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# Structure–Activity Relationships in Antifungal Agents. A Survey[1]

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A survey of the literature has been made to find sets of congeneric antifungal agents whose biological activity has been expressed quantitatively. Linear free energy relations correlating 55 sets of data with hydrophobic and electronic parameters have been formulated. The intrinsic activity of various functional groups under isolipophilic conditions is given on a logarithmic scale. In a number of examples antifungal activity closely parallels antibacterial and hemolytic activity, suggesting that such fungicides bring about their action by membrane perturbation.

We have been interested in the recent efforts to place the discussion of biochemical structure–activity relationships in mathematical terms.[2-7] A useful mathematical model can be constructed from the hypotheses[8,9] formulated in eq 1 and 2. It is assumed

$$\log \frac{1}{C} = -k(\log P)^2 + k' \log P + k'' \log k_X + k''' \quad (1)$$

$$\log k_X = k_1 \log P + k_2(\text{elect}) + k_3(\text{steric}) + k_4 \quad (2)$$

in eq 1 that the first 2 terms on the right side account for hydrophobic interactions in the movement of drug from point of application to the sites of action. $C$ in eq 1 is the molar concentration causing a standard biological response ($LD_{50}$, $ED_{50}$, etc.). Once the drug has reached the site of action, the biological response will be proportional to the rate or equilibrium constant ($k_X$) of a critical chemical or physical reaction. We have suggested that a Hammett-like treatment can be applied to log $k_X$ as shown in eq 2. In these equations, $P$ stands for the octanol–$H_2O$ partition coefficient of the *un-ionized* form of the drug unless otherwise noted, and electronic and steric effects of the different members of a set of congeners can be approximated by the use of suitable substituent constants. In eq 2, log $P$ accounts for the last partitioning step of drug onto the active site or enzyme. Substitution of eq 2 into eq 1 gives a model of some general utility for which the disposable parameters ($k_1$–$k_4$) can be calculated by the method of least squares. It may also be profitable to explore the use of higher order equations.[10-12] It is possible that, for any given set of congeners, modifications have been made in such a way that not all substituent effects (electronic, hydrophobic, and steric) are evident or important. Thus one must employ regression analysis and analysis of variance to establish the validity of any given term. For example, although Taft's steric parameter $E_s$ may not generally be useful, in certain instances critical insight into biochemical reaction mechanisms can be gained through its use.[13] In exploring the electronic effect of substituents on reactions, we have found the constants $\sigma$, $\sigma^+$, $\sigma^-$, and $E_R$ to be most useful.[2]

Since a very large amount of work has been done in studying fungicides and data are available on a variety of congeneric sets of fungicides, it seemed worthwhile to attempt a survey and summary of the results in this field. While we are interested in all aspects of the structure–activity problem, we are particularly interested at present in assessing the usefulness of the parameter log $P_0$. This constant represents[2] the ideal lipophilic character for a set of congeners acting *via* a common mechanism. For 16 different sets of hypnotics we found[9] log $P_0 = 2$. For nonspecific Gram-negative drugs we found[14] log $P_0 \cong 4$ and, for Gram-positive organisms, log $P_0 \cong 6$. We are interested in comparing log $P_0$ for fungicides with the other established log $P_0$ values.

As we have so often observed, while data are available from a wide variety of sets of fungicides, the derivatives chosen are usually not ideal for separating the various substituent effects. Nevertheless, some useful gen-

(1) This work was supported by National Institutes of Health Grant CA 11110.

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(7) A. Cammarata, *J. Med. Chem.*, **11**, 1111 (1968).

(8) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).

(9) (a) C. Hansch, A. R. Steward, S. M. Anderson, and D. L. Bentley, *J. Med. Chem.*, **11**, 1 (1968); (b) J. T. Penniston, L. Beckett, D. L. Bentley, and C. Hansch, *Mol. Pharmacol.*, **5**, 333 (1969).

(10) C. Hansch and S. M. Anderson, *J. Med. Chem.*, **10**, 745 (1967).

(11) T. Fujita and C. Hansch, *ibid.*, **10**, 991 (1967).

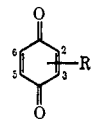
(12) J. A. Singer and W. P. Purcell, *ibid.*, **10**, 1000 (1967).

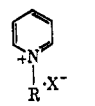
(13) C. Hansch and E. J. Lien, *Biochem. Pharmacol.*, **17**, 709 (1968).

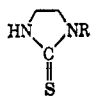
(14) E. J. Lien, C. Hansch, and S. M. Anderson, *J. Med. Chem.*, **11**, 430 (1968).

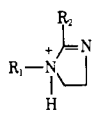
TABLE I

ANTIFUNGAL DATA AND PHYSICAL CONSTANTS USED IN THE REGRESSION ANALYSES

| Ia | R | Log *P* | Log 1/*C* obsd[a] Eq 11 | Eq 13 |
|---|---|---|---|---|
|  | H | 0.20[ss] | 4.19 | 4.43 |
| | 2-Me | 0.70 | 4.00 | 3.19 |
| | 2,5-$Me_2$ | 1.20 | 5.00 | 5.00 |
| | 3,6-$(OH)_2$-2,5-$Cl_2$ | 0.28 | 2.96 | 3.96 |
| | 2,5-$Cl_2$ | 1.62 | 5.52 | 5.10 |
| | 2,6-$Cl_2$ | 1.62 | 5.00 | 5.00 |
| | 2,3,5,6-$Cl_4$ | 3.04 | 5.40 | 5.40 |
| | 5,6-$(C_4H_4)$ | 1.78[ss] | 5.10 | 5.22 |
| | 2-Me-5,6-$(C_4H_4)$ | 2.28 | 5.10 | 5.05 |
| | 2,3-$Cl_2$-5,6-$(C_4H_4)$ | 3.20 | 7.00 | 6.70 |

| Ib | R | X⁻ | Log *P* | Log 1/μm cm$^{-2}$ obsd[b] Eq 37 | Eq 38 | Eq 39 | Eq 40 |
|---|---|---|---|---|---|---|---|
|  | $C_{12}H_{25}$ | Br | 1.05 | 3.07 | 3.09 | | 3.65 |
| | $C_6H_{13}$ | Cl | −1.95 | | 0.91 | 0.33 | 1.18 |
| | $C_8H_{17}$ | Cl | 0.95[ss] | 1.41 | 1.62 | 1.91 | 2.38 |
| | $C_{10}H_{21}$ | Cl | 0.05 | 2.57 | 2.66 | 2.95 | 3.15 |
| | $C_{12}H_{25}$ | Cl | 1.05 | 3.01 | 2.94 | 3.06 | 3.39 |
| | $C_{14}H_{29}$ | Cl | 2.05 | 3.28 | 3.51 | 3.17 | 3.73 |
| | $C_{16}H_{33}$ | Cl | 3.05 | 3.20 | 3.32 | 2.97 | 3.51 |
| | $C_{18}H_{37}$ | Cl | 4.05 | 3.06 | 2.93 | 3.00 | 3.08 |

| Ic | R | Log *P* | Log 1/*C* obsd[c] Eq 26 | Eq 28 |
|---|---|---|---|---|
|  | *n*-Bu | 1.34 | 2.07 | 2.29 |
| | *n*-Am | 1.84 | 2.54 | 2.76 |
| | *n*-Hex | 2.34 | 2.92 | 3.13 |
| | *n*-Hep | 2.84 | 3.10 | 3.55 |
| | *n*-Oct | 3.34 | 3.43 | 3.75 |
| | *n*-Non | 3.84 | 2.99 | |

| Id | $R_1$ | $R_2$ | Log *P* | Log 1/*C* obsd[d] Eq 31 | Eq 32 | Eq 33 | Eq 34 |
|---|---|---|---|---|---|---|---|
|  | HOEt | $C_5H_{11}$ | 0.07 | 1.76 | 2.09 | 2.19 | 2.32 |
| | HOEt | $C_{11}H_{23}$ | 3.07 | 3.65 | 4.13 | 4.43 | 4.28 |
| | HOEt | $C_{13}H_{27}$ | 4.07 | 4.43 | 4.64 | 4.89 | 5.43 |
| | HOEt | $C_{15}H_{31}$ | 5.07 | 4.88 | 4.91 | 4.90 | 5.51 |
| | HOEt | $C_{17}H_{35}$ | 6.07 | 5.04 | 4.99 | 4.99 | 5.77 |
| | HOEt | $C_{17}H_{33}$ | 5.77 | 4.76 | 4.79 | 4.77 | 5.11 |
| | HOEt | $C_{18}H_{35}$ | 6.27 | 4.59 | 4.82 | 4.64 | 5.36 |
| | HOEt | $C_{21}H_{43}$ | 8.07 | 4.98 | 4.57 | 4.29 | 5.01 |
| | HOEt | $C_{25}H_{51}$ | 10.07 | 3.15 | 2.97 | 3.31 | 3.60 |
| | H | $C_{11}H_{23}$ | 3.55 | 3.12 | 3.55 | 3.60 | 3.43[e] |
| | H | $C_{17}H_{35}$ | 6.55 | 4.31 | 4.41 | 4.57 | 5.21 |
| | $H_2NEt$ | $C_{17}H_{35}$ | 6.07 | 4.84 | 4.74 | 4.96 | 5.40 |
| | Allyl | $C_{17}H_{35}$ | 7.75 | 4.83 | 4.54 | 4.77 | 5.31 |
| | Bu | $C_{17}H_{35}$ | 8.55 | 4.87 | 4.60 | 4.67 | 5.20 |
| | Hex | $C_{17}H_{35}$ | 9.55 | 5.08 | 4.45 | 4.34 | 4.95 |

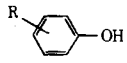
| Ie | R | Log *P* | σ* | $E_s$ | Log 1/*C* obsd[e] Eq 66 | Eq 67 |
|---|---|---|---|---|---|---|
| $BrCH_2CONHR$ | Pr | 0.84 | −0.12 | −0.36 | 4.00 | 3.40 |
| | Allyl | 0.54 | 0.13[f] | −0.22[f] | 4.00 | 3.40 |
| | *i*-Pr | 0.64 | −0.19 | −0.47 | 3.40 | |
| | *n*-Bu | 1.34 | −0.13 | −0.39 | 4.10 | 4.00 |
| | *i*-Bu | 1.14 | −0.13 | −0.93 | 4.00 | 3.40 |
| | *sec*-Bu | 1.14 | −0.21 | −1.13 | 3.10 | 3.00 |
| | *n*-Am | 1.84 | −0.13[f] | −0.40 | 4.40 | |
| | *sec*-Am | 1.64 | −0.21[f] | −1.55[f] | 3.40 | |
| | Cyclohexyl | 1.85 | −0.15 | −0.79 | 4.00 | 3.40 |
| | *n*-Hex | 2.34 | −0.13[f] | −0.40[f] | 5.00 | 4.10 |
| | 2-(EtBu) | 2.14 | −0.23[f] | −1.74[f] | 3.70 | 3.40 |
| | *n*-Hep | 2.84 | −0.13[f] | −0.40[f] | 5.00 | |
| | *n*-Oct | 3.34 | −0.13[f] | −0.40 | 5.00 | 4.40 |
| | *n*-Dec | 4.34 | −0.13[f] | −0.40 | 4.70 | 4.70 |
| | *n*-$C_{14}H_{29}$ | 6.34 | −0.13[f] | −0.40 | 2.00 | |

| If | R | Log *P* | Log 1/*C* obsd[g] Eq 6 | Eq 7 | Eq 8 | Eq 49 | Eq 50 |
|---|---|---|---|---|---|---|---|
| $RCOO^-Na^+$ | $C_{13}H_{27}$ | 1.80 | | | | | 4.36 |

TABLE I (*Continued*)

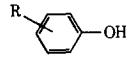
| If | R | Log *P* | Log 1/*C* obsd[g] Eq 6 | Eq 7 | Eq 8 | Eq 49 | Eq 50 |
|---|---|---|---|---|---|---|---|
| | $C_{13}H_{25}$ | 1.50 | | 3.36 | | 3.45 | 4.36 |
| | $C_{12}H_{25}$ | 1.30 | | 3.33 | | 3.86 | 4.16 |
| | $C_{12}H_{21}$ | 0.70 | | 3.02 | | | |
| | $C_{11}H_{23}$ | 0.80 | | 3.13 | | 3.76 | 4.00 |
| | $C_{11}H_{21}$ | 0.50 | | 3.00 | | 3.82 | 4.12 |
| | $C_{10}H_{21}$ | 0.30 | 2.09 | 2.57 | 2.62 | 3.57 | 3.79 |
| | $C_{10}H_{19}$ | 0.00 | 2.09 | 2.49 | 2.66 | 3.66 | 3.96 |
| | $C_9H_{19}$ | −0.20 | 1.94 | 2.12 | 2.46 | 3.36 | 3.54 |
| | $C_8H_{17}$ | −0.70 | | | 2.35 | 3.20 | 3.35 |
| | $C_8H_{15}$ | −1.00 | 1.49 | 1.89 | 2.42 | 3.35 | 3.49 |
| | $C_7H_{15}$ | −1.20 | 1.56 | 1.51 | 1.98 | 2.98 | 3.20 |
| | $C_6H_{13}$ | −1.70 | 1.00 | 1.21 | 1.64 | 2.64 | 2.82 |
| | $C_5H_{11}$ | −2.20[ss] | 0.37 | 0.76 | 1.37 | 1.89 | 2.11 |
| | $C_5H_9$ | −2.50 | 0.36 | 0.58 | 1.66 | 1.88 | 2.15 |
| | $C_2H_5$ | −3.70 | | −0.53 | 0.39 | 1.17 | 1.39 |

Ig



| R | Log *P* | σ | Log 1/*C* obsd[h] Eq 54 |
|---|---|---|---|
| H | 1.46[ss] | 0.00 | 2.35 |
| 4-Cl | 2.39[ss] | 0.23 | 3.35 |
| 2-Me | 1.96 | −0.14 | 2.70 |
| 2-Me-4-Cl | 2.89 | 0.09 | 3.70 |
| 3-Me | 2.02[ss] | −0.07 | 2.68 |
| 3-Me-4-Cl | 2.95 | 0.16 | 3.70 |
| 2,6-$Me_2$ | 2.46 | −0.28 | 3.35 |
| 2,6-$Me_2$-4-Cl | 3.39 | −0.05 | 4.40 |
| 3,5-$Me_2$ | 2.58 | −0.14 | 3.26 |
| 3,5-$Me_2$-4-Cl | 3.51 | 0.09 | 4.22 |
| 2-*i*-Pr | 2.76 | −0.23[i] | 3.35 |
| 2-*i*-Pr-4-Cl | 3.69 | 0.00 | 4.30 |
| 3-Me-6-*tert*-Bu | 3.70 | −0.59 | 3.70 |
| 3-Me-4-Cl-6-*tert*-Bu | 4.63 | −0.36 | 4.30 |
| 2-Cyclohex | 3.97 | −0.23 | 4.00 |
| 2-Cyclohex-4-Cl | 4.90 | 0.00 | 4.40 |
| 2-Ph | 3.59 | 0.00 | 4.10 |
| 2-Ph-4-Cl | 4.52 | 0.23 | 4.52 |

Ih

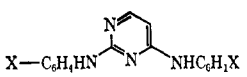


| R | Log *P* | σ | Log 1/*C* obsd[j] Eq 29 |
|---|---|---|---|
| H | 1.46[ss] | 0.00 | 2.35 |
| 2-Cl | 2.15[ss] | 0.21[l] | 2.85 |
| 4-Me | 1.94[ss] | −0.17 | 2.74 |
| 4-Me-2-Cl | 2.63 | 0.04 | 3.07 |
| 2-Me | 1.96 | −0.14[l] | 2.74 |
| 6-Cl-2-Me | 2.65 | 0.07 | 2.77 |
| 4-*i*-Pr | 2.86 | −0.15 | 3.35 |
| 2-Cl-4-*i*-Pr | 3.55 | 0.06 | 3.40 |
| 2-*i*-Pr | 2.76 | −0.23[m] | 3.30 |
| 4-*tert*-Bu | 3.14 | −0.20 | 3.46 |
| 2-Cl-4-*tert*-Bu | 3.83 | 0.01 | 3.52 |
| 4-$C_9H_{19}$ | 5.94 | −0.16[l] | 4.14 |
| 2-Cl-4-$C_9H_{19}$ | 6.65 | 0.05 | 3.82 |
| 4-Ph | 3.59 | 0.01[n] | 4.00 |
| 2-Cl-4-Ph | 4.28 | 0.22 | 4.00 |
| 2-Ph | 3.59 | 0.01 | 4.10 |
| 6-Cl-2-Ph | 4.28 | 0.22 | 4.00 |
| 2-Cyclohex | 3.97 | −0.15[o] | 4.00 |
| 6-Cl-2-Cyclohex | 4.67 | 0.06 | 3.85 |
| 3,5-$Me_2$ | 2.46 | −0.14 | 3.26 |
| 2-Cl-3,5-$Me_2$ | 3.15 | 0.07 | 3.35 |
| 4-*tert*-Bu-2-Me | 3.64 | −0.34 | 3.45 |
| 6-*tert*-Bu-3-Me | 3.64 | −0.59[p] | 3.64 |
| 2-*tert*-Bu-4-Me | 3.64 | −0.69[q] | 3.82 |
| 2,4-*i*-$Pr_2$ | 4.06 | −0.38[m] | 3.66 |
| 2,4-$Am_2$ | 6.46 | −0.30[r] | 4.05 |
| 6-Cl-2-*i*-Pr | | | |
| 6-Cl-4-*tert*-Bu-2-Me[k] | | | |
| 2-Cl-6-*tert*-Bu-3-Me[k] | | | |
| 6-Cl-2-*tert*-Bu-4-Me[k] | | | |
| 6-Cl-2-4-*i*-$Pr_2$[k] | | | |

TABLE I (*Continued*)

| Ii | X | Log $P$ | $\sigma$ | Log $1/C$ obsd[s] Eq 10 |
|---|---|---|---|---|
| $XC_6H_4CH_2NCS$ | H | 2.83[ss] | 0.00 | 4.80 |
| | 4-Cl | 3.53 | 0.23 | 5.09 |
| | 3-Cl | 3.59 | 0.37 | 5.33 |
| | 4-Br | 3.85 | 0.23 | 5.12 |
| | 3-Br | 3.77 | 0.39 | 5.38 |
| | 2-Br | 3.58 | 0.20 | 5.17 |
| | 4-I | 4.09 | 0.28 | 5.62 |
| | 3-I | 3.98 | 0.35 | 5.59 |
| | 4-Me | 3.35 | −0.17 | 4.37[z] |
| | 3-Me | 3.34 | −0.07 | 5.30 |
| | 4-MeO | 2.79 | −0.27 | 4.39[z] |
| | 2-MeO | 2.50 | −0.27 | 4.60 |
| | 4-$NO_2$ | 3.07 | 0.78 | 4.80 |
| | 3-$NO_2$ | 2.94 | 0.71 | 4.80 |
| | 4-CN | 2.51 | 0.63 | 4.85 |

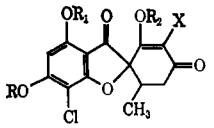
| | | | Log $1/C$ obsd[t] | | | | | |
|---|---|---|---|---|---|---|---|---|
| Ij | R | $\pi_R$ | Eq 42 | Eq 43 | Eq 44 | Eq 45 | Eq 46 | Eq 47 |
| $(CH_3)_2RN^+CH_2C_6H_5 \cdot Cl^-$ | $C_9H_{19}$ | −0.58 | | 2.54 | 2.72 | 2.54 | 2.54 | 2.72 |
| | $C_{10}H_{21}$ | −0.08[ss] | 2.74 | 2.74 | 3.04 | 3.04 | 3.04 | 3.04 |
| | $C_{11}H_{23}$ | 0.42 | 2.46 | 3.59 | 3.59 | 3.59 | 3.59 | 3.76 |
| | $C_{12}H_{25}$ | 0.92 | 3.09 | 4.09 | 4.09 | 4.09 | 4.09 | 4.09 |
| | $C_{13}H_{27}$ | 1.42 | 4.11 | 4.11 | 4.11 | 4.63 | 4.63 | 4.50 |
| | $C_{14}H_{29}$ | 1.92 | 4.12 | 4.12 | 4.82 | 5.12 | 4.82 | 4.82 |
| | $C_{15}H_{31}$ | 2.42 | 4.14 | 4.14 | 4.84 | 5.14 | 5.14 | 4.84 |
| | $C_{16}H_{33}$ | 2.92 | 3.16 | 4.16 | 5.16 | 4.86 | 4.56 | 5.16 |
| | $C_{17}H_{35}$ | 3.42 | 3.18 | 4.18 | 4.88 | 4.88 | 4.16 | 4.88 |
| | $C_{18}H_{37}$ | 3.92 | 2.89 | 3.19 | 4.89 | 4.19 | 3.59 | 4.89 |
| | $C_{19}H_{39}$ | 4.42 | 3.21 | 3.21 | 4.61 | 4.21 | 3.61 | 4.91 |

| Ik | X | Log $P$ | $\sigma$ | Log $1/C$ obsd[y] Eq 14 |
|---|---|---|---|---|
|  | *p*-$NO_2$ | 2.38 | 0.78 | 5.75 |
| | *p*-Cl | 3.26 | 0.23 | 5.60 |
| | *m*-Cl | 3.36 | 0.37 | 5.61 |
| | *o*-Cl | 2.78 | 0.21 | 5.51 |
| | *p*-HO | −0.74 | −0.36 | 3.72 |
| | *p*-MeO | 1.16 | −0.27 | 4.61 |
| | *p*-Me | 2.38 | −0.17 | 5.51 |
| | *p*-$CH_3CO$ | 1.18 | 0.52 | 4.71 |
| | *p*-$H_2NSO_2$ | −1.72 | 0.62 | 5.48[z] |

| Il | $R_1$ | $R_2$ | $R_3$ | Log $P$ | $\Sigma\sigma^*(R_2,R_3)$[v] | Log $RBR$ obsd[w] Eq 24 |
|---|---|---|---|---|---|---|
| $R_1COCH{=}CR_2R_3$ | $C_6H_5$ | H | 4-$NH_2C_6H_4$ | 2.78 | 1.09 | 1.35 |
| | $C_6H_5$ | H | H | 1.88 | 0.98 | 0.42 |
| | 4-$CH_3C_6H_4$ | H | H | 2.38 | 0.98 | −0.36[z] |
| | 4-$CH_3OC_6H_4$ | H | H | 1.85 | 0.98 | −0.32[z] |
| | 4-$ClC_6H_4$ | H | H | 2.59 | 0.98 | 0.52 |
| | 2-$HOC_6H_4$ | H | H | 1.21 | 0.98 | 1.17[z] |
| | 2-HO-5-$ClC_6H_3$ | H | H | 1.92 | 0.98 | 0.26 |
| | 2-HO-5-$CH_3C_6H_3$ | H | H | 1.71 | 0.98 | 1.11 |
| | 2-HO-4-$CH_3C_6H_3$ | H | H | 1.71 | 0.98 | 0.91 |
| | 4-HO-2-$CH_3C_6H_3$ | H | H | 1.71 | 0.98 | −0.32 |
| | 2-HO-3-$CH_3C_6H_3$ | H | H | 1.71 | 0.98 | 0.21 |
| | 4-HO-3-$CH_3C_6H_3$ | H | H | 1.71 | 0.98 | 0.21 |
| | 2-HO-4,6-$(CH_3)_2C_6H_2$ | H | H | 2.21 | 0.98 | 0.72 |
| | 2-HO-5-$CH_3OC_6H_3$ | H | H | 1.19 | 0.98 | −0.05 |
| | 2-$CH_3$-4-HO-5-*i*-$PrC_6H_2$ | H | H | 3.01 | 0.98 | 1.01 |
| | (*trans*) $C_6H_5$ | H | $C_6H_5CO$ | 2.96 | 2.69 | 1.85 |
| | (*cis*) $C_6H_5$ | H | $C_6H_5CO$ | 2.96 | 2.69 | 1.85 |
| | *cis*-Dibenzoyldichloroethylene | | | 4.20 | 5.14 | 1.96 |
| | 2,4,6-$(CH_3)_3C_6H_2$ | H | $C_6H_5CO$ | 4.46 | 2.69 | 1.44 |
| | 4-$CH_3C_6H_4$ | H | 4-$CH_3C_6H_4CO$ | 3.96 | 2.69 | 0.72[z] |
| | 4-$ClC_6H_4$ | H | 4-$ClC_6H_4CO$ | 4.38 | 2.69 | 1.96 |
| | 5-$CH_3$-2-$ClC_6H_3$ | H | 5-$CH_3$-2-$ClC_6H_3CO$ | 5.38 | 2.69 | 2.00 |
| | 3-$CH_3$-4-$ClC_6H_3$ | H | 3-$CH_3$-4-$ClC_6H_3CO$ | 5.38 | 2.69 | 2.00 |

TABLE I (*Continued*)

Im



| R | $R_1$ | $R_2$ | X | Log *P* | σ | Log *MR* obsd[w] Eq 15 |
|---|---|---|---|---|---|---|
| Me | Allyl | Me | H | 2.88 | 0.00 | 0.03 |
| *n*-Pr | Me | Me | H | 3.18 | 0.00 | 0.03 |
| Allyl | Me | Me | H | 2.88 | 0.00 | 0.03 |
| Me | Me | Me | Me | 2.68 | −0.17 | 0.01 |
| Me | Me | Me | *n*-Pr | 3.68 | −0.15 | 0.35 |
| Me | Me | Me | Allyl | 3.38 | −0.10 | 0.35 |
| Me | Me | Me | Cl | 2.57 | 0.23 | 0.64 |
| Me | Me | Me | Br | 2.78 | 0.23 | 0.69 |
| Me | Me | Me | I | 3.18 | 0.28 | 1.03 |
| Me | Me | Et | H | 2.68 | 0.00 | 0.31 |
| Me | Me | *n*-Pr | H | 3.18 | 0.00 | 0.63 |
| Me | Me | *n*-Bu | H | 3.68 | 0.00 | 0.95 |
| Me | Me | Allyl | H | 2.88 | 0.00 | 0.63 |
| Me | Me | Ph | H | 3.81 | 0.00 | 0.67 |
| Me | Me | $PhCH_2$ | H | 4.31 | 0.00 | 0.99 |
| Me | Me | Et | Cl | 3.07 | 0.23 | 0.66 |
| Me | Me | Et | Br | 3.28 | 0.23 | 0.70 |
| Me | Me | Et | I | 3.68 | 0.28 | 1.35 |
| Me | Me | Et | Et | 3.68 | −0.15 | 0.35 |
| Me | Me | Et | $PhCH_2$ | 5.31 | −0.10 | 1.31 |
| Me | Me | *n*-Pr | Br | 3.78 | 0.23 | 1.92 |
| Me | Me | *n*-Pr | *n*-Pr | 4.68 | −0.15 | 0.98 |
| Me | $PhCH_2$ | Me | H | 4.31 | 0.00 | 0.38[z] |
| Et | Me | Me | H | 2.68 | 0.00 | 0.92[z] |
| Me | Me | Me | $PhCH_2$ | 4.81 | −0.10 | 0.40[z] |
| Me | Me | *n*-Pr | I | 4.18 | 0.28 | 2.86[z] |
| Me | Me | *n*-Pr | $PhCH_2$ | 5.83 | −0.10 | 2.83[z] |
| Me | Me | *n*-Bu | $PhCH_2$ | 6.33 | −0.10 | 0.14[z] |

In

$RR'NCSS^-Na^+$

| R | R | Σπ | Σσ | Log 1/*C* obsd[y] Eq 56 |
|---|---|---|---|---|
| Me | H | 0.50 | 0.49 | 4.03 |
| Et | H | 1.00 | 0.39 | 3.91 |
| *n*-Pr | H | 1.50 | 0.37 | 3.74 |
| *n*-Bu | H | 2.00 | 0.36 | 3.25 |
| *i*-Bu | H | 1.80 | 0.36 | 2.96 |
| Me | Me | 1.00 | 0.00 | 4.88 |
| Et | Et | 2.00 | −0.20 | 3.77 |
| *i*-Pr | *i*-Pr | 2.60 | −0.38 | 3.22 |
| *i*-Pr | H | 1.30 | 0.30 | 2.97 |
| $(CH_2)_4$ | | 1.64 | 0.00 | 3.67 |
| $(CH_2)_5$ | | 2.05 | 0.00 | 2.91 |

Io

$RCOO^-Na^+$

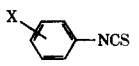
| R | Log *P* | Log 1/*C* obsd[z] Eq 35 |
|---|---|---|
| $C_4H_9$ | −2.70 | 1.70 |
| $C_5H_{11}$ | −2.20 | 2.40 |
| $C_6H_{13}$ | −1.70 | 3.00 |
| $C_7H_{15}$ | −1.20 | 3.00 |
| $C_8H_{17}$ | −0.70 | 3.00 |
| $C_9H_{19}$ | −0.20 | 2.40 |

Ip

ROH

| R | Log *P* | Log 1/*C* obsd[aa] Eq 22 |
|---|---|---|
| $C_6H_{13}$ | 1.84 | 1.90 |
| $C_8H_{17}$ | 2.84 | 2.75 |
| $C_{10}H_{23}$ | 3.84 | 3.60 |
| $C_{11}H_{25}$ | 4.34 | 3.58 |
| $C_{12}H_{17}$ | 4.84 | 2.16 |

Iq



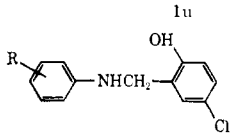
| X | Log *P* | σ | Log 1/*C* obsd[aa] Eq 27 |
|---|---|---|---|
| H | 3.28 | 0.00 | 4.70 |
| 4-Cl | 3.99 | 0.23 | 4.90 |
| 3-Br | 4.14 | 0.39 | 5.15 |
| 4-Br | 4.14 | 0.23 | 5.20 |
| 4-I | 4.40 | 0.28 | 5.35 |
| $4\text{-}EtO_2C$ | 3.77 | 0.45 | 5.10 |
| 4-PhO | 5.36 | −0.32 | 5.30 |
| $4\text{-}NO_2$ | 3.00 | 0.78 | 4.60 |
| $3,4\text{-}(CH)_4$ | 4.63 | 0.17 | 5.30 |
| 4-Ph | 5.41 | 0.01 | 5.20 |

TABLE I (*Continued*)

| Ir | R | Log *P* | Log 1/*C* obsd[bb] Eq 25 |
|---|---|---|---|
| Phenols | H | 1.46[ss] | 0.90 |
| | 4-Br | 2.59[ss] | 1.94 |
| | 2-Me-4-Br | 3.09 | 2.35 |
| | 2-Et-4-Br | 3.59 | 2.70 |
| | 2-Pr-4-Br | 4.09 | 3.18 |
| | 2-Bu-4-Br | 4.59 | 3.66 |
| | 2-Am-4-Br | 4.59 | 3.66 |
| | 2-Am-4-Br | 5.09 | 3.78 |
| | 2-*sec*-Am-4-Br | 4.89 | 3.47 |
| | 2-Hex-4-Br | 5.59 | 3.81 |
| | 2-Cyclohexyl-4-Br | 5.10 | 3.71 |
| | 2-Br | 2.35[ss] | 1.72 |
| | 2-Br-4-*tert*-Am | 4.53 | 3.23 |
| | 2-Br-4-Hex | 5.35 | 3.71 |
| | 2-Br-4-Pr-3,5-$Me_2$ | 4.97 | 3.43 |

| Is | R | Log *P* | Log 1/*C* obsd[cc] Eq 3 |
|---|---|---|---|
| *p*-$HOC_6H_4COOR$ | Me | 1.45 | 1.80 |
| | Et | 1.95 | 2.40 |
| | Pr | 2.45 | 3.00 |
| | Bu | 2.95 | 3.00 |
| | Pent | 3.45 | 3.20 |
| | Hex | 3.95 | 3.60 |
| | Hep | 4.45 | 4.22 |

| It | $R_1$ | $R_2$ | Log *P* | Log 1/*C* obsd[dd] Eq 4 | Log 1/*C* obsd[dd] Eq 5 |
|---|---|---|---|---|---|
| $R_1R_2NCH_2CH_2N(CH_3)_2$ | Ph | Me | 1.93 | 2.73 | 2.73 |
| | Cyclohex | Me | 2.31 | 2.27 | 2.27 |
| | *n*-Oct | *n*-Pr | 4.60 | 2.86 | |
| | *n*-Non | Me | 4.30 | 3.31 | 2.84 |
| | *n*-Hep | *n*-Pr | 4.30 | 3.73 | 2.84 |
| | *n*-Oct | *n*-Pr | 4.80 | 3.82 | 2.86 |
| | *n*-Hep | *n*-Bu | 4.80 | 2.86[z] | 2.39[z] |
| | *n*-$C_{12}H_{25}$ | Me | 5.80 | 4.35 | 4.35 |
| | *n*-Hep | *n*-Pr | 4.00 | 2.84 | |
| | *n*-$C_{14}H_{29}$ | Me | 6.80 | 5.45 | 4.92[z] |
| | *n*-Oct | *n*-Bu | 5.30 | 2.89[z] | 3.36 |
| | Cyclopent | Me | 1.94 | 3.66[z] | 2.71 |
| | 1-Naph | Me | 3.17 | 3.46 | |
| | *n*-Oct | *n*-Hex | 6.30 | 4.45 | 3.41 |
| | 1-Naph | *n*-Bu | 4.67 | 3.53 | |
| | 1-Naph | *n*-Oct | 6.67 | 5.12 | 4.21 |
| | Ph | *n*-Oct | 5.43 | 4.14 | 3.84 |
| | Ph | *n*-Bu | 3.43 | 3.77 | 2.82 |
| | 4-MeO-Ph | *n*-Hep | 4.89 | 4.77 | 2.96 |
| | 1-Naph | *n*-$C_{10}H_{21}$ | 7.67 | 5.15 | |
| | 1-Naph | *n*-Hex | 5.67 | 5.08 | 4.47 |
| | 1-Naph | *n*-Non | 7.17 | 5.42 | 4.53 |
| | $C_{13}H_{27}$ | Me | 6.30 | 3.81 | 4.15 |
| | $C_{18}H_{37}$ | Me | 8.80 | 6.44 | 4.47 |
| | $C_{17}H_{35}$ | Me | 8.30 | 5.42 | 4.45 |
| | 4-Cl-Ph | Hep | 5.86 | 5.87[z] | 3.90 |

| Iu | R | Log *P* | σ | Log 1/*C* obsd[ee] Eq 18 | Eq 19 | Eq 20 |
|---|---|---|---|---|---|---|
|  | H | 3.79 | 0.00 | 3.37 | 3.89 | 4.37 |
| | 4-Me | 4.29 | −0.17 | 3.39 | 4.39 | 4.39 |
| | 2,4-$Me_2$ | 4.79 | −0.31 | 3.42 | 4.42 | 4.42 |
| | 4-Cl | 4.72 | 0.23 | 3.95 | 4.95 | 4.95 |
| | 3-Cl | 4.77 | 0.37 | 3.95 | 4.95 | 4.95 |
| | 2,4-$Cl_2$ | 5.41 | 0.44 | 4.48 | 5.00 | 5.00 |
| | 4-COOH | 3.91 | 0.27[f] | | | |
| | 2-COOH | 3.91 | 0.27 | | 3.44[z] | 3.97[z] |
| | *p*-OH | 2.72 | −0.36 | 2.92 | 3.92 | 3.92 |
| | 2,3-($C_4H_4$) | 5.14 | 0.17 | 3.97 | 4.97 | 4.97 |

| Iv | R | Log *P* | Log 1/*C* obsd[ff] Eq 48 |
|---|---|---|---|
| $RCOO^-Na^+$ | H | −4.70 | 2.09 |
| | Me | −4.20 | 2.27 |
| | Et | −3.70 | 2.37 |

TABLE I (*Continued*)

| Iv | R | Log *P* | Log 1/*C* obsd[ff] Eq 48 |
|---|---|---|---|
| | *n*-Pr | −3.20 | 2.45 |
| | *i*-Pr | −3.40 | 2.17 |
| | *n*-Bu | −2.70 | 2.54 |
| | *n*-Am | −2.20 | 2.89 |
| | *n*-Hex | −1.70 | 3.14 |
| | *n*-Hep | −1.20 | 3.23 |
| | *n*-Oct | −0.70 | 3.39 |
| | *n*-Non | −0.20 | 3.69 |
| | *n*-$C_{10}H_{21}$ | 0.30 | 3.84 |
| | *n*-$C_{10}H_{19}$ | 0.00 | 3.90 |
| | *n*-$C_{11}H_{23}$ | 0.80 | 2.95 |
| | *n*-$C_{12}H_{25}$ | 1.30 | 2.68 |

| Iw | R | Log *P* | Log 1/*C* obsd[gg] Eq 30 |
|---|---|---|---|
| 2-R-4-$ClC_6H_3OH$ | H | 2.39[ss] | 4.00 |
| | Me | 3.07 | 4.00 |
| | $CH(NH_2)CH_3$ | 1.65 | 3.40 |
| | $COCH_3$ | 2.28 | 3.00 |
| | $CH_2Ph$ | 5.02 | 5.30 |
| | $CH(NH_2)Ph$ | 3.28 | 4.30 |
| | COPh | 3.91 | 4.95 |
| | $CH_2$-Pyr-2 | 3.72 | 5.00 |
| | $CH_2$-Thenyl-2 | 4.88 | 5.30 |
| | $CH_2$-Naph-2 | 6.44 | 5.30 |
| | $CH_2$-Furyl-2 | 4.39 | 4.70 |

| Ix | R | Log *P* | Log 1/*C* obsd[ii] Eq 21 |
|---|---|---|---|
|  | *n*-Hex | 3.13 | 3.18 |
| | *n*-Hep | 3.63 | 3.52 |
| | *n*-Oct | 4.13 | 4.26 |
| | *n*-Non | 4.63 | 4.59 |
| | *n*-$C_{10}H_{21}$ | 5.13 | 4.32 |
| | *n*-$C_{11}H_{23}$ | 5.63 | 3.65 |

| Iy | R | Log *P* | Log 1/*C* obsd[hh] Eq 51 |
|---|---|---|---|
| $RCOO^-Na^+$ | *n*-Am | −2.20 | 3.37 |
| | *n*-Hex | −1.70 | 3.42 |
| | *n*-Hep | −1.20 | 3.76 |
| | *n*-Oct | −0.70 | 3.80 |
| | *n*-Non | −0.20 | 4.14 |
| | *n*-$C_{10}H_{21}$ | 0.30 | 4.47 |
| | *n*-$C_{10}H_{19}$ | 0.00 | 4.47 |
| | *n*-$C_{11}H_{23}$ | 0.80 | 4.51 |
| | *n*-$C_{12}H_{25}$ | 1.30 | 4.53 |
| | *n*-$C_{13}H_{27}$ | 1.80 | 3.96 |
| | 1-Me-$C_8H_{16}$ | −0.40 | 3.84 |
| | 1-Me-$C_{11}H_{22}$ | 1.10 | 4.53 |
| | 2-Me-$C_{11}H_{22}$ | 1.10 | 4.23 |
| | 3-Me-$C_{11}H_{22}$ | 1.10 | 4.53 |
| | 3,7,11-$(Me)_3C_{13}H_{24}$ | 2.70 | 4.03 |
| | 2-Me-$C_{13}H_{26}$ | 2.10 | 3.68[z] |

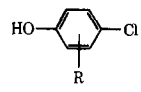
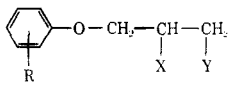
| Iz | R | Log *P* | Log *PC'* obsd[jj] Eq 23 |
|---|---|---|---|
|  | 2-H | 2.39 | 0.76 |
| | 2-Me | 2.89 | 1.25 |
| | 2-Et | 3.39 | 1.66 |
| | 2-*n*-Pr | 3.89 | 2.18 |
| | 2-*n*-Bu | 4.39 | 2.50 |
| | 2-*n*-Am | 4.89 | 2.93 |
| | 2-*sec*-Am | 4.69 | 2.73 |
| | 2-*n*-Nex | 5.39 | 3.36 |
| | 2-Cyclohex | 4.90 | 2.83 |
| | 2-*n*-Nep | 5.89 | 3.21 |
| | 3-Me | 2.95 | 1.22 |
| | 3,5-$Me_2$ | 3.39 | 1.62 |
| | 6-Et-3Me | 3.89 | 2.34 |
| | 6-*n*-Pr-3-Me | 4.39 | 2.47 |
| | 6-*i*-Pr-3-Me | 4.19 | 2.44 |

TABLE I (*Continued*)

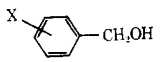
| Iz | R | Log *P* | Log $1/C'$ obsd[jj] Eq 23 |
|---|---|---|---|
| | 2-Et-3,5-$Me_2$ | 4.39 | 2.41 |
| | 6-*sec*-Bu-3-Me | 4.69 | 2.77 |
| | 2-*i*-Pr-3,5-$Me_2$ | 4.69 | 2.77 |
| | 6-$Et_2$-Me-3-Me | 5.19 | 3.05 |
| | 6-*i*-Pr-2-Et-3-Me | 5.19 | 2.52 |
| | 2-*sec*-Bu-3,5-$Me_2$ | 5.19 | 3.09 |
| | 2-$Et_2$Me-3,5-$Me_2$ | 5.69 | 3.23 |

Ia'



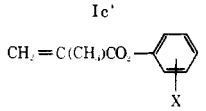
| R | X | Y | Log *P* | $\Sigma\sigma$ | Log $1/C$ obsd[kk] Eq 17 |
|---|---|---|---|---|---|
| 2-Me | OH | OH | 1.38 | −0.14 | 2.26 |
| 2-Me | OH | H | 2.14 | −0.14 | 2.46 |
| 2-Me | H | OH | 2.34 | −0.14 | 2.79 |
| 2-Cl | OH | OH | 1.29 | 0.21 | 2.31 |
| 2-Cl | OH | H | 2.05 | 0.21 | 2.84 |
| 4-Cl | OH | OH | 1.40 | 0.23 | 2.31 |
| 4-Cl | OH | H | 2.16 | 0.23 | 2.81 |
| 4-Cl | H | OH | 2.36 | 0.23 | 3.07 |
| 2,6-$Cl_2$ | OH | OH | 1.88 | 0.42 | 2.37 |
| 2,6-$Cl_2$ | OH | H | 2.64 | 0.42 | 3.04 |
| 2,4-$Cl_2$ | OH | H | 2.75 | 0.44 | 3.35 |
| 2,4-$Cl_2$ | OH | OH | 1.99 | 0.44 | 2.61 |
| 4-Cl-2-Me | OH | H | 2.84 | 0.09 | 3.30 |
| 4-Cl-2-Me | OH | OH | 2.08 | 0.09 | 2.33 |
| 4-Cl-3-Me | OH | OH | 1.91 | 0.16 | 2.90 |
| 4-Cl-3-Me | OH | H | 2.67 | 0.16 | 3.30 |
| 6-Cl-2-Me | OH | OH | 1.97 | 0.07 | 2.33 |
| 6-Cl-2-Me | OH | H | 2.73 | 0.07 | 2.70[z] |
| 6-Cl-2-Me | H | OH | 2.93 | 0.07 | 2.78[z] |
| 4-Cl-2,6-$Me_2$ | OH | OH | 2.76 | −0.05 | 2.76 |
| 4-Cl-2,6-$Me_2$ | OH | H | 3.52 | −0.05 | 3.51 |
| 4-Cl-2,6-$Me_2$ | H | OH | 3.72 | −0.05 | 3.51 |
| 4-Cl-3,5-$Me_2$ | OH | OH | 2.42 | 0.09 | 3.24 |
| 2,6-$Cl_2$-4-Me | OH | OH | 2.40 | 0.25 | 3.10 |
| 4-Cl-3,5-$Me_2$ | OH | H | 3.18 | 0.09 | 3.68 |
| 2,6-$Cl_2$-4-Me | OH | H | 3.16 | 0.25 | 3.47 |
| 4-Cl-3,5-$Me_2$ | H | OH | 3.38 | 0.09 | 3.93 |
| 2,6-$Cl_2$-4-Me | H | OH | 3.36 | 0.25 | 3.67 |

Ib'



| X | Log *P* | $\sigma$ | $F_R$ | Log $1/C$ obsd[ll] Eq 16 |
|---|---|---|---|---|
| H | 1.10[ss] | 0.00 | 0.00 | 1.51 |
| 4-Cl | 1.96[ss] | 0.23 | 0.10 | 2.07 |
| 2,4-$Cl_2$ | 2.55 | 0.45 | 0.20 | 3.07 |
| 3,4-$Cl_2$ | 2.80 | 0.60 | 0.18 | 3.07 |
| 2,4,5-$Cl_3$ | 3.39 | 0.82 | 0.28 | 3.32 |
| 3,4,5-$Cl_3$ | 3.64 | 0.97 | 0.26 | 3.63 |
| 2-Br | 1.86 | 0.20 | 0.12 | 2.15 |
| 4-Br | 2.12 | 0.23 | 0.12 | 2.27 |
| 4-I | 2.36 | 0.28 | 0.12 | 2.75 |
| 4-Me | 1.59[ss] | −0.17 | 0.03 | 1.79 |
| 2,4-$Me_2$ | 2.26 | −0.31 | 0.06 | 2.14 |
| 4-Cl-3,5-$Me_2$ | 2.96 | 0.09 | 0.16 | 3.05 |
| 4-I-3,5-$Me_2$ | 3.36 | 0.14 | 0.28 | 3.42 |
| 2-$NO_2$ | 0.87 | 0.76 | 0.41 | 2.49 |
| 4-$NO_2$ | 1.26[ss] | 0.78 | 0.41 | 2.00 |
| 4-CN | 0.78 | 0.63 | 0.24 | 1.67 |
| 2-OH | 0.56 | −0.36 | 0.17 | 1.39 |
| 3-OH | 0.49[ss] | | | 1.39 |
| 4-OH | 0.25[ss] | −0.36 | 0.17 | 1.39 |

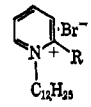
Ic'



| X | Log *P* | $\sigma$ | Log $1/C$ obsd[mm] Eq 55 |
|---|---|---|---|
| H | 1.99 | 0.00 | 2.89 |
| 2-Cl | 2.58 | 0.21 | 3.28 |
| 4-Cl | 2.69 | 0.23 | 3.25 |
| 3-Cl | 2.75 | 0.37 | 3.12 |
| 2,4-$Cl_2$ | 3.28 | 0.44 | 3.49 |
| 2,4,6-$Cl_3$ | 3.87 | 0.65 | 3.46 |
| 2,4,5-$Cl_3$ | 4.04 | 0.81 | 3.54 |
| 2,4,5,6-$Cl_4$ | 4.63 | 1.02 | 3.45 |
| $Cl_5$ | 5.39 | 1.39 | 3.35 |
| $Br_5$ | 6.39 | 1.41 | 3.35 |

TABLE I (*Continued*)

| Id′ | R | Log *P* | Log 1/*C* obsd[oo] Eq 52 | Log 1/*C* obsd[oo] Eq 53 |
|---|---|---|---|---|
| $RNHCNH_2 \cdot CH_3COOH$ ‖ NH | $C_{11}H_{23}$ | 0.65 | 5.30 | 5.15 |
| | $C_{12}H_{25}$ | 1.15[ss] | 5.41 | 5.24 |
| | $C_{13}H_{27}$ | 1.65 | 5.54 | 5.32 |
| | $C_{14}H_{29}$ | 2.15 | 5.51 | 5.38 |
| | $C_{16}H_{33}$ | 3.15 | 5.39 | 5.21 |
| | $C_{18}H_{37}$ | 4.15 | 4.65 | 4.76 |

| Ie′ | R | Log *P* | Log 1/*C* obsd[nn] Eq 41 |
|---|---|---|---|
|  | H | 1.05 | 3.63 |
| | Et | 2.05 | 3.98 |
| | Hex | 4.05 | 4.07 |
| | Hep | 4.55 | 4.12 |
| | 3-Oct | 5.05 | 4.09 |
| | 2-Me-Oct | 5.35 | 3.81 |

| If′ | X | Log *P* | $\sigma$ | Log 1/*C* obsd[pp] Eq 9 | Log 1/*C* obsd[pp] Eq 12 |
|---|---|---|---|---|---|
| $p\text{-}XC_6H_4(CH_2)_2NCS$ | H | 3.33 | 0.00 | 4.32 | 4.80 |
| | Cl | 4.03 | 0.23 | 4.74 | 5.05 |
| | I | 4.59 | 0.28 | 4.85 | 5.15 |
| | Me | 3.85 | −0.17 | 4.60 | 5.28 |
| | MeO | 3.29 | −0.27 | 4.28 | 4.72 |
| | $NO_2$ | 3.57 | 0.78 | 4.41 | 4.72 |

| Ig′ | R | Log *P* | Log 1/*C* obsd[qq] Eq 36 |
|---|---|---|---|
| $RNH_3^+$ | $C_8H_{17}$ | −0.15 | 2.30 |
| | $C_{10}H_{21}$ | 0.85 | 2.58 |
| | $C_{12}H_{25}$ | 1.85[ss] | 2.84 |
| | $C_{14}H_{29}$ | 2.85 | 2.76 |
| | $C_{16}H_{33}$ | 3.85 | 1.76 |
| | $C_{18}H_{37}$ | 4.85 | 1.66 |

[a] From R. G. Owens, *Contrib. Boyce Thompson Inst.*, **17,** 273 (1953). [b] From J. C. LoCicero, D. E. H. Frear, and H. J. Miller, *J. Biol. Chem.*, **172,** 689 (1948); slide germination test employed. [c] From R. G. Ross and R. G. Ludwig, *Can. J. Bot.*, **35,** 65 (1967); *C* is $ED_{50}$ for inhibition of spore germination. [d] From R. H. Wellman and S. E. A. McCallan, *Contrib. Boyce Thompson Inst.*, **14,** 151 (1946); *C* is fungistatic $LD_{50}$ from slide germination test. [e] From J. M. Leonard and V. L. Blackford, *J. Bacteriol.*, **57,** 339 (1947); *C* is lowest *M* concn for 100% inhibn. [f] Estimated from other homologous functions. [g] From O. Wyss, B. J. Ludwig, and R. R. Joiner, *Arch. Biochem.*, **7,** 415 (1945); *C* is *M* concn just inhibiting growth. [h] From H. G. Shirk, R. R. Corey, and P. L. Poelma, *Arch. Biochem. Biophys.*, **32,** 392 (1951); *C* is *M* concn causing 50% growth inhib. [i] $\sigma_0$ of $i\text{-}C_3H_7$ function in phenol. [j] From H. G. Shirk and R. R. Corey, *Arch. Biochem. Biophys.*, **38,** 417 (1952); *C* is same as in *h*. [k] These data points not included in final regression equation because they were very poorly predicted; this is likely due to shielding effects of bulky 2,6-substituents. [l] From A. C. Farthing and B. Nam, "Steric Effects in Conjugated Systems," Academic Press, New York, N. Y., 1958, p 131. [m] See *i*. [n] From R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 595. [o] $\sigma_p$ from M. Charton, *J. Chem. Soc.*, 1205 (1964) used. [p] Taken from report of G. G. Smith and D. A. K. Jones, Abstracts of 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, No. P58M. [q] See *n*, p 591. [r] $\sigma_o$ assumed equal to $\sigma_p$ from M. Charton, *J. Org. Chem.*, **30,** 552 (1965). [s] From L. Drobnica, M. Zemanová, P. Nemec, K. Antos, P. Kristián, A. Štullerová, V. Knoppová, and P. Nemec, Jr., *Appl. Microbiol.*, **15,** 701 (1967); *C* is MIC. [t] From R. A. Cutler, E. B. Cimjotti, T. J. Okolowick, and F. Wetteran, *Soap Chem. Spec.*, **43,** 102 (1967); *C* is minimum fungistatic or fungicidal concn. [u] From W. B. Geiger, *Arch. Biochem.*, **16,** 423 (1948); activity is expressed in relative units, not in concn terms. [v] $\sigma^*$ of $C_6H_5$ was used for $\sigma^*$ of $4\text{-}H_2NC_6H_4$ and $\sigma^*$ of $C_6H_5CO$ for that of $XC_6H_4CO$. [w] From R. Crosse, R. McWilliam, and A. Rhodes, *J. Gen. Microbiol.*, **34,** 51 (1964); activity is rel to griseofulvin. [x] These points not included in derivation of final equation. [y] From G. A. Carter, J. L. Garraway, D. M. Spencer, and R. L. Wain, *Ann. Appl. Biol.*, **51,** 135 (1963); *C* is $ED_{50}$ in spore germination test. [z] From M. Huppert, *Antibiot. Chemother.*, **7,** 29 (1957); *C* is concn causing complete inhib. [aa] From D. Vlachova and L. Drobnica, *Collect. Czech. Chem. Commun.*, **31,** 997 (1966); *C* is $ED_{50}$. [bb] From C. Klarman, L. W. Gates, V. A. Shternov, and P. H. Cox, *J. Amer. Chem. Soc.*, **55,** 4657 (1933). [cc] See *z*. [dd] From F. A. Barkley, G. W. Mast, G. F. Grail, L. E. Tenenbaum, F. E. Anderson, F. Leonard, D. M. Green, J. J. D. Hart, D. P. Kronish, S. Yohimura, and O. L. Ittensohn, *Antibiot. Chemother.*, **6,** 554 (1956); *C* is a fungistatic concn. [ee] From D. B. Reisner and P. M. Borick, *J. Amer. Pharm. Ass.*, **44,** 149 (1955); *C* is lowest concn showing no growth. [ff] From N. E. Rigler and G. A. Greathouse, *Amer. J. Bot.*, **27,** 701 (1940); *C* is concn causing complete inhib. [gg] From J. Hata, M. Tsurukawa, and M. Kakuma, *Tanabe Seiyaku Kenkyu Nempo*, 1, 32 (1956); *Chem. Abstr.*, **51,** 5191c (1957); *C* is min fungistatic concn. [hh] From G. Weitzel and E. Schraufstätter, *Z. Physiol. Chem.*, **285,** 172 (1950); *C* is min effective concn. [ii] From T. Kosuge, H. Okeda, Y. Teraishi, H. Ito, and S. Kosaka, *Yakugaku Zasshi*, **74,** 819 (1954). [jj] From E. Klarman, V. A. Shternov, and L. W. Gates, *J. Amer. Chem. Soc.*, **55,** 2576 (1933); *PC′* is molar phenol coeff. [kk] From F. M. Berger, C. V. Hubbard, and B. J. Ludwig, *Appl. Microbiol.*, 1, 146 (1953); *C* is min fungistatic concn. [ll] From D. V. Carter, P. T. Charlton, A. H. Fenton, J. R. Housey, and B. Lessel, *J. Pharm. Pharmacol.*, **10,** *Suppl.*, 149T (1958); *C* is min inhib concn. [mm] From R. Woodside, M. Zief, and G. Sumrell, *Antibiot. Chemother.*, **9,** 470 (1959); *C* is min inhib concn. [nn] See *b*. [oo] From I. F. Brown and H. D. Sisler, *Phytopathology*, **50,** 830 (1960); *C* is $ED_{50}$. [pp] See *s*. [qq] From R. W. Finholt, M. Weeks, and C. Hathaway, *Ind. Eng. Chem.*, **44,** 101 (1952); *C* is concn inhib radial growth. [rr] From D. Ghosh, *J. Med. Chem.*, **9,** 423 (1966); *C* is $ED_{50}$. [ss] Experimentally determined values.

eralizations can be formulated from this initial effort which we believe will be of help in designing new studies.

## Methods

The constants used in the regression analyses, along with the experimental data, are given in Table I. All log *P* values are

for the *n*-OctOH–$H_2O$ system. The indicated values were detd experimentally. The other values were calcd according to additive principles.[15-18] Biological response was, in most cases, expressed as log $1/C$ where $C$ is the molar concn required to produce a standard effect (*e.g.*, inhibition of spore germination by 50%). In a few cases, molar phenol coefficients ($PC'$) or relative molar activity ($RBR$) were used. In some examples the slide germination test was used, and we have expressed biological response in terms of log $1/\mu$mole cm$^2$.

The Hammett $\sigma$ constants were taken from Jaffe's[19] compilation unless otherwise stated. In a few instances $\sigma_p$ was used to approximate $\sigma_o$ when the latter values were not available. Taft's polar constant, $\sigma^*$, and values for his steric parameter, $E_s$, were taken from Leffler and Grunwald's book.[20]

For calcn of log $P$ it was necessary to measure the p$K_a$ of 2-methylglyoxalidine (2-methylimidazoline). For this purpose the procedure of Albert and Serjeant[21] was followed using a Beckman Model 76 pH meter with an expanded scale. The 2-methylimidazoline was prepd by the method of Chitwood and Reid.[22] In this prepn a reaction temp of 290–300° was found to be necessary rather than 270° reported by Chitwood and Reid. The p$K_a$ at 30° was found to be 10.78 ± 0.04. The p$K_a$ value for the N($HOCH_2CH_2$) derivative of 2-methylimidazoline was 9.6.

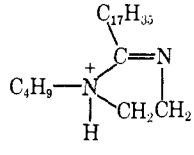
For calcn of partition coefficients the following assumptions have been made:

**Table Ia.**—Log $P$ was measured for benzoquinone (0.20 ± 0.04) and 1,4-naphthoquinone (1.78 ± 0.01). To these values the following constants from the benzene system[15] were added to obtain log $P$: $\pi_{Cl}$, 0.71; $\pi_{CH_3}$, 0.50; $\pi_{OH}$, −0.67. For example, log $P$(3,6-dihydroxy-2,5-dichlorobenzequinone) = log $P$(benzoquinone) + $2\pi_{OH}$ + $2\pi_{Cl}$ = 0.20 − 1.34 + 1.42 = 0.28.

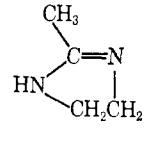
**Table Ib.**—For alkylpyridinium salts, the octyl derivative was measured and used as a reference for the other members. The $Br^-$ and $Cl^-$ were assumed to have about equal log $P$ values. The value of 0.5 was added or subtracted for each $CH_2$ unit. Since it is, presumably, the ion pair which is partitioned into the octanol phase, the $P$ values in this set are *apparent* partition coefficients. The partition coefficient for the higher members of this series may be somewhat lower than the calcd values because of intramolecular hydrophobic interaction. Log $P$ for the higher members is extremely difficult to measure because of possible micelle formation at different concns.

**Table Ic.**—Log $P$ has been calcd by adding $\pi_R$ to the log $P$ of −0.66 ± 0.02 found for ethylenethiourea.

**Table Id.**—Log $P$ for 2-methylimidazoline was found to be 0.52 ± 0.01. For the 1-hydroxyethyl-2-methylimidazoline, log $P$ is 0.04 ± 0.07. Log $P$ for this deriv was also measured in 0.1 $N$ HCl and found to be −1.93 ± 0.12 for the ion pair. We have used log $P$ values for hydrochlorides in Table Id. We have assumed that those molecules without the $HOCH_2CH_2$ function show the same difference in log $P$ (1.97) as the hydroxyethyl derivs. Thus log $P_A$ = log $P_B$ − 1.97 + $\pi_{C_{16}H_{33}}$ + $\pi_{C_4H_9}$ =



A



B

0.52 − 1.97 + 8.00 + 2.00 = 8.55. It is assumed for the $H_2NCH_2CH_2$-contg deriv that only 1 of the basic nitrogens is protonated and that $\pi_{NH_2} \cong \pi_{OH}$. Hence log $P$ for this deriv is taken to be the same as that for the corresponding HO deriv. The difference between log $P_{C_4H_9NH_2}$ and log $P_{C_4H_9OH}$ is only 0.03 log units.

**Table Ie.**—For this set the log $P$ reference compd is $N$-ethyl-α-bromoacetamide of log $P$ 0.34 ± 0.05. Log $P$ for the cyclohexyl deriv was calcd as follows

$$\Delta \log P = \log P(BrCH_2CONHC_6H_{11}) - \log P(BrCH_2CONHEt)$$

$$\Delta \log P = \pi_{C_6H_{11}} - \pi_{Et} = 2.51 - 1.00 = 1.51$$

$$\log P(BrCH_2CONHC_6H_{11}) = \log P(BrCH_2CONHEt) + \Delta \log P = 0.34 + 1.51 = 1.85$$

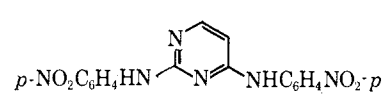
**Table If.**—Hexanoic acid was used as the reference acid. Log $P$ for the un-ionized form is 1.90, while log $P$ for sodium hexanoate is −2.20.

**Table Ig,h.**—Phenol log $P$ values from ref 15 were employed. The value of 2.13 has been employed for $C_6H_5$. Subsequent work has shown that this may be about 0.1 unit too high; however, this is not of consequence for our present purposes. Errors in the biol data are at least of this order.

**Table Ii.**—Benzyl isothiocyanate (log $P$ = 2.83) is the reference compd for this set. $\pi_X$ values used to calc log $P$ for the derivs are from the phenoxyacetic acid series.

**Table Ij.**—The apparent log $P$ for the reference molecule, decyldimethylbenzylammonium bromide, is −0.08.

**Table Ik.**—Log $P$ for pyrimidine was found to be −0.40 ± 0.04. To this value was added that of the substituted anilines.[15]



C

D

For example, log $P_C$ = log $P_D$ + 2 log $P(H_2NC_6H_4NO_2\text{-}p)$, we have used log $P$ from *p*-nitroaniline rather than $PhNH_2$ to account for the inductive effect of the *p*-nitro groups on the lone-pair electrons of the NH units. Where log $P$ values for aniline derivs were missing, these were calcd using log $P$ (aniline) and $\pi$ values from the phenol system.

**Table Il.**—The basic reference molecule, is phenyl vinyl ketone; log $P$ = 1.88 ± 0.03. The value of the benzoyl function was found as follows: log $P_{acetophenone}$ − $\pi_{CH_3}$ = 1.58 − 0.50 = 1.08 = $\pi_{C_6H_5CO}$. $\pi_X$ was taken from the benzene system.[15] The value for Cl attached to a vinyl function[9] is 0.62. Our approach for this set is illustrated as follows: log $P$(dibenzoyldichloroethylene) = log $P$(phenyl vinyl ketone) + $\pi_{C_6H_5CO}$ + $2\pi_{Cl}$ = 1.88 + 1.08 + 1.24 = 4.20.

**Table Im.**—The value of 2.18 ± 0.04 for griseofulvin constituted the reference value for this set. $\pi_X$ for the halogens are Cl = 0.39; Br = 0.60; I = 1.00. These are aliphatic $\pi$ values since a set is not available for the α,β-unsatd ketone system.

**Table In.**—$\pi$ values of 0.5 were used for $CH_2$ and $CH_3$. The value of the cyclic $CH_2$ is taken as 0.41. For a branched chain we have subtracted 0.2 unit; $\pi_{i\text{-}Bu}$ = $\pi_{Bu}$ − 0.20 = 2.00 − 0.20 = 1.80.

Values in Table Io,p were calcd as in Table If.

**Table Ip.**—The value of 0.34 for PrOH was used as the standard.

**Table Iq.**—The reference molecule, phenyl isothiocyanate, has a measured log $P$ of 3.28 ± 0.05. The values used for the derivs are from the benzene system. The value for the CH=CHCH=CH moiety was taken[23] as 1.35.

**Table Ir.**—PhOH values[15] were used for log $P$ calcns.

**Table Is.**—The value for the parent member of the series, methyl 4-hydroxybenzoate, was obtained by adding $\pi_{COOCH_3}$ = −0.01 to log $P_{phenol}$ = 1.46.

**Table It.**—The basic molecule for the calcn of these partition coefficients was $(CH_3)_2NCH_2CH_2N(CH_3)_2$ (un-ionized) of log $P$ = 0.30 ± 0.05. No attempt was made to measure log $P$ for the protonated form of these compds. It seems likely that the monoprotonated form would prevail in the buffer ~pH 7.0.

**Table Iu.**—Log $P(C_6H_5NHCH_2C_6H_3\text{-}2\text{-}OH\text{-}5\text{-}Cl)$ = log $P$(aniline) + $\pi_{CH_2}$ + log $P$(4-chlorophenol) = 0.90 + 0.50 + 2.39 = 3.79. Log $P$ values for the derivs were obtd by adding $\pi$ values from $PhNH_2$ (where possible, and $\pi$ from PhOH where not) to the parent compd. Log $P$ values for this set may be

(15) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964).

(16) J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, **8**, 150 (1965).

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about 0.5 log unit high because no account has been taken of possible folding.

**Table Iv.**—See Table If.

**Table Iw.**—To log $P$ 2.39 for 4-chlorophenol was added $\pi_{2\text{-}CH_3}$ (0.68). The value of 3.07 for 2-methyl-4-chlorophenol was added to log $P$ of the appropriate arom moiety; 0.65 for pyridine, 1.81 for thiophene, 1.32 for furan, and 3.37 for naphthalene to obtain log $P$ for these respective derivs. For the 2-$COC_6H_5$ deriv $\pi$ was calcd as follows

$$\pi_{2\text{-}COC_6H_5} = \log P_{C_6H_5} - \pi_{CH_3} + \pi_{COCH_3}$$
$$= 2.13 - 0.50 - 0.11 = 1.52$$

$$\pi_{CH(NH_3)CH_3} = \log P_{\text{benzylamine}} - \log P_{C_6H_6} + \pi_{CH_3} + \pi_{\text{branching}}$$
$$= 1.09 - 2.13 + 0.50 - 0.20 = -0.74$$

**Table Ix.**—The appropriate value of $\pi$ for R was added to log $P$ of 0.13 ± 0.05 found for pyrazole to give log $P$ for the derivs in this table.

**Table Iy.**—Log $P$ was found as in Table If.

**Table Iz.**—Log $P$ was found as in Table Ig. The calcd log $P$ values for the diortho-substituted phenol are probably a little low since shielding of the OH has not been considered.

**Table Ia'.**—Log $P$ values for the set are calcd from log $P$ of 0.70 ± 0.01 of the 1-Ph ether of glycerol and log $P$ of 1.16 ± 0.01 from 2-phenoxyethanol. $\pi$ values from the phenoxyacetic acids were employed. Log $P$(2-$CH_3C_6H_4OCH_2CHOHCH_3$) = log $P$($C_6H_5OCH_2CH_2OH$) + $\pi_{2\text{-}CH_3}$ + $\pi_{CH_3}$ + $\pi_{\text{branching}}$ = 1.16 + 0.68 + 0.50 − 0.20 = 2.14.

**Table Ib'.**—Where possible, log $P$ for the benzyl alcohol deriv[15] was used. When this value was lacking, $\pi_X$ from the benzene or the phenoxyacetic acid system was added to log $P$ of benzyl alcohol.

**Table Ic'.**—Log $P$($C_6H_5OCOC(CH_3)=CH_2$ = log $P$($C_6H_5OCOCH_3$) − $\pi_{CH_3}$ + $\pi_{CH_2=CH_2}$ + $\pi_{CH_3}$ + $\pi_{\text{branching}}$ = 1.49 − 0.50 + 0.70 + 0.50 − 0.20 = 1.99. The log $P$ values for the derivs were calcd using $\pi_X$ from the phenoxyacetic acid system.

**Table Id'.**—Log $P$ values are based on dodecylguanidinium acetate.

**Table Ie'.**—Log $P$ values were calcd by adding the $\pi$ value for the 2-alkyl moiety to 1.05 for the parent compd. The value of 1.05 for the $N$-dodecyl derivs comes from Table Ib.

**Table If'.**—$\pi_{CH_2}$ was added to the corresponding compd from Table Ii.

**Table Ig'.**—For these molecules, the apparent partition coefficient of $n$-$C_{12}H_{25}NH_3^+Cl^-$ (log $P$ = 1.85 ± 0.11) was used as the reference. This was obtd by partitioning between 0.01 $N$ HCl and octanol.

For the details of the testing procedures used in obtaining the relative biol activities of the different compds, the original work[24-52] should be consulted.

## Results and Discussion

The object of this survey was to uncover as many self-consistent sets of congeners acting on different fungi as possible. At this stage of the development of *quantitative* structure–activity correlations, we sorely need more equations correlating relatively simple systems so that some of the A B C's of quantitative structure–activity relationship work can be established before going on to more difficult problems. The large amount of work done with microorganisms *in vitro* appears to be a good area in which to gain experience before, say, attacking difficult stereochemical problems in whole animals.

The equations obtained in Table II can be compared with those obtained for hemolysis of red cells[53] and those for antibacterial action. In Table IIa are assembled those equations in which antifungal activity is linearly dependent on the single variable, log $P$, and in Table IIc are the structure–activity relationship equations parabolically dependent upon only this variable. The intercepts of such equations are useful parameters of reference for comparing the activity of different sets of congeners acting on totally different systems. For example, we have recently shown that 15 different sets of congeners causing hemolysis of red cells yield linear correlations of log $1/C$ *vs.* log $P$ having a mean slope of 0.93 ± 0.17. The small standard deviation (0.17) was unexpected for work from many different laboratories employing different kinds of red cells. For 7 sets of *neutral* compounds the mean value and standard deviation of the intercept was −0.09 ± 0.23. Using this information, we can construct eq 57 for our expectation of membrane per-

$$\log \frac{1}{C} = 0.93\ (\pm 0.17) \log P - 0.09\ (\pm 0.23) \quad (57)$$

turbation by more or less neutral molecules such as alcohols, esters, ketones, phenols, etc. Of course the intercept of eq 57 can be made to vary somewhat by the kind of hemolysis one elicits (*e.g.*, 100%, 50%, etc.) as well as the time of the experiment, temp, etc. The value of the intercept is determined by the sensitivity of the test and the intrinsic pharmacophoric


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(26) R. G. Ross and R. A. Ludwig, *Can. J. Bot.*, **35**, 65 (1967).
(27) R. H. Wellman and S. E. A. McCallan, *Contrib. Boyce Thompson Inst.*, **14**, 151 (1946).
(28) J. M. Leonard and V. L. Blackford, *J. Bacteriol.*, **57**, 339 (1947).
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(31) H. G. Shirk and R. R. Corey, *ibid.*, **38**, 417 (1952).
(32) Ľ. Drobnica, M. Zemanová, P. Nemec, K. Antós, P. Kristián, A. Štullerová, V. Knoppová, and P. Nemec, Jr., *Appl. Microbiol.*, **15**, 701 (1967).
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(36) M. Huppert, *Antibiot. Chemother.*, **7**, 29 (1957).
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(39) D. B. Reisner and P. M. Borick, *J. Amer. Pharm. Ass.*, **44**, 149 (1955).
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(41) J. Hata, M. Tsurukawa, and M. Kakuma, *Tanabe Seiyaku Kenkyu Nempo*, **1**, 32 (1956); *Chem. Abstr.*, **51**, 5191c (1957).
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Table II

(a) Antifungal Activity Linearly Dependent on Log $P$; Log $1/C = k_1 \log P + k_2$

| Organism | Type compound | Action | $k_1$ | $k_2$ | $n^a$ | $r^b$ | $s^c$ | Eq No. | Data in Table I |
|---|---|---|---|---|---|---|---|---|---|
| *Candida albicans* | $HOC_6H_3COOR$ | Inhib | 0.704 (±0.20) | 0.954 (±0.62) | 7 | 0.971 | 0.205 | 3 | Is |
| *Trychophyton mentagrophytes* | Diamines | Inhib | 0.527 (±0.13) | 1.366 (±0.71) | 22 | 0.890 | 0.504 | 4 | It |
| *C. albicans* | Diamines | Inhib | 0.342 (±0.10) | 1.742 (±0.57) | 19 | 0.862 | 0.399 | 5 | It |
| *Aspergillus niger* | $RCOO^-$ | Kill | 0.671 (±0.16) | 2.075 (±0.23) | 8 | 0.974 | 0.175 | 6 | If |
| *T. interdigitale* | $RCOO^-$ | Kill | 0.757 (±0.05) | 2.431 (±0.08) | 14 | 0.994 | 0.133 | 7 | If |
| *A. niger* | $RCOO^-$ | Inhib | 0.545 (±0.13) | 2.658 (±0.23) | 10 | 0.959 | 0.212 | 8 | If |
| *Penicillium cyclopium* | $XC_6H_4CH_2CH_2NCS$ | Inhib | 0.462 (±0.15) | 2.789 (±0.57) | 6 | 0.974 | 0.060 | 9 | If' |
| *A. niger* | $XC_6H_4CH_2NCS$ | Inhib | 0.545 (±0.17) | 3.283 (±0.59) | 13 | 0.901 | 0.148 | 10 | Ii |
| *Monilia fructicola* | Quinones | Kill | 0.877 (±0.43) | 3.530 (±0.80) | 10 | 0.859 | 0.579 | 11 | Ia |
| *A. niger* | $XC_6H_4CH_2CH_2NCS$ | Inhib | 0.363 (±0.45) | 3.584 (±1.7) | 6 | 0.745 | 0.179 | 12 | If' |
| *A. oleracea* | Quinones | Kill | 0.731 (±0.41) | 3.741 (±0.77) | 10 | 0.825 | 0.555 | 13 | Ia |
| *C. albicans* | 2,4-Bis($XC_6H_4NH$)-pyrimidines | Inhib | 0.497 (±0.15) | 4.149 (±0.35) | 8 | 0.957 | 0.223 | 14 | Ik |

(b) Antifungal Activity Linearly Dependent on Log $P$ and Electronic Effects; Log $1/C = k_1 \log P + k_2 \sigma + k_3$

| Organism | Type compound | Action | $k_1$ | $k_2$ | $k_3$ | $n^a$ | $r^b$ | $s^c$ | Eq No. | Data in Table I |
|---|---|---|---|---|---|---|---|---|---|---|
| *Botyrtis allii* | Griseofulvin analogs | Curling of *hyphae*[d] | 0.555 (±0.17) | 2.193 (±0.77) | −1.322 (±0.61) | 22 | 0.875 | 0.248 | 15 | Im |
| *Aspergillus niger* + 3 molds | $XC_6H_4CH_2OH$ | Inhib | 0.582 (±0.12) | 0.450 (±0.32) | 1.117 (±0.25) | 19 | 0.952 | 0.241 | 16 | Ib' |
| *T. mentagrophytes* + 3 molds | Phenethyl ethers of glycerol and glycol | Inhib | 0.691 (±0.14) | 0.428 (±0.51) | 1.213 (±0.36) | 26 | 0.911 | 0.216 | 17 | Ia' |
| *C. albicans* | $XC_6H_4NHCH_2$-*o*-$ClC_6H_4OH$ | Inhib | 0.270 (±0.18) | 0.962 (±0.49) | 2.433 (±0.77) | 8 | 0.982 | 0.111 | 18 | Iu |
| *T. interdigitale* | $XC_6H_4NHCH_2$-*o*-$ClC_6H_4OH$ | Inhib | 0.339 (±0.37) | 0.572 (±1.0) | 3.026 (±1.6) | 8 | 0.906 | 0.237 | 19 | Iu |
| *Microsporum audouini* | $XC_6H_4NHCH_2$-*o*-$ClC_6H_4OH$ | Inhib | 0.236 (±0.16) | 0.737 (±0.44) | 3.535 (±0.69) | 8 | 0.978 | 0.100 | 20 | Iu |

(c) Antifungal Activity Parabolically Dependent on Log $P$; Log $1/C = k_1 (\log P)^2 + k_2 \log P + k_3$

| Organism | Type compound | Action | $k_1$ | $k_2$ | $k_3$ | Log $P_0$ | $n^a$ | $r^b$ | $s^c$ | Eq No. | Data in Table I |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *T. interdigitale* | Alkylpyrazoles | Inhib | −0.650 | 5.978 | −9.334 (±8.8) | 4.6 (4.3–5.4) | 6 | 0.948 | 0.226 | 21 | Ix |
| *Letinus lepideus* | ROH | Inhib | −0.601 | 4.271 | −4.089 (±12.0) | 3.6 | 5 | 0.877 | 0.534 | 22 | Ip |
| *T. rosaceum* | Alkyl-4-chloro phenols | *PC*'[d] | −0.114 | 1.680 | −2.676 (±1.0) | 7.3 (6.2–11) | 22 | 0.985 | 0.126 | 23 | Iz |
| *A. niger* | $\alpha,\beta$-Unsatd ketones | Inhib[d] | −0.134 | 1.382 | −1.597 (±1.4) | 5.1 | 19 | 0.866 | 0.413 | 24 | Il |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *C. albicans* | Alkylbromo phenols | *PC'*[d] | −0.084 | 1.318 | −0.885 (±0.67) | 7.8 (6.2–15) | 14 | 0.993 | 0.121 | 25 | Ir |
| *A. solani* | *N*-Alkylethylenethioureas | Inhib | −0.339 | 2.183 | −0.290 (±1.9) | 3.2 (2.8–9.8) | 6 | 0.970 | 0.148 | 26 | Ic |
| *C. albicans* | ArNCS | Inhib | −0.192 | 1.909 | 0.555 (±2.3) | 5.0 (4.6–6.5) | 10 | 0.936 | 0.104 | 27 | Iq |
| *M. fructicola* | *N*-Alkylethylenethioureas | Inhib | −0.140 | 1.398 | 0.663 (±1.1) | 5.0 | 5 | 0.999 | 0.045 | 28 | Ic |
| *A. niger* | Phenols | Inhib | −0.105 | 1.169 | 0.829 (±0.59) | 5.5 (5.1–6.4) | 26 | 0.927 | 0.195 | 29 | Ih |
| *T. gypseum* | 2-Alkyl-4-chloro phenols | Inhib | −0.103 | 1.316 | 1.182 (±1.8) | 6.4 | 11 | 0.924 | 0.341 | 30 | Iw |
| *G. cingulata* | Imidazolines | Inhib | −0.069 | 0.965 | 1.443 (±1.0) | 7.0 (6.–8.7) | 15 | 0.875 | 0.500 | 31 | Id |
| *A. solani* | Imidazolines | Inhib | −0.076 | 0.937 | 1.891 (±0.75) | 6.2 (5.6–6.9) | 15 | 0.910 | 0.363 | 32 | Id |
| *Macrosporum sarcinaeforme* | Imidazolines | Inhib | −0.073 | 0.896 | 2.093 (±0.70) | 6.1 (5.6–6.8) | 15 | 0.913 | 0.339 | 33 | Id |
| *M. fructicola* | Imidazolines | Inhib | −0.080 | 1.070 | 2.175 (±0.68) | 6.1 (5.7–6.7) | 14 | 0.946 | 0.324 | 34 | Id |
| *C. albicans* | $RCOO^-$ | Inhib | −0.636 | −1.541 | 2.149 (±0.34) | −1.21 (−1.3–1.0) | 6 | 0.991 | 0.090 | 35 | Io |
| *L. lepideus* | $RNH_3^+$ | Inhib | −0.124 | 0.419 | 2.379 (±0.73) | 1.7 | 6 | 0.903 | 0.281 | 36 | Ig |
| *M. fructicola* | *N*-Alkylpyridinium halides | Kill[d] | −0.156 | 0.780 | 2.383 (±0.16) | 2.5 (2.2–3.0) | 7 | 0.990 | 0.115 | 37 | Ib |
| *Phytophthora infestans* | *N*-Alkylpyridinium halides | Kill[d] | −0.132 | 0.646 | 2.552 (±0.19) | 2.4 (2.–3.2) | 8 | 0.989 | 0.156 | 38 | Ib |
| *A. oleracea* | *N*-Alkylpyridinium halides | Kill[d] | −0.166 | 0.718 | 2.577 (±0.44) | 2.2 (1.6–3.6) | 7 | 0.973 | 0.295 | 39 | Ib |
| *Venturia inaequales* | *N*-Alkylpyridinium halides | Kill[d] | −0.158 | 0.636 | 3.067 (±0.12) | 2 (1.8–2.3) | 8 | 0.995 | 0.098 | 40 | Ib |
| *V. inaequales* | *N*-Dodecyl-2-R-pyridinium $Br^-$ | Kill[d] | −0.083 | 0.594 | 3.100 (±0.67) | 3.6 (3.1–11) | 6 | 0.925 | 0.095 | 41 | Ie |
| *A. niger* | $C_6H_5CH_2N^+R(CH_3)_2 \cdot Cl^-$ | Kill | −0.223 | 1.027 | 2.592 (±0.83) | 2.3 (1.5–4.0) | 10 | 0.720 | 0.477 | 42 | Ij |
| *A. niger* | $C_6H_5CH_2N^+R(CH_3)_2 \cdot Cl^-$ | Inhib | −0.237 | 1.040 | 3.114 (+0.26) | 2.2 (2.0–2.5) | 11 | 0.947 | 0.224 | 43 | Ij |
| *T. mentagrophytes* | $C_6H_5CH_2N^+R(CH_3)_2 \cdot Cl^-$ | Kill | −0.164 | 1.059 | 3.232 (±0.19) | 3.2 (2.9–3.9) | 11 | 0.983 | 0.166 | 44 | Ij |
| *C. albicans* | $C_6H_5CH_2N^+R(CH_3)_2 \cdot Cl^-$ | Inhib | −0.264 | 1.358 | 3.236 (±0.23) | 2.6 (2.4–2.8) | 11 | 0.978 | 0.199 | 45 | Ij |
| *C. albicans* | $C_6H_5CH_2N^+R(CH_3)_2 \cdot Cl^-$ | Kill | −0.297 | 2.037 | 3.253 (±0.28) | 2.2 (2.1–2.5) | 11 | 0.961 | 0.243 | 46 | Ij |
| *T. mentagrophytes* | $C_6H_5CH_2N^+R(CH_3)_2 \cdot Cl^-$ | Inhib | −0.160 | 1.055 | 3.294 (±0.14) | 3.3 (3.0–3.7) | 11 | 0.992 | 0.119 | 47 | Ij |
| *Phymatotrichum omnivorum* | $RCOO^-$ | Inhib | −0.028 | −0.078 | 3.354 (±0.27) | −0.18 (−1.0–10) | 15 | 0.845 | 0.351 | 48 | Iv |
| *T. interdigitale* | $RCOO^-$ | Inhib | −0.099 | 0.328 | 3.500 (±0.16) | 1.6 (0.7–5.0) | 14 | 0.972 | 0.216 | 49 | If |
| *T. purpureum* | $RCOO^-$ | Inhib | −0.059 | 0.460 | 3.754 (±0.12) | 4.2 (2.3–11) | 15 | 0.985 | 0.166 | 50 | If |
| *T. gypseum* | $RCOO^-$ | Inhib | −0.118 | 0.236 | 4.254 (±0.15) | 1.0 (0.6–2.0) | 15 | 0.884 | 0.205 | 51 | Iy |
| *Stemphylium pastorianus* | Alkylguanidine acetates | Inhib | −0.181 | 0.706 | 4.877 (±0.37) | 1.9 (1.5–2.2) | 6 | 0.987 | 0.069 | 52 | Id' |
| *M. fructicola* | Alkylguanidine acetates | Inhib | −0.129 | 0.517 | 4.844 (±0.17) | 2.0 (1.8–2.2) | 6 | 0.994 | 0.031 | 53 | Id' |

(d) Antifungal Activity Parabolically Dependent on Log $P$ and Linearly Dependent on Electronic Character; $\text{Log } 1/C = k_1 (\log P)^2 + k_2 \log P + k_3 \sigma + k_4$

| Organism | Type compound | Action | $k_1$ | $k_2$ | $k_3$ | $k_4$ | Log $P_0$ or $\pi_0$ | $n$[a] | $r$[b] | $s$[c] | Eq No. | Data in Table I |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *A. niger* | Phenols | Inhib | −0.190 | 1.859 | 0.627 (±0.39) | −0.092 (±0.86) | 4.9 (4.3–6.3) | 18 | 0.975 | 0.160 | 54 | Ig |
| *H. anomala* | Phenyl methacrylates | Inhib | −0.102 | 1.234 | −0.880 (±0.75) | 0.878 (±0.93) | 6.0 (4.8–7.3) | 10 | 0.958 | 0.069 | 55 | Ic |
| *B. cinerea* | $RR'NCSSNa^+$ | Inhib | −0.282 | −0.207 | −1.531 (±1.1) | 5.063 (±1.4) | −0.4[e] | 9 | 0.921 | 0.278 | 56 | In |

[a] Number of data points used in deriving equation. [b] Correlation coefficient. [c] Standard deviation from regression. [d] Activity given in terms of relative biological response; not comparable with log $1/C$. [e] $\pi$ employed in this equation instead of log $P$.

character of the set of congeners under consideration. The only equations in Table IIa which are comparable to eq 57 are eq 3 and 9–13. Equations 4–8 are for molecules which will be largely ionized under the experimental conditions. For the neutral molecules only one set is close in form to eq 57; that is eq 3 for the phenols. The confidence intervals on the slope, and especially the intercept of eq 3, are rather large. In fact, they essentially overlap with those of eq 57, indicating the considerable similarity in the two processes. This can be taken as one small piece of evidence that the fungicidal action of phenols is through membrane perturbation.

A more direct comparison can be made *via* eq 58. interval on the intercept of eq 30 is too large to allow its use in fruitful comparisons.

Unfortunately, most of the enormous amount of work done with phenols on bacteria has been reported in terms of phenol coefficients and hence is not directly comparable with log $1/C$ data. Exceptions to this are the results embodied in eq 59 and 60. The intercepts and coefficients with log $P$ in eq 59 and 60 are quite close to those of eq 3 and 58, again underscoring the close relationship between hemolysis, antibacterial, and antifungal action of phenols and alcohols.

These results can be compared *via* our extrathermodynamic equations[53] with other kinds of processes

Phenols and Alcohols Causing Hemolysis of Human Red Cells

| | $n$ | $r$ | $s$ | |
|---|---|---|---|---|
| $\log \frac{1}{C} = 0.78\ (\pm 0.16) \log P + 0.21\ (\pm 0.20)$ | 8 | 0.997 | 0.037 | (58) |

Phenols Acting on *Pseudomonas aeruginosa*[14]

| | | | | |
|---|---|---|---|---|
| $\log \frac{1}{C} = 0.68\ (\pm 0.24) \log P - 0.92\ (\pm 0.72)\sigma + 0.27\ (\pm 0.49)$ | 21 | 0.847 | 0.222 | (59) |

Alcohols Acting on *Staphylococcus aureus*[14]

| | | | | |
|---|---|---|---|---|
| $\log \frac{1}{C} = 0.65\ (\pm 0.12) \log P + 0.06\ (\pm 0.08)$ | 9 | 0.979 | 0.087 | (60) |

ROH Causing −5 mV Change in Rest Potential of Lobster Axon

| | | | | |
|---|---|---|---|---|
| $\log \frac{1}{C} = 0.86\ (\pm 0.16) \log P - 0.10\ (\pm 0.13)$ | 5 | 0.995 | 0.082 | (61) |

ROH Toxicity to Red Spider

| | | | | |
|---|---|---|---|---|
| $\log \frac{1}{C} = 0.69\ (\pm 0.09) \log P + 0.16\ (\pm 0.08)$ | 14 | 0.979 | 0.087 | (62) |

100% Inhibition of Frog Heart by Misc Neutral Compounds

| | | | | |
|---|---|---|---|---|
| $\log \frac{1}{C} = 0.93\ (\pm 0.09) + 0.11\ (\pm 0.12)$ | 28 | 0.975 | 0.182 | (63) |

Benzyldimethylalkylammonium Chlorides Inhibiting *S. aureus*[53]

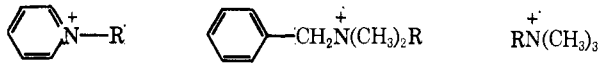
| | | | | |
|---|---|---|---|---|
| $\log \frac{1}{C} = -0.173\ (\log P)^2 + 0.884 \log P + 2.956\ (\pm 0.14)$ | 45 | 0.898 | 0.288 | (64) |
| $\log P_0 = 2.6$ | | | | |
| $\log \frac{1}{C} = 0.640\ (\pm 0.09) \log P + 1.981\ (\pm 0.85)E_R + 0.767\ (\pm 0.24)$ | 19 | 0.971 | 0.190 | (65) |
| $\log \frac{1}{C} = -0.264\ (\log P)^2 + 1.592 \log P + 2.061\sigma^*\ (\pm 1.8) + 0.830E_s\ (\pm 0.30) + 3.199\ (\pm 0.40)$ | 15 | 0.976 | 0.208 | (66) |
| $\log P_0 = 3.0\ (2.8\text{–}3.2)$ | | | | |
| $\log \frac{1}{C} = 0.369\ (\pm 0.13) \log P + 0.514\ (\pm 0.32)\ E_s + 3.366\ (\pm 0.37)$ | 10 | 0.949 | 0.195 | (67) |

The similarity between eq 58 and 3 is striking. Although the correlation of eq 3 is not as sharp as that of eq 58, it appears that a somewhat higher concentration of phenol or alcohol is required to cause hemolysis than is needed to inhibit *C. albicans*. Comparison of the intercepts of eq 3 and 58 with the more complex eq 29 and 54 shows reasonable agreement. The confidence as shown in eq 61–63. The one common mechanism which might be used to explain the great similarity in action of phenols and alcohols in hemolysis, narcotic action (as in eq 61–63), antibacterial action, and antifungal action is that of membrane perturbation. This need not necessarily mean rupture as in hemolysis. Since an extensive oxidative enzyme system is part of

the membrane structure, disturbing the membrane structure could easily turn off or diminish this vital system.

Turning now to the other neutral molecules of Table IIa, higher intercepts are found for the quinones and arylalkyl isothiocyanates. The average intercept for the quinones is 3.6 and that for the isothiocyanates is 3.2. This indicates their much greater intrinsic toxicity. Since these equations are linear in log $P$, more toxic members of each of these series could be prepared by making more lipophilic derivatives. The aliphatic isothiocyanate function is much more toxic than the aromatic analog. The intercept of eq 27 is what one expects to find for the nonspecific membrane perturbation discussed above.

Before considering the acids of Table IIa in which either the ionic or neutral form of the molecule may be the active species, it is important to consider the completely ionized benzyl ammonium derivatives of eq 42–47. Unfortunately, the pyridinium compounds of eq 37–41 cannot be compared with respect to intercepts since these data are not on the log $1/C$ scale. For the three sets of ammonium compounds killing fungi, the mean intercept is 3.03. For the 3 sets inhibiting fungi, the mean intercept is 3.21. For our purpose, the difference between the killing and inhibiting concentration is small and we shall ignore it by taking the mean and standard deviation for the 6 sets as $3.12 \pm 0.26$. The mean values for these 2 parameters can be compared with results obtained by quaternary ammonium compounds of 3 types causing hemolysis of red



cells.[53] For 6 such equations we find a mean intercept of $2.91 \pm 0.21$. This is very close indeed to the value for fungicidal activity.

The antibacterial action of a large set of quaternary ammonium compounds of varying alkyl chain length and different ring substituents is summarized in eq 64. The intercept of eq 64 agrees very well with the average found for hemolysis as well as that found for antifungal action.

Since the action of the benzylammonium compounds against fungi appears to parallel their hemolytic action, one might expect the same to be true for fatty acids. For this reason we have used log $P$ values for the ion pair, RCOONa, in correlating these compounds instead of log $P$ for the neutral RCOOH. Equation 35 will not be considered with the others since this work was done at pH 5.6 rather than the pH 6.5 employed in the other work. Two equations (6 and 7) are for killing action and have, as expected, a lower mean intercept of 2.3 while five equations (8, 48–51) are for inhibitory action and have a mean intercept of $3.5 \pm 0.7$. The intercepts for 2 sets of acids, RCOOH and RCHBrCOOH, causing hemolysis[53] are 2.60 and 2.58, respectively. These figures are closer to the intercepts for the killing log $1/C$ equations, indicating that killing action more closely resembles hemolysis.

There are a number of equations in Table II (15, 23–25, 37–40, 56) which cannot be compared with the others either because activity could not be placed on the log $1/C$ scale or because $\pi$ values had to be used instead of log $P$ values. In addition to these, eq 4 and 5 for the diamines are not comparable to the others because under test conditions these molecules are protonated and we have had to employ log $P$ values for the neutral compounds. It seems most likely that it is the protonated amine which is the pharmacophore.

From a practical point of view, one of the most interesting sets of data in Table II is that correlated by eq 15 for the griseofulvin analogs. These derivatives cannot be compared directly with the other sets of Table II in terms of intercepts since the activity of these compounds was expressed on a relative basis rather than as log $1/C$. Although the correlation with this group of very complex molecules is not as sharp as one would like, it is reasonable considering the fact that we do not have ideal substituent constants. Suitable steric parameters are not available, and for $\sigma$ we have had to assume that $\sigma_p$ for aromatic functions is suitable for the groups (X, Table Im) directly conjugated with the carbonyl group as well as the ether function. A finding of importance is the large coefficient with $\sigma$, indicating that activity is highly dependent on the electron-attracting groups $\alpha$ to the carbonyl function. $\alpha,\beta$-Unsaturated ketones react *via* addition with mercaptans and inactivate enzymes such as succinic, alcohol, and triosephosphate dehydrogenases and urease which have essential SH groups.[34] It is known that griseofulvin kills young and actively metabolizing cells but not the older, more dormant elements.[54] Also, it has been hypothesized that the antifungal activity of griseofulvin is due at least in part to its inhibition of nucleic acid synthesis at steps either prior to or at the polymerization stage. The partial reversal of growth inhibition by purines and purine derivatives has led to the suggestion that griseofulvin may be a structural analog of a purine nucleotide.[55] Interferences with the replication mechanism of fungal cells have also been suggested, although at present no clear answer to the mechanism of action is generally accepted.[56] The spiro linkage has also attracted attention in structure–activity work.[57] Since the role of $\sigma$ in our analysis supports the idea of reaction of the $\alpha,\beta$-unsaturated ketone linkage with an SH group, it would be interesting to investigate the interaction between griseofulvins and SH-possessing enzymes involved in the synthesis of intermediates for nucleic acids; *e.g.*, inosinate dehydrogenase.[58]

The fact that activity for the set of griseofulvins at hand depends linearly on electron withdrawal and lipophilic character indicates that replacing X (Table Im) by functions such as $CF_3$, $SF_5$, or $C_6H_4CN$ should give derivatives with higher *in vitro* activity. In trying to get higher *in vivo* activity one should first establish log $P_0$ from *in vivo* studies. For a variety of drugs acting *in vivo*, log $P_0$ has been found to be about 2. Griseofulvin itself has log $P$ of 2.18.

The benzyl alcohols of eq 16 also show a modest degree of specificity. Recent work with benzyl derivatives[59] indicates that for this function one often finds better correlations in biological work using the radical parameter $E_R$ instead of $\sigma$. Making this change in eq 16, we obtain eq 65. The positive coefficient with the

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$E_R$ term of eq 65 indicates that free radical stabilizing substituents yield more active derivatives.

The *N*-phenylbenzylamines of eq 18–20 show a rather high degree of specificity, in so far as the intercept is a measure of this property. The coefficients with the log $P$ terms in these equations are quite low, indicating that variation in log $P$ has less than half the usual effect on activity. Hence, although the equations are linear in log $P$, not much increase in activity is to be expected by further increases in lipophilicity. The highest log $P$ in this set is 5.41 and, from general experience with neutral molecules, it is rarely found that log $P_0$ is much above 6. In this set there are two pharmacophoric functions to consider. Is the phenol or the benzylamine function the active one? The intercepts of equations correlating the toxicity of phenols are usually in the range of 0.5–1.0. Therefore, the high activity appears to reside in the benzylamine moiety. Again our interest is drawn to the highly active benzylic hydrogens as a source of toxicity. Unfortunately, lack of $E_R$ constants and the small variation in the substituents studied prevent our study of this interesting point.

The benzyl function is also present in the isocyanates of eq 10. The isocyanate function has a much greater intercept than the benzyl alcohol, indicating the much greater toxicity of this function. The replacement of $\sigma$ by $E_R$ or simply the addition of an $E_R$ term to eq 10 does not result in an improved correlation. This would seem to be the result of the fact that the toxic character of benzylic hydrogens is 2 orders of magnitude lower than the isocyanate function and that their activation might, if anything, lower activity *via* metabolic loss.

Lukens and Horsfall, in a recent study of antisporulants, made the interesting observation that phenoxyacetic acids inhibit glycolate oxidase of *A. solani*.[60] Moreover, the inhibition closely paralleled the antisporulation activity. Both kinds of inhibition paralleled the $\Sigma\pi$ for the substituents. Unfortunately, only 6 derivatives were tested and so little variation was made in the attached groups (all but one were polychloro compounds) that we cannot subject the set to regression analysis to see if the radical stabilizing ability of the substituent plays a discernible role. Since it has been possible to show[60] through substituent constant analysis that radical stabilizing substituents have pronounced effects on a number of oxidase reactions, it would be worthwhile to make such a study of the glycolate oxidase–phenoxyacetic acid interaction.

The most specific antifungal agents in Table IIa are the bisanilinopyrimidines of eq 14. The reason for the high specificity is not obvious. More insight could be gained by the study of a better selection of substituents. Adding a term in $E_R$ does result in considerable improvement ($F_{1,5} = 3.9$; $F_{1,5\ \alpha.1} = 4.1$) in correlation but does not quite reach our arbitrary cutoff level of significance at $\alpha \leqq 0.1$.

In Table IIc, the confidence interval on the alkylpyrazoles of eq 21 is extremely wide. Even so, it seems safe to say that little specificity resides in the pyrazole function.

Equations 31–34 with the imidazolines are interesting from the point of view of the intercepts. The mean for the 4 equations is $1.93 \pm 0.3$. For these combinations we have employed the log $P$ for the hydrochloride since, because of their basicity, they would be essentially completely ionized under test conditions. The intercept for imidazolines is close to that of 2.4 found for simple aliphatic amines (eq 36). This would indicate no special toxicity for the heterocycle function. These intercepts can be compared with the value of 1.6 found for hemolysis[53] by $RNH_2 \cdot HCl$. The agreement is close enough to suggest membrane perturbation as the cause of toxicity. This is supported by Rich and Horsfall's suggestion that alkylimidazolines disrupt the membrane permeability of *Conidia*. Miller, *et al.*,[61] have shown that spores of *Neurospora sitophila* accumulated a $10^4$-fold concentration of 2-heptadecylimidazoline from an aqueous solution of 2 $\mu$g/ml. Our results would indicate that the high lipophilic character of this molecule is the primary driving force for its accumulation rather than any special kind of active transport.[62]

In Table IId are listed equations in which activity depends linearly on the electronic effect of the molecular modification and parabolically on log $P$.

The dithiocarbamates cannot be compared with the other sets because for these salts we have had to use $\pi$ instead of log $P$. Since their activity depends so little on lipophilic character ($\pi_0 = -0.4$), it would appear that they must bring about their effect in an aqueous phase. Albert[63] has discussed the importance of the connection of the chelating power of dimethyldithiocarbamic acid with $Cu^{2+}$ for fungicidal action. The relative unimportance of hydrophobic bonding apparent from eq 56 is also clear from the work of Weuffen[64] on antifungals of the type $C_6H_5CH_2CH_2NHC(S)SR$ (R = $CH_3$ to $n$-$C_5H_{11}$). Activity in this series is practically independent of the nature of R. Of interest is the negative sign of the coefficient associated with $\sigma^*$ in eq 56. This indicates that electron-releasing groups which raise the electron density on the N atom increase activity. This is to be expected if chelating is the primary cause of toxicity. It must be kept in mind for this set of compounds that $\pi$ for the alkyl groups and the steric effects of these groups ($E_s$) tend to vary in a similar manner. From the limited set of derivatives we have not been able to dissect out the two independent roles for R.

Wherever appropriate, attempts were made to evaluate steric effects of substituents using Taft's $E_s$ parameter. Statistically valid results were not obtained with the set of congeners in Table II. For the bromoacetanilides of Table Ie, the steric nature of the R attached to the amide N appears significant. Equation 66 correlates the results with *A. niger* and eq 67 those with *T. viride*. For the work summarized in eq 67 with *T. viride*, fewer derivatives were studied and it is not possible to estimate log $P_0$ or to estimate the role of $\sigma^*$. The steric effects of R, as revealed by the $E_s$ term, are essentially the same in each equation. The positive coefficient with this term indicates that bulky groups hinder activity. Log $P_0$ for eq 66 is considerably lower than that found for most of the other sets of congeners and indicates the possibility for a different mode of activity for the bromoamides. The large inter-

(60) R. J. Lukens and J. G. Horsfall, *Phytopathology*, **58**, 1671 (1968).

(61) L. P. Miller, S. E. A. McCallan, and R. M. Weed, *Contrib. Boyce Thompson Inst.*, **17**, 173 (1953).

(62) R. J. W. Byrde in "The Fungi," Vol. I, G. G. Anisworth and A. S. Sussman, Ed., Academic Press, New York, N. Y., 1965, p 526.

(63) A. Albert, "Selective Toxicity," 3rd ed, Wiley, New York, N. Y., 1965, p 259.

(64) W. Weuffen, *Pharmazie*, **21**, 686 (1966).

cepts indicate the high intrinsic activity of the bromoamide function.

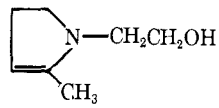
In addition to the intercepts, another generally useful parameter in the correlation equations is log $P_0$. This is the optimum lipophilic character for a given set of congeners.[9] For the 6 sets of eq 21, 23, 27, 29, 54, and 55 where we have reasonably sharp 95% confidence intervals on this parameter, a mean value of $5.6 \pm 1.0$ is found. This compares with a mean value for 8 sets of neutral drugs acting on Gram-negative bacteria of $4.4 \pm 0.4$. For 6 sets of *neutral* drugs acting on Gram-positive cells, a mean value of $5.7 \pm 0.5$ was found. By this crude measure the fungi resemble Gram-positive cells more closely than Gram-negative cells. Of course it is well known that fungi like *C. albicans* give the Gram-positive test.

The mean log $P_0$ for 6 sets (eq 42–47) of quaternary ammonium compounds having antifungal activity is $2.6 \pm 0.5$. This figure agrees well with the value of 2.6 found in eq 64 for antibacterial action. However, these values are lower than the mean figure of $3.7 \pm 0.4$ found for quaternary ammonium compounds causing hemolysis. The higher log $P_0$ for hemolysis indicates that more lipophilic derivatives can be made before reaching maximum activity for a given series. Log $P_0$ is highly time dependent; that is, more lipophilic molecules require a longer period of time to reach their sites of action. Log $P_0$ is also dependent on the nature of the material in the system. The red cell is a much simpler system in which the partitioning of the drug directly onto the surface of the cell is essentially the same as reaching the site of action. The process is much more complex with the fungi and bacteria, in part because of involvement with the growth media and in part because of the more complex nature of the organisms. The hydrophobic surface of an ammonium salt of log $P$ = 2.6 is large (*e.g.*, log $P(C_{16}H_{33}N^+(CH_3)_2CH_2C_6H_5)$ = 2.92). The fact that such molecules form micelles easily means that they tend to bind tightly to *any* hydrophobic area with which they come in contact. This greatly hinders their random movement to the critical sites of action in the membranes.

Neutral molecules acting on fungi and Gram-positive cells have log $P_0$ values of about 5.6 which is about 3 log units higher than charged ammonium ions. The greater number of C atoms for lipophilicity using the log $P$ scale for charged compounds plus, very likely, the interaction of the charge itself with the proteinaceous material of the cell must somehow combine to set lower log $P_0$ values on the charged molecules.

The same appears to be true for the anions. However, with the fatty acids of eq 48–51 there is such wide variation that the mean value of 1.7 has little meaning except that the values are much lower than for neutral compounds.

From the point of view of log $P_0$, the imidazolines are most interesting. Since the $pK_a$ of this compound is rather high (9.6 for E), log $P$ for the protonated form of the amine has been employed. The log $P_0$ found using these values is not at all close to that found for the other




E

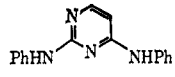
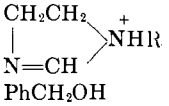
ions of Table IIc. While the intercepts of the imidazolines are close to those found for the amines of eq 36 which are assumed to be acting in their protonated forms, the log $P_0$ values are very much different. The log $P_0$ values for the imidazolines are like those found for neutral molecules and it may be that this is their active form. If one uses log $P$ for the neutral form of the imidazolines in, say, eq 34, an intercept of $-0.81 \pm 1.0$ is found. This would indicate no specificity for this function.

When dealing with very long aliphatic chains attached to a polar function, one cannot be sure that the additivity principle of calculating log $P$ by the addition of 0.5 for each $CH_2$ unit holds. We have made some attempt to investigate[65] this problem by studying the apparent partition coefficients of *N*-alkylpyridinium bromides. The difficulty of getting accurate log $P$ values of the higher members of the series precludes any statement at present about additivity for members of the series beyond $C_{14}$. However, it is clear when one works at very low concentrations to avoid micelle formation or premicelle dimerization that additivity is almost constant in the $C_{14}$–$C_{18}$ range. Whether this small departure from additivity is the result of molecular oil droplet formation as Kauzmann[66] has suggested or whether it is due to some premicellar dimerization[67] is not clear. It does not seem to be a serious problem for our present level of comparison of log $P_0$ values.

In summary, the intrinsic antifungal activity of isolipophilic functions can be tentatively ordered on a logarithmic scale according to intercepts of Table II as in Table III. The ordering is of course crude and it

TABLE III

LOGARITHMIC SCALE OF ISOLIPOPHILIC ANTIFUNGAL ACTIVITY

| | |
|---|---|
| $RNHC(=NH_2)NH_2^+$ | 5 |
|  | 4 |
| 1,4-Cyclohexadienone | 3.5 |
| $R_4N^+$ | 3.2 |
| $RCH_2NCS$ | 3.2 |
| $BrCH_2CONHR$ | 3 |
| $PhNHCH_2Ph$ | 3 |
| $RNH_3^+$ | 2 |
|  | 2 |
| $PhCH_2OH$ | 1 |
| $PhOCH_2CHOHCH_2OH$ | 1 |
| Phenols | 0.5 |
| PhNCS | 0.5 |
| $CH_2=C(CH_3)CO_2Ph$ | 0.5 |
| $RNHC(=S)NHR$ | 0.2 |

will vary by at least 0.5 log unit, depending on what kind of response one uses in measuring activity (*i.e.*, inhibition or killing action). It will of course vary somewhat from one type of fungus to another. Nevertheless, it does enable one to compare different sets of congeners, setting aside the sometimes confusing factor of nonspecific toxicity due to simple lipophilic character. This factor alone can account for a large amount of

(65) R. N. Smith, D. Soderberg, and C. Hansch, unpublished results.
(66) W. Kauzmann, *Advan. Protein Chem.*, **14**, 37 (1959).
(67) P. Mukerjee, *J. Phys. Chem.*, **69**, 2821 (1965).

variation in the activity of a set of congeners. For example, in a set of neutral congeners having log $P_0$ of 5.5 and a dependence of activity on log $P$ of 0.6 (slope) in the linear relation between log $1/C$ and log $P$, the difference in activity of derivatives of log $P$ = 0 and log $P$ = 5 will be 3 log units. Unless this large variation in activity can be separated in structure–activity relationship discussions, it is quite difficult to begin to mechanistically classify different functional groups, especially when one gets beyond simple homologous series. How valuable such scales as that in Table III will ultimately be will not be known until more extensive studies have been made.

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# Crystal Structure of *dl*-Brompheniramine Maleate [1-(*p*-Bromophenyl)-1-(2-pyridyl)-3-*N*,*N*-dimethylpropylamine maleate]

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Racemic brompheniramine maleate crystallizes in space group $P2_1/c$ with $a$ = 9.863 Å, $b$ = 10.836 Å, $c$ = 21.494 Å, and $\beta$ = 115.83°. The crystal structure was solved by conventional Patterson and Fourier techniques and refined by least squares to weighted and unweighted $R$ factors of 6.37 and 4.55%, respectively. The propylamine chain is fully extended and adopts an asymmetrical disposition with respect to the 2 aryl moieties. The *p*-bromobenzyl group is partially occluded by the asymmetry and the 2-pyridyl ring is exposed, thus giving the molecule an open side. The maleic acid is in the monoanion form and is H bonded to the $NMe_2$ group. Molecular parameters are close to expected values with the exception of the location of the second base dissociable proton of the maleate, which is engaged in a very short asymmetric intraion H bond of length 2.415 Å.

The antihistaminic drugs as a class are thought to exert their action by successful competition with histamine for the allergic (H1) receptor site on the walls of smooth muscle tissue.[1] The title compound is a potent histamine antagonist and, because receptor sites are difficult to study directly, it was thought that useful information regarding molecular conformations of antihistaminic drugs could be obtained by defining the structure of this effector molecule.

The structure of histamine has recently been completed by two independent groups[2] and, more recently, one of these groups has published their preliminary results of the first X-ray study of an antihistamine.[3] The present work was begun in an attempt to delineate some of the seemingly relevant structural parameters for antihistaminic action. It is reasonable to suppose that if the antihistamine acts as a competitive inhibitor of histamine then there should be some points of significant structural similarity between them. In particular it seemed important to know if the N–N distance in brompheniramine was comparable to the 4.55-Å distance Kier[4] has postulated for the allergically active conformer of histamine. Another molecular parameter of interest was the dihedral angle between the 2 aromatic rings of brompheniramine since these have been implicated in the binding of this molecule to the H1 site.[5]

## Experimental Section

Suitable crystals were easily grown by diffusion of $Et_2O$ into a soln of the complex in EtOH. Preliminary oscillation and Weissenberg photographs of a crystal exhibiting $2/m$ symmetry and max dimensions of 0.20 × 0.18 × 0.20 mm, showed the space group to be $P2_1/c$. The crystal lattice data are summarized in Table I, the unit cell parameters being derived by least-squares

TABLE I

| | |
|---|---|
| Morphology | $2/m$ |
| Space group | $P2_1/c$ |
| $a$ | 9.863 ± 0.01 Å |
| $b$ | 10.836 ± 0.007 Å |
| $c$ | 21.494 ± 0.01 Å |
| cos $\beta$ | −0.4356 ± 0.0009 |
| $\beta$ | 115.83 ± 0.05° |
| $V$ | 2067.67 Å$^3$ |
| $\rho_{calcd}$ 4]$C_{20}H_{23}O_4BrN_2$]/cell | 1.42 g/cm$^3$ |
| $\rho_{meas}$]$(C_2H_5)_2O/CH_2Br_2$] | 1.43 g/cm$^3$ |
| $\mu$ | 32.6 cm$^{-1}$ |

refinement of these parameters using the $2\theta$, $\chi$, and $\phi$ values for 12 reflections during the initial stages of data collection on a Picker FACS 1 diffractometer. A total of 3374 different reciprocal lattice points were examined using Ni-filtered Cu K radiation and the diffractometer in the coupled $\theta/2\theta$ scan mode. The $2\theta$ scan speed was 1°/min over a basic peak width of 1.8°, this width being increased as a function of $\theta$ to cope with the dispersion of the Cu K$\alpha$ doublet.[6] Ten-second, fixed-position, background counts were taken on both sides of every Bragg reflection. A check was kept on the stability of the experimental situation during the 5-day course of the data collection by measuring 3 standard reflections after every 30 data reflections. An examination of the standards as a function of time implied no significant crystal slippage or decomposition and so the data were judged accept-

(1) Barlow, R. B., "Introduction to Chemical Pharmacology," Methuen, London, 2nd ed, 1964, p 369.
(2) M. V. Veidis, G. J. Palenik, R. Schaffrin, and J. Trotter, *J. Chem. Soc. A*, 2659 (1969).
(3) G. R. Clark and G. J. Palenik, *J. Amer. Chem. Soc.*, **92**, 1777 (1970).
(4) L. B. Kier, *J. Med. Chem.*, **11**, 441 (1968).
(5) Ref 1, pp 372–373.
(6) Arndt and Willis, "Single Crystal Diffractometry," Cambridge University Press, New York, N. Y., 1966, pp 173–174.