.23$ $6_{1}0-DI-BR$ $N-BU2$ $163321^o$ $65p$ $3.22$ $5.74$ $0.86$ $0.88$ $1.74$ $0.39$ $0.54$ $0.93$ $4+BR, 6-CF3$ $N-BU2$ $138499m$ $67$ $3.17$ $7.36$ $1.68$ $1.68$ $3.36$ $-0.20$ $-0.40$ $3.6-DI-T-BU$ $N-BU2$ $163324^l$ $68$ $3.13$ $8.74$ $0.86$ $0.88$ $1.74$ $0.23$ $0.54$ $0.77$ $1-BR, 6-CF3$ $N-HEPT2$ $123937$ $69$ $3.12$ $7.88$ $0.88$ $0.0$ $0.88$ $0.54$ $0.0$ $0.54$ $3-CF3$ $N-HEPT2$ $123937$ $69$ $3.12$ $7.88$ $0.88$ $0.0$ $0.88$ $0.54$ $0.0$ $0.54$ $3-CF3$ $N-HEPT2$ $123937$ $70$ $3.12$ $8.42$ $0.71$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ $N-HEPT2$ $125676k$ $71$ $3.09$ $7.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$	61	3.29	9.00	1.12	0.88	2.00	0.18	0.54	0.72	3-I,6-CF 3 N-HEPT2	149856
$63$ $3.23$ $2.41$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $6-BR 2-PIP$ $112321$ $64$ $3.23$ $5.72$ $0.86$ $0.86$ $1.72$ $0.0$ $0.23$ $0.23$ $6.10$ -DI-BR N-BU2 $163321^o$ $65p$ $3.22$ $5.74$ $0.86$ $0.88$ $1.74$ $0.39$ $0.54$ $0.93$ $4-BR, 6-CF3$ N-BU2 $136914$ $66$ $3.22$ $4.41$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $6-BR 2-PIP-N-BU$ $15899m$ $67$ $3.17$ $7.36$ $1.68$ $1.68$ $3.36$ $-0.20$ $-0.40$ $3.6-DI-T-BU$ N-BU2 $163324^i$ $68$ $3.13$ $8.74$ $0.86$ $0.88$ $1.74$ $0.23$ $0.54$ $0.77$ $1-BR, 6-CF3$ N-HEPT2 $123937$ $69$ $3.12$ $7.88$ $0.88$ $0.0$ $0.88$ $0.54$ $0.0$ $0.54$ $3-CF3$ N-HEPT2 $125756$ $70$ $3.12$ $8.42$ $0.71$ $0.71$ $1.42$ $0.23$ $0.23$ $0.46$ $3.6-DI-CL$ N-HEPT2 $125676k$ $71$ $3.09$ $7.71$ $0.71$ $0.71$ $0.0$ $0.37$ $0.27$ $0.37$ $5-CL$ N-HEPT2 $11531k$ $72$ $3.08$ $7.14$ $0.0$ $0.14$ $0.0$ $0.35$ $0.35$ $6-OCF3$ $2-PIP$ $136911k$ $73$ $3.06$ $2.59$ $0.0$ $1.04$ $1.04$ $0.0$ $0.35$ $0.35$ $6-OCF3$ $2-PIP$ $136911k$ $75$ <t< td=""><td>62</td><td>3.23</td><td>4.88</td><td>0.0</td><td>0.88</td><td>0.88</td><td>0.0</td><td>0.54</td><td>0.54</td><td>6-CF3 N-BU2</td><td>91186</td></t<>	62	3.23	4.88	0.0	0.88	0.88	0.0	0.54	0.54	6-CF3 N-BU2	91186
64 $3.23$ $5.72$ $0.86$ $0.86$ $1.72$ $0.0$ $0.23$ $0.23$ $6,10$ -DI-BR N-BU2 $163321^{\circ}$ 65p $3.22$ $5.74$ $0.86$ $0.88$ $1.74$ $0.39$ $0.54$ $0.93$ $4$ -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 $136914$ 67 $3.17$ $7.36$ $1.68$ $1.68$ $3.36$ $-0.20$ $-0.20$ $-0.40$ $3,6$ -DI-T-BU N-BU2 $163324^{i}$ 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 $3.12$ $8.42$ $0.71$ $0.71$ $0.423$ $0.23$ $0.23$ $0.46$ $3,6$ -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 $11531^{k}$ 72 $3.09$ $7.71$ $0.0$ $0.71$ $0.37$ $0.06$ $0.06$ $6$ -FF N-HEPT2 $129390^{k}$ 73 $3.08$ $7.14$ $0.0$ $0.14$ $0.0$ $0.35$ $0.35$ $6$ -OCF 3 2-PIP $136911^{k}$ 74 $3.06$ $2.59$ $0.0$ $1.04$ $0.0$ $0.35$ $0.35$ $6$ -OCF 3 2-PIP $152110$ 76 $3.01$ $4.71$ <	63	3.23	2.41	0.0	0.86	0.86	0.0	0.23	0.23	6-BR 2-PIP	112321
65p $3.22$ $5.74$ $0.86$ $0.88$ $1.74$ $0.39$ $0.54$ $0.93$ $4$ -BR,6-CF3 N-BU2 $136914$ 66 $3.22$ $4.41$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $6-BR$ $2-PIP-N-BU$ $158499m$ 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 $3.12$ $7.88$ $0.88$ $0.0$ $0.88$ $0.54$ $0.0$ $0.54$ $3-CF3$ $N-HEPT2$ $123937$ 70 $3.12$ $8.42$ $0.71$ $0.71$ $0.423$ $0.23$ $0.24$ $3,6-DI-CL N-HEPT2$ $125676^{k}$ 71 $3.09$ $7.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL N-HEPT2$ $11531^{k}$ 72 $3.09$ $7.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $5-CL N-HEPT2$ $122390^{k}$ 73 $3.08$ $7.14$ $0.0$ $0.14$ $0.0$ $0.06$ $0.06$ $6-GF3$ $2-PIP$ $136911^{k}$ 74 $3.06$ $2.59$ $0.0$ $1.04$ $0.0$ $0.35$ $0.35$ $6-OCF3$ $2-PIP$ $152110$ 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<	64	3.23	5.72	0.86	0.86	1.72	0.0	0.23	0.23	6,10-DI-BR N-BU2	1633210
$66$ $3.22$ $4.41$ $0.0$ $0.86$ $0.86$ $0.0$ $0.23$ $0.23$ $6-BR$ $2-PIP-N-BU$ $158499^{m}$ $67$ $3.17$ $7.36$ $1.68$ $1.68$ $3.36$ $-0.20$ $-0.20$ $-0.40$ $3,6-DI-T-BU$ $N-BU2$ $163324^{l}$ $68$ $3.13$ $8.74$ $0.86$ $0.88$ $1.74$ $0.23$ $0.54$ $0.77$ $1-BR,6-CF3$ $N-HEPT2$ $123937$ $69$ $3.12$ $7.88$ $0.88$ $0.0$ $0.88$ $0.54$ $0.0$ $0.54$ $3-CF3$ $N-HEPT2$ $105756$ $70$ $3.12$ $8.42$ $0.71$ $0.71$ $1.42$ $0.23$ $0.23$ $0.46$ $3,6-DI-CL$ $N-HEPT2$ $125676^{k}$ $71$ $3.09$ $7.71$ $0.71$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ $N-HEPT2$ $129390^{k}$ $72$ $3.09$ $7.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $5-CL$ $N-HEPT2$ $129390^{k}$ $73$ $3.08$ $7.14$ $0.0$ $0.14$ $0.14$ $0.0$ $0.35$ $0.35$ $6-OCF3$ $2-PIP$ $136911^{k}$ $74$ $3.06$ $2.59$ $0.0$ $1.04$ $1.04$ $0.0$ $0.37$ $2-CL$ $N-BU2$ $129388^{k}$ $76$ $3.01$ $4.71$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ $N-BU2$ $129388^{k}$	65 <sup>p</sup>	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	1584997
68 $3.13$ $8.74$ $0.86$ $0.88$ $1.74$ $0.23$ $0.54$ $0.77$ $1-BR, 6-CF 3 N-HEP12$ $123937$ 69 $3.12$ $7.88$ $0.88$ $0.0$ $0.88$ $0.54$ $0.0$ $0.54$ $3-CF 3 N-HEP12$ $105756$ 70 $3.12$ $8.42$ $0.71$ $0.71$ $1.42$ $0.23$ $0.23$ $0.46$ $3, 6-DI-CL N-HEP12$ $125676^k$ 71 $3.09$ $7.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL N-HEP12$ $111531^k$ 72 $3.09$ $7.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL N-HEP12$ $129390^k$ 73 $3.08$ $7.14$ $0.0$ $0.14$ $0.14$ $0.0$ $0.06$ $6-F$ N-HEP12 $91185^k$ 74 $3.06$ $2.59$ $0.0$ $1.04$ $1.04$ $0.0$ $0.35$ $6-OCF3$ $2-PIP$ $136911^k$ 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 $3.01$ $4.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL N-BU2$ $129388^k$	67	3.17	7.36	1.68	1.68	3.36	-0.20	-0.20	-0.40	3,6-DI-T-BU N-BU2	103324
69 $3.12$ $7.88$ $0.88$ $0.0$ $0.88$ $0.54$ $0.0$ $0.54$ $3-CF3$ $N-HEF12$ $105736$ 70 $3.12$ $8.42$ $0.71$ $0.71$ $1.42$ $0.23$ $0.23$ $0.46$ $3,6-DI-CL$ $N-HEP12$ $125676^k$ 71 $3.09$ $7.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ $N-HEP12$ $11531^k$ 72 $3.09$ $7.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ $N-HEP12$ $129390^k$ 73 $3.08$ $7.14$ $0.0$ $0.71$ $0.71$ $0.0$ $0.37$ $0.37$ $5-CL$ $N-HEP12$ $129390^k$ 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 $3.01$ $4.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ $N-BU2$ $129388^k$	68	3.13	8.74	0.86	0.88	1.74	0.23	0.54	0.77	1-BR, 6-CF 3 N-HEFT2	12373/
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	69	3.12	7.88	0.88	0.0	0.88	0.54	0.0	0.54	3-CF3 N-HEF12	105/30 125676k
$71$ $3.09$ $7.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ N-HE I 2 $111331^{n}$ $72$ $3.09$ $7.71$ $0.0$ $0.71$ $0.71$ $0.0$ $0.37$ $0.37$ $5-CL$ N-HE PT 2 $129390k$ $73$ $3.08$ $7.14$ $0.0$ $0.14$ $0.14$ $0.0$ $0.06$ $6-F$ N-HE PT 2 $91185^{k}$ $74$ $3.06$ $2.59$ $0.0$ $1.04$ $1.04$ $0.0$ $0.35$ $0.35$ $6-OCF 3 2-PIP$ $136911k$ $75$ $3.05$ $2.93$ $0.88$ $0.50$ $1.38$ $0.54$ $-0.17$ $0.37$ $3-CF 3, 6-ME 2-PIP$ $152110$ $76$ $3.01$ $4.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2-CL$ N-BU2 $129388^{k}$	70	3.12	8.42	0.71	0.71	1.42	0.23	0.23	0.46	SOULCE N-HEFT2	111531k
$72$ $3.09$ $7.11$ $0.0$ $0.71$ $0.0$ $0.37$ $0.37$ $5.01$ $N-HEF12$ $129390^{-1}$ $73$ $3.08$ $7.14$ $0.0$ $0.14$ $0.0$ $0.06$ $0.06$ $6$ -F $N-HEF12$ $91185k$ $74$ $3.06$ $2.59$ $0.0$ $1.04$ $1.04$ $0.0$ $0.35$ $6$ -OCF3 $2.PIP$ $136911k$ $75$ $3.05$ $2.93$ $0.88$ $0.50$ $1.38$ $0.54$ $-0.17$ $0.37$ $3$ -CF3 $6$ -PIP $152110$ $76$ $3.01$ $4.71$ $0.71$ $0.0$ $0.71$ $0.37$ $0.0$ $0.37$ $2$ -CL N-BU2 $129388k$	71	3.09	7.71	0.71	0.0	0.71	0.37	0.0	0.37	2-CL N-HEPT?	120200k
73 3.08 7.14 0.0 0.14 0.14 0.0 0.06 0.10 0.16 91103   74 3.06 2.59 0.0 1.04 1.04 0.0 0.35 0.35 6-OCF3 2-PIP 136911k   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 0.37 0.0 0.37 2-CLN-BU2 129388k	72	3.09	7.71	0.0	0./1	0./1	0.0	0.37	0.37	5-02 N-ПБ- 12 6-е N.НЕРТ?	91185k
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 <sup>k</sup>	/5	3.08	1.14	0.0	0.14	1.04	0.0	0.00	0.00	6-00F3 2-PIP	136911k
76 3.01 4.71 0.71 0.0 0.71 0.37 0.0 0.37 2-CL N-BU2 129388k	74	3.00 2.05	2.39	0.0	1.04	1.04	0.0	-0.33	0.33	3-CF 3.6-ME 2-PIP	152110
	76 76	3.03	2.73	0.88	0.00	0.71	0.37	0.0	0.37	2-CL N-BU2	129388 <sup>k</sup>

no.	Log 1/C <sup>a</sup>	$\pi_{sum}^{b}$	$\pi_{\boldsymbol{x}}^{c}$	$\pi_y^d$	$\pi_{x+y}^{e}$	σ <sub>x</sub> f	ay8	$\sigma_{x+y}^{h}$	Structure <sup>i</sup>	Wr no. <sup>j</sup>
77	2.98	7.69	0.71	-0.02	0.69	0.23	-0.27	-0.04	3-CL,6-OCH3 N-HEPT2	121499 <sup>k</sup>
78	2.97	7.71	0.0	0.71	0.71	0.0	0.37	0.37	7-CL N-HEPT2	129394 <i>k</i>
79	2.92	7.00	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-HEPT2	94197 <sup>1</sup>
80	2.88	8.59	0.88	0.71	1.59	0.54	0.23	0.77	3-CF 3,6-CL N-HEPT 2	131751
81	2.83	2.05	0.0	0.50	0.50	0.0	-0.17	-0.17	6-CH3 2-PIP	15065 <b>6</b> k
82	2.82	4.50	0.50	0.0	0.50	-0.17	0.0	-0.17	10-ME N-BU2	1589720
83	2.82	7.71	0.71	0.0	0.71	0.37	0.0	0.37	4-CL N-HEPT2	106941 <sup>k</sup>
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 <i>k</i>
86	2.74	4.71	0.0	0.71	0.71	0.0	0.37	0.37	5-CL N-BU2	129389 <i>k</i>
87	2.65	4.71	0.71	0.0	0.71	0.23	0.0	0.23	1-CL N-BU2	100351 <i>k</i>
88	2.62	8.00	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-OCTYL2	941994
89	2.59	7.71	0.71	0.0	0.71	0.23	0.0	0.23	3-CL N-HEPT2	5999
<b>9</b> 0	2.59	7.71	0.0	0.71	0.71	0.0	0.23	0.23	6-CL N-HEPT2	129392*
91	2.58	7.14	0.14	0.0	0.14	0.0 <b>6</b>	0.0	0.06	3-F N-HEPT2	88433 <i>k</i>
92p	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 <sup>k</sup>
94	2.56	2.26	0.71	0.0	0.71	0.37	0.0	0.37	2-CL N-PIP	138705 <i>*</i>
95	2.54	4.69	0.71	-0.02	0. <b>69</b>	0.23	-0.27	-0.04	3-CL,6-OCH3 N-BU2	122454 <i>K</i>
96	2.53	6.00	0.0	0.0	0.0	0.0	0.0	0.0	UNSUBST N-HEX2	94407
97	2.49	4.14	0.0	0.14	0.14	0.0	0.06	0.06	6-F N-BU2	91187 <i>k</i>
98	2.43	4.14	0.14	0.0	0.14	0.06	0.0	0.06	3-F N-BU2	84588 <i>k</i>
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
10 <b>2</b> <i>p</i>	2.32	4.71	0.0	0.71	0.71	0.0	0.37	0.37	7-CL N-BU2	13085 <b>6</b> <sup>k</sup>
103P	2.32	4.71	0.0	0.71	0.71	0.0	0.23	0.23	8-CL N-BU2	133561 <i>k</i>
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

<sup>a</sup>C represents the molar concentration (mol of drug/kg of animal) which resulted in 50% cures (see ref 7).  $b_{\pi_{sum}} = sum$  of all substituents in positions 1-8 plus the substituents on the amino group.  $c_{\pi_X} = sum$  of  $\pi$  values for all substituents in positions 1-4 of the phenanthrene ring.  $d_{\pi_Y} = sum$  of  $\pi$  values for all substituents in position 5-8 of the phenanthrene ring.  $e_{\pi_X+y} = sum$  of  $\pi$  values for all substituents in positions 1-8 of the phenanthrene ring.  $f_X$  are of  $\sigma$  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  $\sigma$  effect. \$Sum of  $\sigma$  constants for groups in positions 5-8, based upon position 9; hence, a group at position 6 is considered as para. hSum of  $\sigma_X + \sigma_y$ . iThe following abbreviations have been used: PIP = 2-piperidyl, BU2 = dibutyl, PR 2 = dipropyl, I-PR = isopropyl, AMYL2 = diamyl, HEX2 = dihexyl, HEPT2 = diheptyl, T-BU = tert-butyl, NO = N-oxide, SO2ME = methylsulfonyl, OCTYL2 = dioctyl, DI-2VQ = (CH<sub>2</sub>CH<sub>2</sub>COOH)<sub>2</sub>, CYHEX = cyclohexyl, CYANOET = cyanoethyl. Number assigned by Walter Reed Army Institute of Research. kCompound prepared by E. A. Nodiff and coworkers, Germantown Labs., Philadelphia, Pa. 19144. iCompound prepared by D. W. Henry and coworkers, Stanford Research Institute, Menlo Park, Calif. 94025. mCompound prepared by C. C. Cheng and coworkers, Midwest Research Institute, Kansas City, Mo. 64110. nCompound prepared by C. L. Stevens and coworkers, Ash-Stevens, Inc., Detroit, Mich. 48202.  $\sigma$ Compound prepared by D. P. Pearson and coworkers, Vanderbilt University, Nashville, Tenn. 37203. PCompound 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  $\sigma$ constants.<sup>5</sup> It was also found that no reasonable correlations were obtained using Yamamoto's  $E_R$  constants.<sup>6</sup>

Three dissimilar equations were obtained, involving  $\pi$ and/or  $\sigma$  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<sub>3</sub>, I, Br, Cl, F, OCH<sub>3</sub>, and, of course, H) were seen to lie essentially on a straight line (covariance correlation coefficient = 0.919) when their  $\sigma$  constants values were plotted against their  $\pi$ substituent values.<sup>7</sup> Thus, either  $\pi$  or  $\sigma$  values for this limited series of substituents would be expected to give similar results in correlation studies.<sup>†</sup> 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

<sup>&</sup>lt;sup>†</sup>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.

$\log 1/C = 2.699 (\pm 0.141) + 0.557 (\pm 0.092) \pi_{x+\nu}$
$\log 1/C = 3.324 (\pm 0.286) + 0.017 (\pm 0.053) \pi_{sum}$
$\log 1/C = 2.721 (\pm 0.120) + 1.218 (\pm 0.173)\sigma_{sum}$
$\log 1/C = 2.522 (\pm 0.105) + 0.327 (\pm 0.079) \pi_{x+y} + 0.833 (\pm 0.163) \sigma_{sum}$
$\log 1/C = 2.723 (\pm 0.121) + 1.115 (\pm 0.331)\sigma_x + 1.315 (\pm 0.315)\sigma_y$
$\log 1/C = 2.666 \ (\pm 0.140) + 0.728 \ (\pm 0.165)\pi_{\nu} + 0.444 \ (\pm 0.129)\pi_{x}$
$\log 1/C = 2.588 (\pm 0.409) + 0.409 (\pm 0.175) \pi_{sum} - 0.041 (\pm 0.017) \pi_{sum}^2$

$$\log 1/C = 2.350 (\pm 0.195) + 0.313 (\pm 0.079) \pi_{x+y} + 0.134 (\pm 0.088) \pi_{sum} - 0.015 (\pm 0.009) \pi^2_{sum} + 0.791 (\pm 0.157) \sigma_{sum}$$

$$\log 1/C = 2.335 (\pm 0.194) + 0.396 (\pm 0.134)\pi_y + 0.270 (\pm 0.105)\pi_x + 0.654 (\pm 0.280)\sigma_x + 0.878 (\pm 0.269)\sigma_y + 0.137 (\pm 0.087)\pi_{sum} - 0.015 (\pm 0.009)\pi_{sum}^2$$

$$\log 1/C = 2.511 (\pm 0.105) + 0.281 (\pm 0.106)\pi_x + 0.416 (\pm 0.141)\pi_y + 0.724 (\pm 0.292)\sigma_x + 0.894 (\pm 0.286)\sigma_y$$

equations very well; eq 8 predicts all but six of the 102 compounds used in its derivation to within less than  $(\pm)$  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  $\pi_{x+y}$  or  $\sigma_{sum}$  alone nor  $(\pi_x + \pi_y)$  or  $(\sigma_x + \sigma_y)$  can account satisfactorily for the biological variability in these compounds ( $R^2 = \langle 0.70 \rangle$ ). 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  $\pi_{sum}$  and  $\pi^{2}_{sum}$  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).<sup>8</sup> Consideration of eq 4 and 8, and 9 and 10, as sets, indicates that the overall partition value for the entire molecule  $(\pi_{sum})$  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  $\pi_{sum}$  of about  $4.4\pi$  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  $2\pi$  units, leaving about  $2.5\pi$  units for the amino substituents. Thus, the diheptyl and dibutyl substituents (7 and  $4\pi$  units) would exceed this optimum  $\pi_{sum}$  value, with typical aromatic ring substituents.

In the preliminary work, the published value of  $\pi = 1.16$ was used for the aromatic CF<sub>3</sub>  $\pi$  constant.<sup>9</sup> During the course of this work, the value of  $\pi$  (octanol-H<sub>2</sub>O) for this important pharmacophoric group was redetermined, and the revised value of 0.88 was used in the derivation of eq 1-10.<sup>§</sup> 102 0.899 0.275 (10) 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  $\pi$  and  $\sigma$  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  $\pi$  and  $\sigma$  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.<sup>10</sup>

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.<sup>11</sup> 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

п	R	s‡	
102	0.768	0.395	(1)
102	0.069	0.616	(2)
102	0.814	0.359	(3)
102	0.894	0.278	(4)
102	0.815	0.360	(5)
102	0.783	0.386	(6)
102	0.426	0.561	(7)
[ideal $\pi_s$	um = 5.0	5 (4.43-5.76)]	
102	0.908	0.263	(8)
[ideal $\pi_s$	um = 4.42	2 (3.15-5.22]	
102 [ideal $\pi_s$	0.913 um = 4.44	0.258 4 (3.25-5.21)]	(9)
102	0.899	0.275	(10)

 $<sup>\</sup>ddagger n =$  number of compounds, R = correlation coefficient, s = standard deviation.

<sup>&</sup>lt;sup>§</sup>Determined by D. Nikaitani at Pomona College, 1972.

Table	II
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		R,			R <sub>2</sub>					R <sub>3</sub>				R4					R,				В		
Log 1/C	н	C1	BR	Н	Cl	CF,	Н	F	C1	Br	I	CF <sub>3</sub>	Н	C1	CF <sub>3</sub>	н	F	C1	BR	CF,	OCH,	2-Pip	N-Bu <sub>2</sub>	N-Hept <sub>2</sub>	WR no.
4.21	1				1				1				1	• • • • •			- , · · ·			1		1			148763
4.10	1			1								1	1							1			1		14380 <b>3</b> ª
4.07	1				1		1						1							1		1			131834
4.03		1		1					1				1							1		1			146459
2.98	1			1						1		1	1							1		1			148/494
3.85	1			1								1	1					1		1		1	1		122455-
3.87	1			1					1			1	1					1		1			1		1022374
3.85	1			-		1	1		1				1							1		1	-		136913
3.81	1			1			_		1				ī							ī		1			138400a
3.72	1			1							1		1							1			1		148762 <sup>a</sup>
3.72	1			1					1				1							1				1	101680a
3.72	1				1		1						1							1				1	125675
3.69	1.				1		1						1							1			1	,	126927
3.09	1			1			1						1						1	1				1	330634
3.54	1			1			1						1		1				1	1		1		1	144800
3.50	ī			1			1		1				1					1		1		1			1487484
3.40	1			1								1	ī			1						ī			1098244
3.37	1			1			1						1							1		1			126980 <sup>a</sup>
3.23	1			1			1						1							1			1		91186 <sup>a</sup>
3.23	1			1			1						1						1			1			1123214
3.13			1	1			1						1							1				1	123937
3.12	1			1					•			1	1			1		,						1	105/564
3.12	1			1	1		1		1				1			1		1						1	111531
3.08	1			1	1		1						1			1	1							1	911854
3.01	i			-	1		i						1			1	1						1	1	129388
2.98	1			1	_		-		1				ī			-					1		_	1	121499a
2.92	1			1			1						1			1								1	941974
2.88	1			1								1	1					1						1	131751ª
2.82	1			1			1							1		1								1	106941
2.78	1			1								1	1			1							1		90410 <sup>a</sup>
2.74	1	,		1			1						1					1					1		1293914
2.03	1	1		1			1		1				1			1							1	1	50004
2.39	1			1			1		1				1			1		1						1	1703074
2.59	1			1			1	1					1			1		1						1	884334
2.56	i			-	1		1	Ŧ					1			i						1		T	138705
2.56	-	1		1	-		ī						1			ī						-		1	106940
2.54	1			1					1				1								1		1		1224544
2.49	1			1			1						1				1						1		91187 <b>a</b>
2.43	1			1	_			1				_	1			1							1		84588ª
<u>n</u>	39	3	1	35	7	1	22	2	10	1	1	7	41	1	1	13	2	6	2	18	2	13	13	17	

<sup>a</sup>Free-Wilson matrix using substituents at positions at 3, 6, and 9 only.

Table IIIa

Position	Group	No. of examples	Substituent constant	Range
	C1	3	0.130	
R,	Н	39	-0.001	
Ri	Br	1	-0.338	0.468
R,	Cl	7	0.301	
R,	CF <sub>3</sub>	1	0.292	
$\tilde{R_2}$	н	35	-0.069	0.370
R3	CF <sub>3</sub>	7	0.384	
R,	Br	1	0.296	
R,	C1	10	0.155	
R,	Ι	1	0.129	
R,	F	2	-0.193	
R₃	н	22	-0.194	0.578
R₄	C1	1	0.273	
R₄	CF,	1	0.043	
R₄	н	41	-0.008	0.280
R,	CF <sub>3</sub>	18	0.451	
R <sub>6</sub>	Br	2	0.363	
R,	C1	6	-0.187	
R <sub>6</sub>	F	2	-0.196	
R <sub>6</sub>	н	13	-0.477	
R <sub>6</sub>	OCH3	2	-0.570	1.021
В	2-Piperidyl	13	0.037	
В	N-Bu <sub>2</sub>	13	0.0142	
В	N-Hept <sub>2</sub>	17	-0.056	0.093
/For th		$D^2 = 0.95^2$	2 = 0.274 E = 7.92	(F

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

Table IV<sup>a</sup>

Position	Group	No. of examples	Substituent constant	Range
R <sub>3</sub>	CF,	7	0.330	
R	Br	1	0.221	
R,	Ι	1	0.076	
R	C1	8	0.066	
R,	н	10	-0.260	
R <sub>3</sub>	F	2	-0.268	0.598
R₅	CF <sub>3</sub>	10	0.460	
R	Br	2	0.372	
R	Cl	6	-0.135	
R <sub>6</sub>	F	2	-0.175	
R	н	7	-0.447	
R <sub>6</sub>	OCH3	2	-0.526	0.986
В	2-Piperidyl	7	0.058	
В	N.Hept,	12	0.014	
B	N·Bu <sub>2</sub> <sup>1</sup>	10	-0.057	0.115

<sup>a</sup>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  $\pi_{sum}$  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

Group	R₃ subst const	π	$\sigma_{para}$	R <sub>6</sub> subst const
CF,	0.332	0.88	0.54	0.476
Br	0.223	0.86	0.23	0.388
C1	0.069	0.71	0.23	0.118
н	-0.257	0	0	-0.431
F	0.265	0.14	0.06	-0.159
OCH,		-0.02	-0.27	-0.510
Range	0.60			0.98

Table VI. Simple Correlation Matrix

	π	σ
R <sub>3</sub> subst const	0.971	0.910
R <sub>6</sub> subst const	0.910	0.885
π	1.00	0.919

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.

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  $\sigma$  and  $\pi$  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  $\pi$  and  $\sigma$  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,<sup>12</sup> 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.<sup>1</sup> $3\beta$ -Phenyltropan-2-ols

## Sol J. Daum,\* Mario D. Aceto, and Robert L. Clarke

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. Received November 20, 1972

A group of  $3\beta$ -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  $2\beta$ -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  $(\pm)$ -3-phenyltropidine.  $(\pm)$ -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  $3\beta$  position of the tropane ring and the  $2\beta$ -carbomethoxy group is replaced by hydroxyl or acetoxyl in either the  $\alpha$  or  $\beta$  configuration.



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

Similarly 2b was converted to the  $2\alpha$ -acetate 3b.<sup>†</sup> Treatment of 3b with methyl chloroformate afforded the ure-

thane 6b which was saponified to give 5b. Jones oxidation followed by LiAlH<sub>4</sub> reduction gave equal amounts of the equatorial  $2\alpha$ -alcohol 2b and the axial  $2\beta$ -alcohol 8b. We did not try to isolate the isomer 9b. The axial  $2\beta$ -alcohol 8b had a band in its ir spectrum at 3450 cm<sup>-1</sup> 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<sup>5</sup> was resolved by means of its bitartrate salt and the resulting enantiomers were hydroborated using Lyle's<sup>2</sup> 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-3piperidinol 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<sup>6</sup> 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  $(\pm)$ -8a showed activity, being perhaps slightly more active than cocaine. In the ptosis reversal test, compounds  $(\pm)$ -8a and  $(\pm)$ -3a were quite active;  $(\pm)$ -2a and  $(\pm)$ -8b were minimally active. It is interesting that conversion of the 2-equatorial hydroxyl of  $(\pm)$ -2a to the axial configuration  $(\pm)$ -8a resulted in a substantial increase in activity in the ptosis reversal test. Acetylation of this axial isomer [forming  $(\pm)$ -10] produced a drop in this activity. In sharp contrast, acetylation of the equatorial isomer  $(\pm)$ -2a caused an increase in ptosis reversal activity. Introduction of a *p*-methoxyl group into the aromatic ring of  $(\pm)$ -3a lowered its activity [see  $(\pm)$ -3b].

The signs of overt stimulation paralleled the results of the ptosis screen, with indications that stimulation lasted as long as 3 hr with  $(\pm)$ -8a and  $(\pm)$ -10.  $(\pm)$ -3a and  $(\pm)$ -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

<sup>†</sup>Ellefson<sup>3</sup> reported failure in the preparation of  $2\alpha$ -acetates 3a and 3b using Ac<sub>2</sub>O; 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.