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REVIEW ARTICLE

Lipophilic Character and Biological Activity of Drugs II: The Parabolic Case

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Keyphrases ☐ Lipophilicity–biological activity nonlinear relationships—review ☐ Partition coefficients—determination of nonlinear relationships between lipophilicity and biological activity ☐ Hydrophobic binding—effect on drug activity ☐ Structure–activity relationships—lipophilicity and biological activity, review

In the first part of this review (1), examples were considered in which there was a linear relationship between the response to drug action and the relative lipophilic character of the drug. Relative drug response was defined in terms of log $1/C$ (pC), where C is the molar concentration of drug producing a standard response; relative lipophilic character was defined by log P, where P is the octanol–water partition coefficient. The present review extends this survey to the more general problem of the nonlinear relationship between pC and log P.

The term "drug" is difficult to define. In these discussions it is employed in the widest sense possible. A drug is considered to be any chemical capable of causing a biochemical or biological response. A better term might be pharmacon, which has been employed by Ariëns (2).

Ever since Meyer (3) and Overton (4) discovered that the narcotic potency of the members of a set of congeners tends to increase as their oil–water partition coefficients increase, there has been interest in defining "lipophilic character" and its role in the activity of drugs. The analyses in this review are all based on the operational definition of lipophilic character by log P from the octanol–water system. There is, of course, great advantage in using a single reference system. The reasons behind the choice of octanol–water were discussed previously (1, 5). It is possible to compare work in other solvent systems with that obtained in octanol–water *via* Eq. 1:

$$\log P_1 = a \log P_2 + b \qquad \text{(Eq. 1)}$$

In Eq. 1, first formulated by Collander and recently (6) applied to a variety of systems, P_1 represents the partition coefficient of a solute between one solvent and water, and P_2 is that for the solute between a second solvent and water. Equation 1 holds well when P_1 and P_2 are from similar apolar solvents such as alcohols, esters, and ethers. It fails completely when comparisons are between hydrocarbons (such as heptane or benzene) and solvents with hydrogen-bonding ability such as alcohols, esters, and ethers.

Much of the early work seeking correlations with partition coefficients was concerned with nonspecific narcotic effects. Recently, it has become clear that by using log P to define hydrophobic character operationally, one can correlate the binding of organic compounds (drugs) to proteins (7–20), enzymes (7, 21–31), and membranes (32). Equations 2–4 are typical examples:

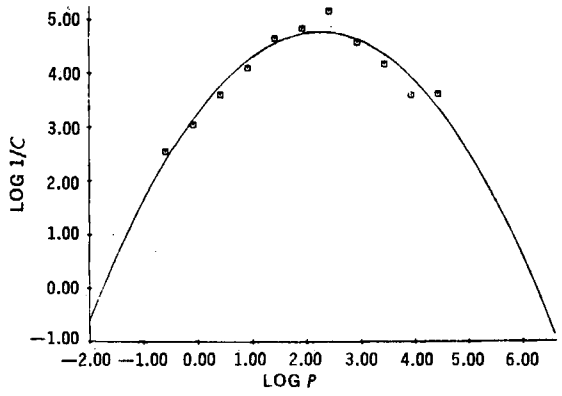


Figure 1—*Bactericidal activity of benzyldimethylalkylammonium chlorides against* Candida albicans [*log 1/C = −0.30 (log P)² + 1.34 log P + 3.25*].

binding of organic compounds by serum albumin (10)

	n	*r*	*s*	
$pC = 0.75 \log P + 2.30$	42	0.960	0.159	(Eq. 2)

hemolysis of red cells by alcohols and esters (32)

	n	*r*	*s*	
$pC = 0.90 \log P - 0.24$	19	0.993	0.096	(Eq. 3)

binding of barbiturates by liver homogenate (5)

	n	*r*	*s*	
$\log (B/F) = 0.52 \log P - 1.14$	5	0.973	0.124	(Eq. 4)

In Eqs. 2 and 3, C is the molar concentration of drug that produces a 1:1 complex *via* equilibrium dialysis. In Eq. 4, B is the percent of barbiturates bound and F is the percent free. For the equations throughout this report, n represents the number of data points used in deriving the equation, r is the correlation coefficient, and s is the standard deviation. Equations 2–4 and hundreds of others like them (1, 5, 33) establish the fact that drugs are bound in varying degrees by a large percentage of the macromolecules they encounter in living tissue. Moreover, this is a partitioning-like process, which is well modeled by the way the drugs partition between octanol and water. This partitioning has a profound effect on the random walk process drugs follow in finding their sites of action.

Under equilibrium conditions as in Eqs. 2–4, one expects and finds linear relations between pC and log P. The higher the value of log P, the tighter is the binding. As log P values become large or the time of the experiment becomes short, linearity is not the rule and one finds a much better correlation by a second-order

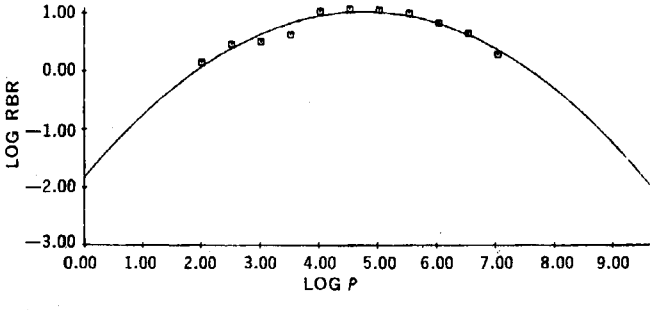


Figure 2—*Mycelia inhibition of 5-alkyl-8-hydroxyquinolines against* Aspergillus niger [*log RBR = −0.13 (log P)² + 1.20 log P − 1.84*].

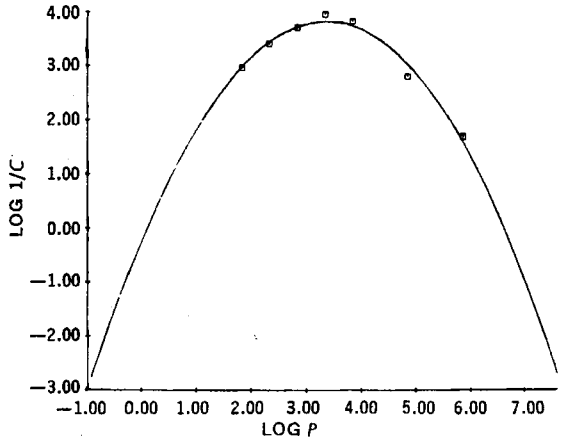


Figure 3—*Hemolytic activity of α-monoglycerides against dove red blood cells* [*log 1/C = −0.36 (log P)² + 2.43 log P − 0.27*].

equation as in Eq. 5:

concentration of X—$C_6H_4B(OH)_2$ localized in mouse brain in 15 min. (34)

	n	*r*	*s*	
$\log C = -0.54(\log P)^2 + 2.47 \log P - 1.05$	14	0.915	0.214	(Eq. 5)

This equation, based on the work of Soloway *et al.* (35), correlates the localization of benzeneboronic acids (injected interperitoneally) in mouse brain. In this time-dependent process, the parabola of Eq. 5 correlates the data much better than linear relations such as Eqs. 2–4. Equations 2–4, from *in vitro* studies, actually lead one to expect nonlinear relationships such as Eq. 5 from living systems. Since one finds tighter and tighter binding between organic compounds and macromolecules as the log P values of the former are increased, it is clear that eventually a point is reached where this restriction of movement is rate controlling. The length of time allowed for attainment of equilibrium is, of course, important in setting the degree of linearity found in any given case.

In early structure–activity studies, a departure from linearity in response and lipophilic character was often observed and was termed the "cutoff" point. Ferguson (36–38) was one of the first to assume that there might be a general "rational" explanation for this phenomenon. He attempted to explain it by arguing that the higher members of a homologous series would become so insoluble that concentrations high enough to cause a standard response could not be obtained. While this might explain certain special situations, in the light of Eqs. 2–4 it is hard to know what one is talking about in terms of solubility when the drug is injected into an animal or added to a complex medium of bacteria and nutrient. Depending on the lipophilic character of the drug, it will be more or less bound to all kinds of macromolecules present.

It is probably best to abandon any traditional ideas of solubility of drugs in an aqueous phase when considering the kind of data presented in this report. One is faced with a highly complex set of equilibria of drugs in an aqueous phase and drugs bound with varying degrees of firmness by a large variety of macromolecules which make up living cells and tissue. For this

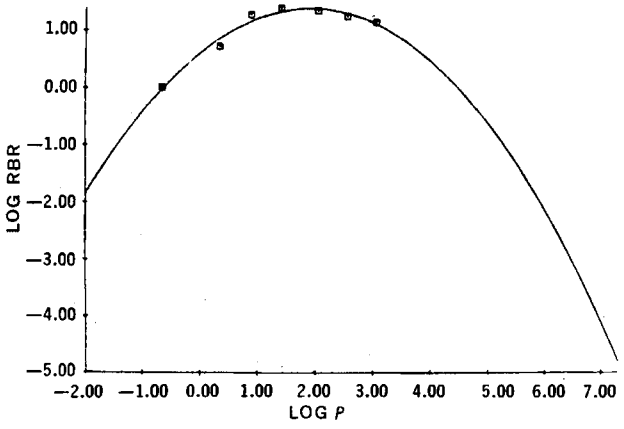


Figure 4—*Survival time of* Calliphora erythrocephala *blowfly larva in aliphatic alcohols [log RBR = −0.21 (log P)² + 0.80 log P + 0.59].*

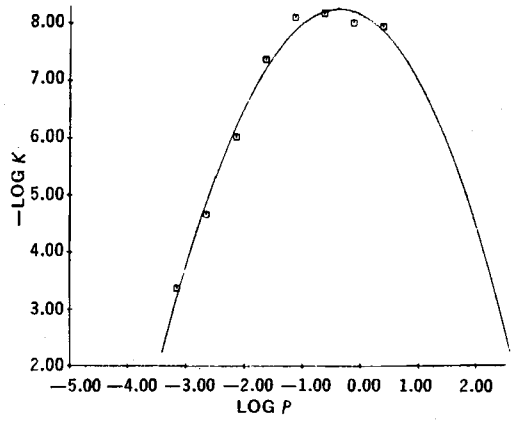


Figure 5—*Inhibitory activity of aliphatic amines against human liver mitochondrial MAO [log K_i' = −0.67 (log P)² − 0.53 log P + 8.14].*

reason, the authors have stressed the advantage of considering in probabilistic terms (34, 39, 40) the movement of drug from the point of introduction to the active sites.

For some time this laboratory has been collecting examples of what can be loosely termed "parabolic" relationships between log $1/C$ and log P. A large amount of evidence is now in hand which clearly shows that the "break" in the linear relation between log $1/C$ and log P is not precipitous (see examples in Figs. 1–6) and that the term "cutoff" is not well suited to describe the phenomenon. In Figs. 1–6, the solid line is the least-squares parabola drawn through the experimental points. These six examples are representative of the cases in Table I. In the present survey, about 230 examples were plotted (by computer). From a study of these plots it was not possible to visualize any kind of curve that would fit the data better than a parabolic expression such as Eq. 6:

$$pC(k) = -a(\log P)^2 + b \log P + \text{constant} \qquad \text{(Eq. 6)}$$

where $pC = \log 1/C$, and C is the molar concentration of drug producing a standard response in constant time. Other rate or equilibrium constants (k) may also be used. Not all of these examples have been included in the present data base, partly for reasons of space but also because it seemed important to select the best examples for study.

For Table I, sets were selected having five or more data points and where the F test (41) indicated that the addition of the $(\log P)^2$ term to the linear equation in log P is significant at the 0.99 level of significance or higher. With a few exceptions, the equations of Table I have correlation coefficients of 0.95 or higher. Some sets meeting these standards were rejected because, from an inspection of the plotted curve, it could be seen that the log P values of the most active compounds (also most hydrophobic compounds) were considerably below log P_0 (the apex of the parabola). In these examples the confidence intervals on log P_0 were very wide or could not be established (40). Ideally, one would want to include only examples where the data points covered the complete parabola from zero activity with a low partition coefficient to zero activity with a high partition coefficient. Such data are rare indeed and sorely needed. For practical reasons it is not very interesting to test the higher members of a homologous series once activity begins to decline. For this reason, many investigators stop studying the more lipophilic homologs once activity is found to drop. Moreover, the very lipophilic members of a series are often extremely difficult to study because of their limited aqueous solubility. Some of the best data this study has uncovered were obtained with carboxylate anions and quaternary salts where the difficulties of solubility can be circumvented.

For the present review, only those data sets were selected where the single variable log P in Eq. 6 gave a high correlation of the data. While about 230 of these sets are now in hand, several hundred others, where an additional term such as one in σ or E_s is necessary for high correlation, support the general importance of the parabolic relationship between the logarithm of a biological rate or equilibrium constants and log P. The data for the results in Table I are contained in Table III. In Table II a set of equations is given for which the limitations are not as severe. In these examples, the $(\log P)^2$ term is significant at the 0.95 level. To conserve space, the experimental data are not included for these examples. However, most of the log P values are in Table III and the pC values can be found in the cited references.

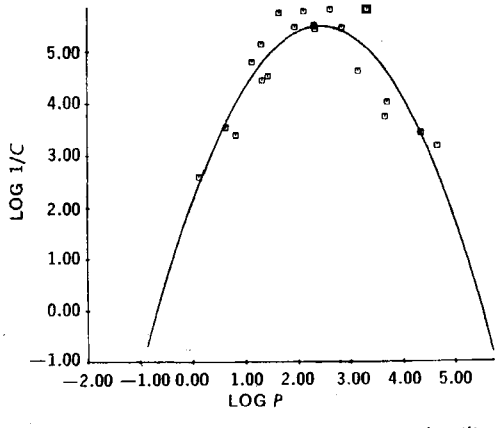


Figure 6—*Inhibitory activity of aminopyridines and anilines against* Mycobacterium tuberculosis *[log 1/C = −0.57 (log P)² + 2.73 log P + 2.22].*

Table I—$pC = a(\log P)^2 + b \log P + c$

Equation Number	b	a	c	$\log P_0$	Confidence Interval	n	r	s	Compound	Type Biological Activity[a]	References 1	References 2
					Part A							
7	−0.53 ± 0.50	−0.67 ± 0.17	8.14 ± 0.32	−0.40	(−0.63, −0.03)	8	0.995	0.213	$R\overset{+}{N}H_3$	MAO, K_i'	III-1	42
8	−0.51 ± 0.71	−0.68 ± 0.24	6.33 ± 0.57	−0.38	(−0.69, 0.22)	6	0.995	0.235	$R\overset{+}{N}H_3$	MAO, K_i	III-2	42
9	0.07 ± 0.15	−0.16 ± 0.07	4.48 ± 0.45	0.23	(−0.28, 0.72)	11	0.883	0.437	$RCOO^-$	*M. audouinii*, MIC	III-5	43
10	0.21 ± 0.10	−0.41 ± 0.08	3.75 ± 0.21	0.26	(0.13, 0.43)	5	0.999	0.069	$RCHOHCOO^-$	*V. cholerae*, pH 6.5, MKC	III-7	44
11	0.28 ± 0.24	−0.10 ± 0.06	2.77 ± 0.27	1.44	(0.14, 7.19)	11	0.982	0.239	Alkylguanidines	Rat liver mitochondria, I_{50}	III-12	45
12	1.11 ± 0.58	−0.77 ± 0.61	4.48 ± 0.46	0.72	(0.21, 4.70)	6	0.993	0.233	$RCONH_2$	ADH, binding ($K_{ER\cdot I}$)	III-13	46
13	1.19 ± 0.34	−0.40 ± 0.14	4.43 ± 0.17	1.49	(1.32, 1.78)	6	0.990	0.097	Isonicotinic acid hydrazides	MAO, I_{50}	III-14	47
14	1.23 ± 0.17	−0.56 ± 0.08	3.96 ± 0.20	1.10	(1.01, 1.22)	5	0.999	0.073	$RCHOHCOO^-$	*S. aureus*, pH 6.5, MKC	III-8	44
					Part B							
15	0.31 ± 0.10	−0.09 ± 0.04	4.32 ± 0.21	1.82	(1.32, 3.00)	7	0.974	0.141	$RCOO^-$	*M. tuberculosis*, MIC	III-6	48
16	0.44 ± 0.17	−0.11 ± 0.05	3.03 ± 0.34	2.03	(1.49, 3.06)	7	0.963	0.245	$RCHOHCOO^-$	*B. lepisepticus*, pH 7.5, MKC	III-9	44
17	0.44 ± 0.16	−0.11 ± 0.03	4.89 ± 0.16	1.93	(1.68, 2.10)	6	0.994	0.030	Alkylguanidine acetates	*M. fructicola*, ED_{50}	III-15	49
18	0.51 ± 0.17	−0.13 ± 0.07	6.33 ± 0.47	1.94	(1.10, 4.26)	10	0.953	0.430	$(CH_3)_3\overset{+}{N}(CH_2)_n\overset{+}{N}(CH_3)_3$	Rabbit, head drop	III-17	50
19	0.55 ± 0.30	−0.13 ± 0.07	2.85 ± 0.26	2.13	(1.70, 2.70)	9	0.880	0.208	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*P. aeruginosa*, MIC	III-19	51
20	0.57 ± 0.18	−0.12 ± 0.05	4.08 ± 0.17	2.38	(1.99, 3.09)	10	0.949	0.183	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*S. typhosa*, MIC	III-20	51
21	0.58 ± 0.09	−0.16 ± 0.06	3.06 ± 0.21	1.85	(1.38, 2.80)	6	0.997	0.108	$RCHOHCOO^-$	*B. lepisepticus*, pH 8.5, MKC	III-10	44
22	0.60 ± 0.22	−0.18 ± 0.09	1.89 ± 0.13	1.69	(1.47, 2.21)	13	0.918	0.079	*N,N'*-Diacylureas	Mouse, MHD	40	52
23	0.61 ± 0.25	−0.17 ± 0.08	2.61 ± 0.38	1.76	(1.36, 2.40)	7	0.958	0.264	$RCHBrCOO^-$	*V. cholerae*, pH 7.5, MKC	III-30	53
24	0.61 ± 0.23	−0.19 ± 0.08	1.78 ± 0.15	1.64	(1.42, 2.00)	5	0.993	0.043	Acetals	Rat, MHD	III-41	54
25	0.64 ± 0.07	−0.16 ± 0.03	3.07 ± 0.12	2.02	(1.82, 2.26)	8	0.995	0.097	$C_5H_5\overset{+}{N}R$	*V. inaequales*, KS	55	56
26	0.65 ± 0.11	−0.13 ± 0.04	2.55 ± 0.19	2.44	(2.03, 3.15)	8	0.989	0.156	$C_5H_5\overset{+}{N}R$	*P. infestans*, KS	55	56
27	0.72 ± 0.24	−0.17 ± 0.09	2.58 ± 0.44	2.16	(1.61, 3.63)	7	0.973	0.295	$C_5H_5\overset{+}{N}R$	*A. oleracea*, KS	55	56
28	0.75 ± 0.18	−0.15 ± 0.08	2.08 ± 0.11	2.46	(1.90, 4.26)	10	0.983	0.110	Misc.	Chick embryo, MED Inh hatching	57, 58	59
29	0.77 ± 0.42	−0.19 ± 0.11	2.17 ± 0.39	1.97	(1.54, 2.54)	6	0.959	0.206	$RCHBrCOO^-$	*V. cholerae*, pH 8.5, MKC	III-31	53
30	0.78 ± 0.16	−0.18 ± 0.04	2.93 ± 0.15	2.21	(2.04, 2.43)	10	0.974	0.123	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*P. vulgaris*, MIC	III-21	51
31	0.78 ± 0.17	−0.16 ± 0.05	2.38 ± 0.16	2.50	(2.19, 3.00)	7	0.990	0.115	$C_5H_5\overset{+}{N}R$	*M. fructicola*, KS	55	56
32	0.80 ± 0.21	−0.21 ± 0.08	0.59 ± 0.16	1.90	(1.63, 2.40)	7	0.985	0.102	ROH	Blowfly, survival time (RBR)	III-42	60
33	0.80 ± 0.35	−0.20 ± 0.07	4.81 ± 0.35	1.99	(1.67, 2.18)	6	0.990	0.065	Alkylguanidine acetates	*S. pastorianus*, ED_{50}	III-16	49
34	0.82 ± 0.14	−0.15 ± 0.03	2.89 ± 0.15	2.71	(2.52, 2.95)	46	0.878	0.306	$XC_6H_4CH_2\overset{+}{N}(R)(CH_3)_2$	*S. typhosa*, MKC	III-45	61
35	0.84 ± 0.47	−0.23 ± 0.12	2.42 ± 0.43	1.78	(1.48, 1.99)	12	0.841	0.100	Barbiturates	Rabbit, MLD	III-48	62
36	0.84 ± 0.23	−0.21 ± 0.06	2.94 ± 0.20	1.97	(1.77, 2.17)	10	0.960	0.172	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*P. vulgaris*, MKC	III-22	51
37	0.85 ± 0.11	−0.22 ± 0.04	4.69 ± 0.17	1.93	(1.71, 2.22)	7	0.995	0.119	$(CH_3)_3\overset{+}{N}(CH_2)_n\overset{+}{N}(CH_3)_3$	ChE Rabbit, I_{50}	III-18	50
38	0.86 ± 0.12	−0.14 ± 0.02	4.48 ± 0.18	3.00	(2.80, 3.22)	6	0.997	0.100	$R_3SnOCOCH_3$	*A. niger*, MIC	III-53	63
39	0.87 ± 0.14	−0.17 ± 0.03	2.93 ± 0.16	2.62	(2.45, 2.82)	45	0.884	0.306	$XC_6H_4CH_2\overset{+}{N}(R)(CH_3)_2$	*S. aureus*, MKC	III-46	61

Table I—(*Continued*)

Equation Number	*b*	*a*	*c*	log P_0	Confidence Interval	*n*	*r*	*s*	Compound	Type Biological Activity[a]	References 1	References 2
40	0.89 ± 0.24	−0.17 ± 0.10	2.84 ± 0.53	2.62	(1.91, 4.97)	7	0.986	0.305	$R\overset{+}{N}(CH_3)_3$	*E. typhosa*, MKC	III-55	64
41	0.89 ± 0.25	−0.19 ± 0.08	2.60 ± 0.24	2.40	(1.96, 3.43)	8	0.978	0.214	$RCOO^-$	Red cell dove, MHC	32	65
42	0.90 ± 0.14	−0.21 ± 0.04	4.80 ± 0.14	2.18	(2.02, 2.38)	12	0.979	0.158	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*S. aureus*, MIC	III-23	51
43	0.91 ± 0.21	−0.17 ± 0.06	3.87 ± 0.21	2.68	(2.34, 3.28)	12	0.966	0.230	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*Cl. welchii*, MIC	III-24	51
44	0.91 ± 0.47	−0.18 ± 0.09	4.67 ± 0.66	2.61	(1.98, 3.31)	5	0.988	0.271	$R_3SnOCOCH_3$	*R. nigricans*, MIC	III-54	63
45	0.93 ± 0.20	−0.23 ± 0.05	2.76 ± 0.20	1.99	(1.81, 2.21)	12	0.962	0.220	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*P. aeruginosa*, MKC	III-25	51
46	0.95 ± 0.45	−0.25 ± 0.11	3.11 ± 0.42	1.93	(1.57, 2.34)	6	0.971	0.219	$RCHBrCOO^-$	*V. cholerae*, pH 6.0, MKC	III-32	53
47	0.98 ± 0.35	−0.27 ± 0.09	3.03 ± 0.33	1.79	(1.53, 2.04)	6	0.985	0.171	$RCHBrCOO^-$	*B. lepisepticus*, pH 6.0, MKC	III-33	53
48	0.99 ± 0.17	−0.19 ± 0.05	3.80 ± 0.17	2.65	(2.39, 3.05)	12	0.980	0.190	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*Cl. welchii*, MKC	III-26	51
49	1.00 ± 0.57	−0.26 ± 0.14	2.54 ± 0.53	1.89	(1.43, 2.39)	6	0.959	0.277	$RCHBrCOO^-$	*B. lepisepticus*, pH 7.5, MKC	III-34	53
50	1.02 ± 0.16	−0.29 ± 0.06	−0.44 ± 0.14	1.78	(1.60, 2.02)	8	0.992	0.105	4-R-Lincomycin	*S. lutea*, curve assay (RBR)	III-57	66
51	1.04 ± 0.29	−0.24 ± 0.07	3.11 ± 0.26	2.19	(1.98, 2.45)	11	0.947	0.224	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*A. niger*, MIC	55	51
52	1.12 ± 0.44	−0.29 ± 0.18	1.85 ± 0.23	1.91	(1.57, 3.23)	25	0.864	0.208	Ethers	Mouse, LD_{50}	III-58	67
53	1.21 ± 0.70	−0.21 ± 0.12	3.50 ± 0.91	2.91	(2.26, 3.64)	8	0.898	0.593	$RCHBrCOO^-$	*D. pneumoniae*, pH 6.5, MKC	III-35	53
54	1.23 ± 0.74	−0.22 ± 0.12	3.12 ± 0.95	2.82	(2.14, 3.50)	8	0.898	0.620	$RCHBrCOO^-$	*S. haemolyticus*, pH 6.0, MKC	III-36	53
55	1.26 ± 0.35	−0.24 ± 0.11	3.31 ± 0.37	2.59	(2.13, 3.68)	6	0.991	0.213	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	Red cell sheep, $C_{H_{50}}$	III-27	68
56	1.28 ± 0.45	−0.37 ± 0.15	0.70 ± 0.30	1.72	(1.56, 1.97)	10	0.936	0.124	ROH	Rabbit, excretion (RBR)	III-43	69
57	1.33 ± 0.42	−0.25 ± 0.08	3.97 ± 0.48	2.71	(2.49, 2.97)	5	0.995	0.089	$R\overset{+}{N}H_3$	*S. viridans*, MIC	III-3	70
58	1.34 ± 0.31	−0.30 ± 0.08	3.25 ± 0.28	2.25	(2.06, 2.48)	11	0.961	0.243	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*C. albicans*, MKC	III-28	51
59	1.36 ± 0.26	−0.26 ± 0.06	3.24 ± 0.23	2.57	(2.37, 2.84)	11	0.978	0.199	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*C. albicans*, MIC	55	51
60	1.37 ± 0.49	−0.35 ± 0.15	2.32 ± 0.38	1.96	(1.78, 2.30)	10	0.951	0.071	Barbiturates	Rabbit, MHD	III-49	62
61	1.50 ± 0.63	−0.26 ± 0.12	2.50 ± 0.72	2.86	(2.55, 3.31)	5	0.991	0.133	$R\overset{+}{N}H_3$	*S. aureus*, MIC	III-4	70
62	1.55 ± 0.42	−0.42 ± 0.17	1.92 ± 0.24	1.84	(1.64, 2.27)	12	0.973	0.096	Barbiturates	Mouse, AD_{50}	III-50	71, 72
63	1.57 ± 0.55	−0.45 ± 0.16	2.25 ± 0.44	1.73	(1.61, 1.88)	14	0.884	0.115	Barbiturates	Rat, MHD	III-51	73
64	1.79 ± 0.42	−0.33 ± 0.09	0.90 ± 0.44	2.69	(2.57, 2.89)	7	0.994	0.034	Thiobarbiturates	Mouse, AD_{50}	40	71
65	1.96 ± 0.64	−0.49 ± 0.26	4.61 ± 0.33	2.02	(1.67, 3.05)	13	0.951	0.289	1,2,4-Triazine-4-amino-5-one	Chloroplast, I_{50}	74	74
66	2.10 ± 0.87	−0.67 ± 0.30	1.66 ± 0.57	1.56	(1.45, 1.73)	8	0.947	0.082	1,1-Dialkyl-propynyl carbamates	Mouse, HD_{50}	40	75
67	2.16 ± 1.11	−0.52 ± 0.32	0.84 ± 0.91	2.09	(1.90, 2.72)	9	0.944	0.096	1,1-Dialkyl-1-propynols	Mouse, HD_{50}	III-59	76
68	2.25 ± 0.59	−0.37 ± 0.17	0.03 ± 0.47	3.01	(2.56, 4.18)	10	0.991	0.096	Barbiturates	Brain rat, I_{50}	III-52	77
69	2.45 ± 0.81	−0.69 ± 0.24	0.72 ± 0.64	1.79	(1.69, 1.92)	8	0.965	0.058	1,1-Dialkyl-1-propynols	Mouse, HD_{50}	40	76
70	2.73 ± 0.70	−0.57 ± 0.14	2.22 ± 0.75	2.38	(2.22, 2.55)	20	0.898	0.474	Aminopyridines and anilines	*M. tuberculosis*, MIC	III-60	78
71	3.05 ± 1.37	−0.63 ± 0.33	−1.78 ± 1.37	2.43	(2.24, 2.91)	8	0.958	0.134	$RC_6H_4COO^-$	Rabbit, excretion (RBR)	III-61	79
72	3.72 ± 2.39	−0.68 ± 0.41	−0.42 ± 3.14	2.74	(2.32, 2.98)	8	0.900	0.359	β-Carbolines	MAO, I_{50} M	80	81
					Part C							
73	0.71 ± 0.29	−0.09 ± 0.06	3.22 ± 0.28	4.07	(3.25, 8.63)	12	0.955	0.174	$XC_6H_4CH_2\overset{+}{N}(R)(CH_3)_2$	Red cell rabbit, $C_{H_{100}}$	III-47	82
74	0.76 ± 0.18	−0.11 ± 0.06	3.32 ± 0.35	3.38	(2.54, 5.59)	7	0.987	0.259	$RCHOHCOO^-$	*D. pneumoniae*, pH 7.5, MKC	III-11	44
75	0.88 ± 0.52	−0.14 ± 0.09	2.58 ± 0.67	3.21	(2.56, 4.38)	8	0.891	0.436	$RCHBrCOO^-$	Red cell sheep, $C_{H_{100}}$	32	53

(*continued*)

Table I—(*Continued*)

Equation Number	*b*	*a*	*c*	log P_0	Confidence Interval	*n*	*r*	*s*	Compound	Type Biological Activity[a]	References 1	References 2
76	1.04 ± 0.14	−0.16 ± 0.04	3.05 ± 0.15	3.15	(2.74, 3.82)	6	0.998	0.084	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	Red cell sheep, $C_{H_{50}}$	III-29	68
77	1.06 ± 0.15	−0.16 ± 0.04	3.29 ± 0.14	3.29	(2.99, 3.75)	11	0.992	0.119	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*T. mentagrophytes*, MIC	55	51
78	1.06 ± 0.21	−0.16 ± 0.05	3.23 ± 0.19	3.23	(2.86, 3.90)	11	0.983	0.166	$C_6H_5CH_2\overset{+}{N}(R)(CH_3)_2$	*T. mentagrophytes*, MKC	55	51
79	1.19 ± 0.34	−0.19 ± 0.10	2.40 ± 0.40	3.06	(2.44, 4.66)	6	0.991	0.200	$C_5H_5\overset{+}{N}R$	*E. typhosa*, MKC	III-62	83
80	1.20 ± 0.31	−0.13 ± 0.03	−1.84 ± 0.64	4.74	(4.56, 4.96)	11	0.955	0.106	5-Alkyl-8-hydroxy-quinolines	*A. niger*, Inh (RBR)	III-64	84
81	1.20 ± 0.18	−0.16 ± 0.05	0.32 ± 0.14	3.64	(3.14, 4.57)	9	0.996	0.097	9-(1-Hydroxy-2-alkyl)adenines	HAD, Inh $[I/S]_{0.5}$	III-66	85
82	1.21 ± 0.71	−0.20 ± 0.12	2.88 ± 0.92	3.05	(2.40, 3.94)	8	0.893	0.596	$RCHBrCOO^-$	*D. pneumoniae*, pH 7.5, MKC	III-37	53
83	1.22 ± 0.27	−0.18 ± 0.08	2.36 ± 0.33	3.35	(2.68, 5.09)	6	0.996	0.160	$R\overset{+}{N}(CH_3)_3$	*S. aureus*, MKC	III-56	64
84	1.22 ± 0.64	−0.19 ± 0.11	2.60 ± 0.83	3.15	(2.58, 4.03)	8	0.909	0.542	$RCHBrCOO^-$	*D. pneumoniae* pH 8.5, MKC	III-38	53
85	1.23 ± 0.24	−0.17 ± 0.06	2.59 ± 0.19	3.56	(3.07, 4.56)	9	0.993	0.139	$C_5H_5\overset{+}{N}R$	Red cell dove, MHC	32	86
86	1.24 ± 0.31	−0.17 ± 0.07	2.33 ± 0.30	3.72	(3.18, 4.98)	6	0.996	0.135	$ROSO_3^-Na^+$	Red cell sheep, $C_{H_{50}}$	32	68
87	1.24 ± 0.81	−0.21 ± 0.14	2.51 ± 1.05	3.02	(2.26, 4.08)	8	0.872	0.685	$RCHBrCOO^-$	*S. haemolyticus*, pH 7.5, MKC	III-39	53
88	1.25 ± 0.81	−0.21 ± 0.14	2.20 ± 1.05	3.02	(2.26, 4.08)	8	0.872	0.686	$RCHBrCOO^-$	*S. haemolyticus*, pH 8.5, MKC	III-40	53
89	1.31 ± 0.26	−0.18 ± 0.08	2.78 ± 0.26	3.63	(2.87, 5.56)	6	0.997	0.152	$R\overset{+}{N}(CH_3)_3$	Red cell sheep, $C_{H_{50}}$	32	87
90	1.37 ± 0.32	−0.23 ± 0.09	2.37 ± 0.38	3.01	(2.49, 4.08)	6	0.994	0.190	$C_5H_5\overset{+}{N}R$	*S. aureus*, MKC	III-63	83
91	1.52 ± 0.25	−0.18 ± 0.04	1.01 ± 0.30	4.25	(3.92, 4.78)	11	0.992	0.141	*N*-Alkylpiperidinium$^+$	Red cell dove, MHC	32	86
92	1.71 ± 0.34	−0.21 ± 0.07	−1.57 ± 0.41	4.03	(3.62, 4.78)	8	0.995	0.086	4-Alkylresorcinol	*S. typhosa*, *PC'*	III-67	88
93	1.74 ± 0.13	−0.27 ± 0.04	3.84 ± 0.11	3.18	(2.97, 3.44)	8	0.999	0.087	ROH	Blowfly, ED_{50}	III-44	89
94	1.91 ± 1.11	−0.19 ± 0.13	0.55 ± 2.33	4.97	(4.61, 6.49)	10	0.936	0.104	XC_6H_4NCS	*C. albicans*, I_{50}	55	90
95	1.98 ± 0.37	−0.24 ± 0.04	0.17 ± 0.72	4.16	(4.03, 4.29)	8	0.989	0.107	α-Monoglycerides	Red cell dove, MHC	III-68	91
96	2.34 ± 1.27	−0.27 ± 0.17	−1.81 ± 2.33	4.33	(4.03, 5.33)	9	0.944	0.118	4-(5*H*)-Imidazolones	Mouse, HD_{50}	III-69	92
97	2.43 ± 0.80	−0.36 ± 0.10	−0.27 ± 1.40	3.36	(3.09, 3.55)	7	0.987	0.152	α-Monoglycerides	Red cell dove, MHC	32	91
98	2.88 ± 1.02	−0.48 ± 0.19	−0.15 ± 1.32	3.01	(2.86, 3.28)	7	0.989	0.062	Thiobarbiturates	Rat, MAD	III-70	93
99	2.95 ± 1.55	−0.46 ± 0.25	−0.76 ± 2.26	3.20	(2.93, 3.64)	9	0.890	0.233	Benzoxathiols	*C. albicans*, MIC	III-71	94
					Part D							
100	0.80 ± 0.25	−0.06 ± 0.02	0.36 ± 0.66	6.26	(5.95, 6.77)	6	0.991	0.044	RSCN	Aphid, LD_{50}	III-72	95
101	1.07 ± 0.38	−0.10 ± 0.04	1.06 ± 0.77	5.27	(4.88, 6.08)	8	0.973	0.104	X-Phenylmethacrylates	*S. faecalis*, MIC	III-73	96
102	1.13 ± 0.54	−0.10 ± 0.05	1.37 ± 1.24	5.87	(5.36, 7.12)	7	0.962	0.176	RSCN	Aphid, % kill (RBR)	58, 97	95
103	1.36 ± 0.24	−0.14 ± 0.03	−2.35 ± 0.53	5.03	(4.86, 5.22)	9	0.986	0.076	5-Alkyl-8-hydroxy-quinolines	*A. niger*, Inh (RBR)	III-65	84
104	1.43 ± 0.32	−0.12 ± 0.03	1.16 ± 0.72	5.81	(5.50, 6.20)	17	0.936	0.300	Hydrocupreines	*B. diphtheriae*, MIC	98	99
105	2.30 ± 0.51	−0.23 ± 0.06	−3.47 ± 1.02	5.10	(4.85, 5.51)	17	0.966	0.178	Phenols	*E. dysenteriae*, *PC'*	III-74	100
106	2.45 ± 1.15	−0.24 ± 0.11	−2.03 ± 2.61	5.15	(4.72, 5.66)	7	0.948	0.370	RSCN	Thrip, percent kill (RBR)	5, 97	95

[a] Abbreviations for biological systems and activities include: MAO = monoamine oxidase; K_i' = pH-independent, enzyme inhibitory rate constant; K_i = apparent enzyme inhibitor constant; MIC = minimum inhibitory concentration, either bacteriostatic or fungistatic; I_{50} = concentration for 50% inhibition; MKC = minimum killing concentration, either bactericidal or fungicidal; ADH = alcohol dehydrogenase; $K_{ER\cdot I}$ = enzyme binding constant; ED_{50} = effective dose for 50% of the population; MED = minimum effective dose; KS = dose necessary to kill spores (a relative biological response); MLD = minimum lethal dose; ChE = plasma hydrolase cholinesterase; MHC = minimum concentration for hemolysis; LD_{50} = lethal dose for 50% of the population; $C_{H_{50}}$ = minimum concentration for 50% hemolysis; AD_{50} = minimum anesthetic dose for 50% of the population; HD_{50} = minimum hypnotic dose for 50% of the population; HAD = hydrolase adenosine deaminase; $C_{H_{100}}$ = minimum concentration for 100% hemolysis; MAD = minimum anesthetic dose; RBR = relative biological response rather than p*C*; MHD = minimum hypnotic dose; Inh = inhibition; *K* = binding constant; $K_{E\cdot I}$ = dissociation constant for effect of inhibitor on enzyme; MDD_{50} = minimum dose causing 50% reduction in motor activity; DFR = dihydrofolate reductase; *PC'* = molar phenol coefficient; and $[I/S]_{0.5}$ = ratio of the millimolar concentration of inhibitor for 50% inhibition to the millimolar concentration of substrate.

Table II—$pC = a(\log P)^2 + b \log P + c$

Equation Number	b	a	c	$\log P_0$	Confidence Interval	n	r	s	Compound	Type Biological Activity[a]	Reference
					Part A						
107	−0.34 ± 0.20	−0.12 ± 0.05	1.81 ± 0.20	−1.37	(−1.65, −0.87)	12	0.950	0.073	$R\overset{+}{N}H_3$	Liver cat, deamination (RBR)	101
108	−0.03 ± 0.25	−0.08 ± 0.07	3.35 ± 0.27	−0.18	(−1.06, 10.26)	15	0.845	0.351	$RCOO^-$	*P. omnivorum*, MIC (100%)	55, 102
109	0.13 ± 0.05	−0.05 ± 0.02	0.10 ± 0.03	1.32	(1.17, 1.50)	6	0.983	0.016	ROH	Blowfly, survival time (RBR)	60
110	0.19 ± 0.25	−0.32 ± 0.20	2.97 ± 0.51	0.29	(−0.08, 1.26)	5	0.989	0.171	$RCHOHCOO^-$	*B. melitensis*, pH 7.5, MKC	44
111	0.21 ± 0.66	−0.12 ± 0.11	3.03 ± 0.67	0.88	(−21.66, 1.93)	5	0.997	0.102	RSCN	Mouse, MLD	103
112	0.27 ± 0.20	−0.35 ± 0.12	2.55 ± 0.22	0.38	(0.10, 0.75)	23	0.826	0.437	$XC_6H_4COO(CH_2)_nR$	Cornea rabbit, MAD	104
113	0.29 ± 0.12	−0.10 ± 0.05	3.53 ± 0.13	1.42	(0.62, 3.39)	13	0.979	0.178	$RCOO^-$	*T. interdigitale*, pH 6.5, MIC	105
114	0.31 ± 0.42	−0.20 ± 0.16	7.06 ± 0.64	0.78	(−0.94, 1.66)	7	0.870	0.440	$(CH_3)_3\overset{+}{N}(CH_2)_n\overset{+}{N}(CH_3)_3$	Cat muscle, 95% paralysis, MED	50
115	0.33 ± 0.27	−0.14 ± 0.12	2.03 ± 0.13	1.20	(0.12, 15.47)	7	0.994	0.087	$RCOO^-$	*A. niger*, pH 6.5, KS	105
116	0.56 ± 0.28	−0.31 ± 0.18	4.23 ± 0.67	0.90	(0.47, 1.92)	6	0.973	0.339	$RCHOHCOO^-$	*B. lepisepticus*, pH 6.5, MKC	44
117	0.64 ± 0.33	−0.24 ± 0.17	2.81 ± 0.40	1.35	(0.92, 2.93)	5	0.986	0.146	$RCHOHCOO^-$	*S. haemolyticus*, pH 8.5, MKC	44
118	0.66 ± 0.45	−0.35 ± 0.23	2.95 ± 0.55	0.95	(0.52, 1.67)	5	0.978	0.202	$RCHOHCOO^-$	*V. cholerae*, pH 8.5, MKC	44
119	0.66 ± 0.45	−0.35 ± 0.23	2.95 ± 0.55	0.95	(0.52, 1.67)	5	0.978	0.202	$RCHOHCOO^-$	*V. cholerae*, pH 7.5, MKC	44
120	0.72 ± 0.47	−0.34 ± 0.24	2.90 ± 0.56	1.04	(0.62, 1.94)	5	0.979	0.207	$RCHOHCOO^-$	*B. typhosa*, pH 8.5, MKC	44
121	1.01 ± 0.91	−0.42 ± 0.39	4.79 ± 0.46	1.21	(0.63, 3.08)	6	0.899	0.259	Isonicotinic acid hydrazides	MAO, I_{50} ammonia	47
122	1.03 ± 0.46	−0.55 ± 0.48	3.24 ± 0.37	0.94	(0.30, 11.17)	6	0.994	0.186	$RCONH_2$	ADH, binding ($K_{E.I}$)	46
123	1.06 ± 0.79	−0.47 ± 0.39	3.39 ± 0.93	1.12	(0.60, 3.06)	5	0.972	0.344	$RCOO^-$	*B. lepisepticus*, pH 7.5, MKC	44
					Part B						
124	0.13 ± 0.04	−0.02 ± 0.01	1.59 ± 0.10	2.70	(2.08, 3.90)	13	0.927	0.111	$RCOO^-$	Gut turtle, percent adsorption (RBR)	106
125	0.22 ± 0.27	−0.06 ± 0.05	0.42 ± 0.30	1.94	(−3.43, 2.46)	8	0.889	0.072	Misc.	Ant, alarm release (RBR)	107
126	0.43 ± 0.13	−0.07 ± 0.04	5.58 ± 0.37	2.98	(1.48, 8.63)	12	0.961	0.390	$(CH_3)_3\overset{+}{N}(CH_2)_n\overset{+}{N}(CH_3)_3$	Mouse, LD_{50}	50
127	0.49 ± 0.15	−0.13 ± 0.12	2.69 ± 0.31	1.90	(0.80, 36.36)	5	0.997	0.105	$RCHOHCOO^-$	*B. melitensis*, pH 8.5, MKC	44
128	0.60 ± 0.30	−0.15 ± 0.11	1.25 ± 0.18	2.00	(1.56, 4.50)	8	0.948	0.117	*sec*-Amines$^+$	Amine oxidase, deamination (RBR)	101
129	0.70 ± 0.20	−0.12 ± 0.09	2.47 ± 0.32	2.85	(1.89, 8.66)	6	0.991	0.174	$RCHBrCOO^-$	*B. melitensis*, pH 7.5, MKC	53
130	0.79 ± 0.39	−0.21 ± 0.15	1.33 ± 0.27	1.90	(1.48, 3.75)	8	0.935	0.210	$R\overset{+}{N}H_3$	Amine oxidase, deamination (RBR)	101
131	0.88 ± 0.24	−0.18 ± 0.10	−1.57 ± 0.12	2.48	(1.99, 4.09)	5	0.999	0.034	4-Alkylsulfadiazines	RNA yeast, binding (K)	17
132	0.94 ± 0.58	−0.24 ± 0.15	2.22 ± 0.54	1.98	(1.48, 2.70)	6	0.949	0.285	$RCHBrCOO^-$	*B. lepisepticus*, pH 8.5, MKC	53

(continued)

Table II—(*Continued*)

Equation Number	*b*	*a*	*c*	log P_0	Confidence Interval	*n*	*r*	*s*	Compound	Type Biological Activity[a]	Reference
133	0.95 ± 0.31	−0.30 ± 0.16	2.85 ± 0.37	1.58	(1.20, 2.56)	5	0.995	0.136	$RCHOHCOO^-$	*B. diphtheriae*, pH 8.5, MKC	44
134	1.01 ± 0.20	−0.22 ± 0.07	2.19 ± 0.13	2.34	(2.07, 2.86)	27	0.960	0.107	Ethers	Mouse, AD_{50}	67
135	1.02 ± 0.49	−0.27 ± 0.19	1.86 ± 0.28	1.93	(1.59, 3.76)	13	0.923	0.113	Barbiturates	Mouse, LD_{50}	71, 72
136	1.53 ± 0.08	−0.39 ± 0.11	1.69 ± 0.06	1.94	(1.56, 2.62)	5	0.999	0.020	Carbamates	Tadpole, Inh movement (100%), MED	108
137	1.59 ± 0.95	−0.41 ± 0.27	1.32 ± 0.79	1.92	(1.72, 2.42)	12	0.805	0.130	ROH	Guinea pig, HD_{50}	109
138[b]	2.53 ± 1.17	−0.56 ± 0.34	−1.07 ± 0.94	2.25	(1.98, 3.21)	14	0.912	0.217	Benzeneboronic acids	Mouse brain, localization (RBR)	34, 35
139	3.68 ± 1.16	−0.72 ± 0.33	−0.07 ± 0.77	2.56	(2.26, 3.31)	5	0.998	0.118	ROH	MAO, K_i	42
					Part C						
140	0.45 ± 0.06	−0.05 ± 0.03	3.75 ± 0.09	4.15	(2.45, 9.27)	13	0.993	0.117	$RCOO^-$	*T. purpureum*, pH 6.5, MIC	55, 105
141	0.59 ± 0.51	−0.08 ± 0.08	3.10 ± 0.67	3.57	(3.10, 11.14)	6	0.925	0.094	2-Alkyl-*N*-dodecylpyridinium	*V. inaequales*, KS	55, 56
142	0.66 ± 0.32	−0.10 ± 0.08	2.38 ± 0.31	3.44	(2.80, 8.33)	34	0.885	0.106	Thioureas	Mouse, MHD	110
143	0.96 ± 0.15	−0.16 ± 0.09	4.16 ± 0.36	3.07	(1.96, 7.47)	6	0.996	0.181	$RCHOHCOO^-$	*D. pneumoniae*, pH 6.5, MKC	44
144	1.03 ± 0.38	−0.15 ± 0.09	2.93 ± 0.36	3.47	(2.86, 5.41)	6	0.989	0.164	$ROSO_3^-Na^+$	Red cell sheep, $C_{H_{50}}$	68
145	1.19 ± 0.80	−0.19 ± 0.15	2.91 ± 0.91	3.19	(2.63, 5.90)	5	0.981	0.169	$R\overset{+}{N}H_3$	*Cl. welchii*, MIC	70
146	1.25 ± 0.78	−0.19 ± 0.14	2.83 ± 0.89	3.29	(2.74, 5.80)	5	0.985	0.164	$R\overset{+}{N}H_3$	*Cl. sporogenes*, MIC	70
147	1.36 ± 0.49	−0.16 ± 0.07	2.64 ± 0.77	4.17	(3.75, 5.11)	15	0.912	0.190	1-R-$(CH_2)_n$-3-(*m*-X-C_6H_4)-Imidazolin-2-ones	Mouse, MDD_{50}	111, 112
148	1.47 ± 0.75	−0.23 ± 0.21	1.82 ± 0.56	3.17	(2.41, 14.33)	12	0.927	0.385	2-Amino-5-alkyl-6-methylpyrimidine-4-ol	DFR, I_{50}	113
149	1.55 ± 0.58	−0.17 ± 0.11	−1.71 ± 0.71	4.68	(3.84, 8.39)	11	0.980	0.185	Phenols	*S. typhosa*, *PC'*	114
150	2.18 ± 1.62	−0.34 ± 0.31	−0.29 ± 1.95	3.22	(2.82, 9.76)	6	0.970	0.148	Thioureas	*A. solani*, I_{50} spores	55, 115
151	2.22 ± 1.29	−0.33 ± 0.25	0.63 ± 1.63	3.40	(3.01, 5.96)	10	0.960	0.097	Thiobarbiturates	Rabbit, MHD	116
152	3.22 ± 0.70	−0.37 ± 0.09	−4.87 ± 1.29	4.36	(4.21, 4.58)	25	0.945	0.173	Phenols	*S. typhosa*, *PC'*	100
153	5.98 ± 4.13	−0.65 ± 0.47	−9.33 ± 8.81	4.60	(4.34, 5.36)	6	0.948	0.226	3-Alkylpyrazoles	*T. interdigitale*, MIC	55, 117
154	8.07 ± 4.99	−0.88 ± 0.57	−13.32 ± 10.65	4.60	(4.36, 5.15)	6	0.957	0.272	3-Alkylpyrazoles	*S. aureus*, MIC	117
					Part D						
155	0.69 ± 0.06	−0.04 ± 0.03	2.51 ± 0.08	9.25	(4.96, 36.05)	13	0.997	0.098	$RCOO^-$	*T. interdigitale*, pH 6.5, KS	105
156	0.90 ± 0.25	−0.07 ± 0.02	2.09 ± 0.70	6.11	(5.60, 6.77)	15	0.913	0.339	Glyoxalidines	*M. sarcinaeforme*, LD_{50}	55, 118
157	0.94 ± 0.27	−0.08 ± 0.02	1.89 ± 0.75	6.16	(5.63, 6.86)	15	0.910	0.363	Glyoxalidines	*A. solani*, LD_{50}	55, 118
158	0.96 ± 0.37	−0.07 ± 0.03	1.44 ± 1.03	6.95	(6.09, 8.72)	15	0.875	0.500	Glyoxalidines	*G. cingulata*, LD_{50}	55, 118
159	1.05 ± 0.24	−0.09 ± 0.03	1.05 ± 0.45	5.64	(5.19, 6.45)	23	0.960	0.141	Phenols	*A. niger*, I_{50}	119
160	1.07 ± 0.24	−0.09 ± 0.02	2.17 ± 0.68	6.14	(5.70, 6.68)	14	0.946	0.324	Glyoxalidines	*M. fructicola*, LD_{50}	55, 118
161	1.22 ± 0.84	−0.11 ± 0.10	0.66 ± 1.68	5.64	(4.84, 15.81)	9	0.915	0.243	Phenylmethacrylates	*B. cereus*, MIC	96
162	1.24 ± 0.26	−0.07 ± 0.04	−0.77 ± 0.44	8.41	(6.85, 12.79)	13	0.997	0.078	Phenols	*C. albicans*, MKC	120
163	1.26 ± 0.23	−0.05 ± 0.05	0.49 ± 0.23	12.03	(7.53, 76.65)	10	0.998	0.143	ROH	Tadpole, reflex response, MED	121
164	1.33 ± 0.40	−0.11 ± 0.07	0.49 ± 0.41	6.25	(4.68, 14.21)	13	0.973	0.445	Misc.	Ventricle frog, I_{50}	122

Table II—(*Continued*)

Equation Number	b	a	c	log P_0	Confidence Interval	n	r	s	Compound	Type Biological Activity[a]	Reference
165	1.35 ± 0.78	−0.10 ± 0.07	−0.13 ± 1.95	6.56	(5.79, 9.18)	7	0.944	0.325	RSCN	Aphid, percent killed (RBR)	95
166	1.38 ± 0.34	−0.08 ± 0.07	0.52 ± 0.34	8.69	(5.78, 43.43)	10	0.995	0.210	ROH	Tadpole, narcosis, MED	123
167	1.42 ± 0.47	−0.07 ± 0.06	−2.28 ± 0.92	9.65	(7.20, 28.61)	32	0.983	0.161	Phenols	*S. haemolyticus, PC'*	100
168	1.57 ± 0.36	−0.10 ± 0.04	−2.45 ± 0.75	8.17	(6.95, 11.28)	34	0.983	0.157	Phenols	*S. aureus, PC'*	100
169	1.67 ± 0.29	−0.11 ± 0.03	−2.68 ± 0.58	7.55	(6.74, 9.07)	21	0.996	0.070	Phenols	*T. rosaceum, PC'*	100
170	1.74 ± 0.46	−0.12 ± 0.06	−2.79 ± 0.90	7.33	(6.27, 10.25)	33	0.981	0.160	Phenols	*M. smegmatis, PC'*	100
171	1.78 ± 0.45	−0.15 ± 0.07	−2.27 ± 0.68	5.76	(4.92, 8.02)	12	0.994	0.098	4-RS-Phenols	*S. aureus, PC'*	88
172	2.25 ± 0.63	−0.17 ± 0.05	−5.47 ± 1.83	6.55	(6.29, 6.93)	14	0.938	0.199	Testosterone esters	Red cell rat, percent hemolysis (RBR)	124
173	2.32 ± 0.91	−0.21 ± 0.13	−5.61 ± 1.55	5.52	(4.72, 8.84)	17	0.983	0.117	Benzene derivatives	Red cell rabbit, acceleration of 100% hemolysis by saponin	32, 125

[a] See *Footnote a*, Table I. [b] This equation varies slightly from that previously reported (34) due to minor refinements in the values of log P (6).

Most of the equations in Tables I and II are based on homologous series. This is not simply a chance occurrence. When elements other than CH_2 units are incorporated into a parent molecule, important electronic and possibly steric effects are brought into the structure–activity relationship. These must be accounted for by the addition of other terms to Eq. 6.

One main reason that the strong and often quantitatively definable dependence of drug activity on lipophilic character has been so slow in coming into focus has been the shortage of partition coefficients from a suitable reference system. This is still a handicap. Values are not available for all of the data used for the correlations of Tables I and II. Unknown values have been calculated from additivity principles (6).

From the values in the section on data, the equations in Tables I and II were derived by the standard nonweighted least-squares method (41). In addition to fitting the data to Eq. 6, each set was fit to the third-order equation in which a term in $(\log P)^3$ was added to Eq. 6. Out of 233 cases tested, the cubic term yielded an improved correlation (significance at >0.95 in F test) in 28 examples. Twelve of these examples were with equations in Table I. Examination of the plots of the cubic equations did not uncover any general pattern of correlation. The results do not appear to warrant further consideration at present.

RESULTS

The resulting equations selected for this study are listed in Tables I and II. In these tables, a represents the coefficient of the parabolic $(\log P)^2$ term, b is the coefficient of the linear $(\log P)$ term, and c is the regression constant generated by the least-squares analysis. The 95% confidence interval for each of these values is also given. The calculated ideal value of log P, log P_0, is also listed along with its 95% confidence limits.

For convenience in analysis, the equations in Tables I and II have been factored into four sets based on the range of their log P_0 values, namely, equations (Table I, Part A and Table II, Part A) with log P_0 less than 1.5, those (Table I, Part B and Table II, Part B) with log P_0 between 1.5 and 3.0, those (Table I, Part C and Table II, Part C) with log P_0 varying between 3.0 and 5.0, and those (Table I, Part D and Table II, Part D) with log P_0 greater than 5.0. Within each set the equations have been ordered by increasing values of the coefficient (b) of the linear (log P) term. Most of the equations in Table I were derived from the data listed in Table III. *Reference 1* in Table I refers to the location in Table III of the corresponding data or to the appropriate literature reference if the equation was previously reported in the literature. *Reference 2* indicates the original literature source of the biological activity data used in the equation.

A summary of the distribution and ranges of the values of log P_0, b, a, c, and log P for the 100 equations in Table I is given in Table IV. From these results, it is interesting to note that while the ranges of the coefficients (b) of the linear term within each group (Table I, Part A–Table I, Part D) vary from group to group, the range of the coefficients (a) of the parabolic term within

Table III—Data for Table I

R	log *P*	III-1 $1/K_i'$ Obs.	III-2 $1/K_i$ Obs.	III-3 p*C* Obs.	III-4 p*C* Obs.
C_2H_5	−3.15	3.37	1.44	—	—
C_3H_7	−2.65	4.67	2.70	—	—
C_4H_9	−2.15	6.02	4.14	—	—
C_5H_{11}	−1.65	7.37	5.46	—	—
C_6H_{13}	−1.15	8.10	6.17	—	—
C_7H_{15}	−0.65	8.17	—	—	—
C_8H_{17}	−0.15	8.01	—	—	—
C_9H_{19}	0.35	7.95	6.02	4.43	2.95
$C_{12}H_{25}$	1.85[a]	—	—	5.52	4.52
$C_{14}H_{29}$	2.85	—	—	5.87	4.57
$C_{16}H_{33}$	3.85	—	—	5.44	4.32
$C_{18}H_{37}$	4.85	—	—	4.66	3.66

R	log *P*	III-5 p*C* Obs.	III-6 p*C* Obs.
C_3H_7	−3.20	3.04	—
C_4H_9	−2.70	3.01	—
C_5H_{11}	−2.20[a]	2.77	3.24
C_6H_{13}	−1.70	4.41	—
C_7H_{15}	−1.20	3.86	3.76
C_8H_{17}	−0.70	4.60	—
C_9H_{19}	−0.20	4.24	4.31
$C_{10}H_{21}$	0.30	4.67	—
$C_{11}H_{23}$	0.80	—	4.51
$C_{12}H_{25}$	1.30	4.64	—
$C_{13}H_{27}$	1.80	—	4.74
$C_{15}H_{31}$	2.80	3.11	4.31
$C_{17}H_{35}$	3.80	2.55	4.36

R	log *P*[b]	III-7 p*C* Obs.	III-8 p*C* Obs.	III-9 p*C* Obs.	III-10 p*C* Obs.	III-11 p*C* Obs.
C_6H_{13}	−2.22	1.30	—	1.30	1.00	1.30
C_8H_{17}	−1.22	2.81	1.60	2.50	2.20	1.90
$C_{10}H_{21}$	−0.22	3.71	3.71	3.11	2.81	3.11
$C_{12}H_{25}$	0.78	3.71	4.61	3.41	3.41	3.71
$C_{14}H_{29}$	1.78	2.81	4.31	3.41	3.71	4.61
$C_{16}H_{33}$	2.78	—	3.11	3.11	3.41	4.61
$C_{20}H_{41}$	4.78	—	—	2.81	—	4.31

R	log *P*	III-12 RBR Obs.
Methyl	−4.38	0.04
Ethyl	−3.88	0.23
Propyl	−3.38	0.65
Isopropyl	−3.58	0.08
Butyl	−2.88	1.03
Amyl	−2.38	1.50
Hexyl	−1.88	1.90
Heptyl	−1.38	2.38
Octyl	−0.88[a]	2.70
Decyl	0.12	2.79
Dodecyl	1.12	2.85

R	log *P*	III-13 $1/K_{ER,I}$ Obs.
H	−1.46[a]	0.99
CH_3	−1.21	2.30
C_2H_5	−0.71	3.30
C_3H_7	−0.21[a]	4.19
C_4H_9	0.29	4.60
C_6H_{11}	0.79	4.96

R	log P^c	III-14 p*C* Obs.
Methyl	−0.43	3.80
Ethyl	0.07	4.60
Propyl	0.57	4.90
Butyl	1.07	5.30
Hexyl	2.07	5.10
Heptyl	2.57	4.90

R	log *P*	III-15 p*C* Obs.	III-16 p*C* Obs.
$C_{11}H_{23}$	0.65	5.15	5.30
$C_{12}H_{25}$	1.15[a]	5.22	5.40
$C_{13}H_{27}$	1.65	5.30	5.60
$C_{14}H_{29}$	2.15	5.30	5.58
$C_{16}H_{33}$	3.15	5.18	5.40
$C_{18}H_{37}$	4.15	4.74	4.64

n	log *P*	III-17 p*C* Obs.	III-18 p*C* Obs.
4	−3.34	3.42	—
5	−2.84	3.73	—
6	−2.34	4.03	—
7	−1.84	4.54	2.46
8	−1.34	5.72	3.00
9	−0.84	6.35	3.92
10	−0.34[a]	6.53	4.35
11	0.16	6.35	4.74
12	0.66	6.01	5.25
18	3.66	6.50	4.85

R	log *P*	III-19 p*C* Obs.	III-20 p*C* Obs.	III-21 p*C* Obs.	III-22 p*C* Obs.	III-23 p*C* Obs.	III-24 p*C* Obs.	III-25 p*C* Obs.	III-26 p*C* Obs.	III-27 p*C* Obs.	III-28 p*C* Obs.	III-29 p*C* Obs.
C_8H_{17}	−1.08	—	3.52	—	—	3.69	3.00	1.68	2.69	1.52	—	1.76
C_9H_{19}	−0.58	2.54	3.72	2.54	2.54	4.02	3.02	2.08	3.02	—	2.54	—
$C_{10}H_{21}$	−0.08[a]	2.57	3.74	2.74	2.74	4.74	3.57	2.41	3.57	3.45	3.04	2.95
$C_{11}H_{23}$	0.42	3.06	4.06	3.06	3.06	5.06	4.06	2.92	4.06	—	3.59	—
$C_{12}H_{25}$	0.92	3.48	4.61	3.61	3.61	5.61	4.61	3.45	4.61	4.34	4.09	3.82
$C_{13}H_{27}$	1.42	3.50	4.80	3.80	3.80	5.80	5.10	3.85	5.10	—	4.63	—
$C_{14}H_{29}$	1.92	3.52	4.82	3.65	3.65	5.82	5.12	3.96	5.12	4.63	4.82	4.40
$C_{15}H_{31}$	2.42	3.14	4.84	3.84	3.84	5.84	5.14	3.74	5.14	—	5.14	—
$C_{16}H_{33}$	2.92	—	4.68	3.68	3.68	5.56	5.16	3.30	5.16	4.88	4.56	4.79
$C_{17}H_{35}$	3.42	—	—	3.57	—	5.18	4.70	3.06	4.70	—	4.16	—
$C_{18}H_{37}$	3.92	2.89	—	—	2.71	5.19	4.71	2.63	4.71	4.60	3.59	4.52
$C_{19}H_{39}$	4.42	2.91	4.21	2.91	2.60	4.91	4.73	2.52	4.73	—	3.61	—

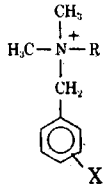
R	log P^d	III-30 p*C* Obs.	III-31 p*C* Obs.	III-32 p*C* Obs.	III-33 p*C* Obs.	III-34 p*C* Obs.	III-35 p*C* Obs.	III-36 p*C* Obs.	III-37 p*C* Obs.	III-38 p*C* Obs.	III-39 p*C* Obs.	III-40 p*C* Obs.
C_4H_9	−1.68	1.30	—	—	—	—	—	—	—	—	—	—
C_6H_{13}	−0.68	1.90	1.60	2.50	2.20	1.90	2.81	2.50	2.20	1.90	1.90	1.60
C_8H_{17}	0.32	2.50	2.20	3.11	3.41	2.50	3.71	3.41	3.11	2.81	2.81	2.50

Table III—(*Continued*)

R	log P^d	III-30 pC Obs.	III-31 pC Obs.	III-32 pC Obs.	III-33 pC Obs.	III-34 pC Obs.	III-35 pC Obs.	III-36 pC Obs.	III-37 pC Obs.	III-38 pC Obs.	III-39 pC Obs.	III-40 pC Obs.
					RCHBrCOO$^-$							
$C_{10}H_{21}$	1.32	3.41	3.11	4.01	3.71	3.41	4.31	3.71	3.71	3.41	3.11	2.81
$C_{12}H_{25}$	2.32	3.11	2.81	4.01	4.01	3.71	5.21	4.61	4.61	4.61	4.01	3.71
$C_{14}H_{29}$	3.32	2.81	2.50	3.71	3.11	2.81	5.52	5.21	4.91	4.61	4.91	4.61
$C_{16}H_{33}$	4.32	1.90	1.90	2.51	2.20	1.90	5.52	5.21	5.21	4.91	4.91	4.61
$C_{18}H_{37}$	5.32	—	—	—	—	—	3.11	2.81	2.81	2.81	2.50	2.20
$C_{20}H_{41}$	6.32	—	—	—	—	—	3.11	2.20	2.81	2.81	2.20	1.90

R	log *P*	III-41 pC Obs.
	$CH_3CH(OR)_2$	
Methyl	−0.15	1.70
Ethyl	0.85[a]	2.12
Propyl	1.85	2.30
Isopropyl	1.45	2.30
Butyl	2.85	2.00

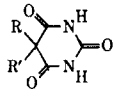
Alcohol	log *P*	III-42 RBR Obs.	III-43 RBR Obs.	III-44 pC Obs.
Methanol	−0.66[a]	0.00	—	2.57
Ethanol	−0.16	—	—	3.62
Propanol	0.34[a]	0.70	—	4.27
Isopropanol	0.14	—	1.01	—
Butanol	0.88[a]	1.25	—	5.24
sec-Butanol	0.61[a]	—	1.16	—
Pentanol	1.40[a]	1.36	—	5.66
Hexanol	2.03[a]	1.32	—	6.24
Heptanol	2.53	1.22	—	6.55
Octanol	3.03	1.12	—	—
Decanol	4.03	—	—	6.38
Dipropylcarbinol	2.18	—	1.83	—
Diisopropylcarbinol	1.75	—	1.82	—
Ethylbutylcarbinol	2.20	—	1.79	—
Methylamylcarbinol	2.33	—	1.74	—
2-Hexanol	1.83	—	1.74	—
2-Pentanol	1.11	—	1.65	—
3-Pentanol	1.11	—	1.59	—
Methylhexylcarbinol	2.83	—	1.19	—



X	R	log *P*	III-45 pC Obs.	III-46 pC Obs.	III-47 pC Obs.
H	$C_{10}H_{21}$	−0.08[a]	2.70	2.79	3.11
H	$C_{12}H_{25}$	0.92	3.79	3.74	4.04
H	$C_{14}H_{29}$	1.92	4.07	4.17	4.52
H	$C_{16}H_{33}$	2.92	3.92	3.92	4.54
H	$C_{18}H_{37}$	3.92	3.23	3.34	4.62
2-Cl	C_8H_{17}	−0.32	1.92	2.02	—
2-Cl	$C_{10}H_{21}$	0.68	3.11	3.41	3.47
2-Cl	$C_{12}H_{25}$	1.68	3.85	4.14	—
2-Cl	$C_{14}H_{29}$	2.68	4.18	4.14	—
2-Cl	$C_{16}H_{33}$	3.68	3.65	3.74	4.66
2-Cl	$C_{18}H_{37}$	4.68	3.46	3.43	4.74
4-Cl	C_8H_{17}	−0.38	2.88	2.60	—
4-Cl	$C_{10}H_{21}$	0.62	3.53	3.60	3.70
4-Cl	$C_{12}H_{25}$	1.62	4.23	4.04	—
4-Cl	$C_{14}H_{29}$	2.62	—	4.34	—
4-Cl	$C_{16}H_{33}$	3.62	3.54	3.85	—
4-Cl	$C_{18}H_{37}$	4.62	3.53	3.17	—
4-NO_2	C_8H_{17}	−0.84	1.92	2.11	—
4-NO_2	$C_{10}H_{21}$	0.16	3.11	3.11	—
4-NO_2	$C_{12}H_{25}$	1.16	3.65	4.20	—
4-NO_2	$C_{14}H_{29}$	2.16	4.25	4.23	—
4-NO_2	$C_{16}H_{33}$	3.16	3.82	4.00	—
4-NO_2	$C_{18}H_{37}$	4.16	3.54	3.46	—
2-Cl, 4-Cl	C_8H_{17}	0.38	2.50	2.63	—
2-Cl, 4-Cl	$C_{10}H_{21}$	1.38	3.58	3.65	3.85
2-Cl, 4-Cl	$C_{12}H_{25}$	2.38	4.14	4.25	4.43
2-Cl, 4-Cl	$C_{14}H_{29}$	3.38	4.13	4.28	4.39
2-Cl, 4-Cl	$C_{16}H_{33}$	4.38	3.46	3.41	—
2-Cl, 4-Cl	$C_{18}H_{37}$	5.38	3.49	3.30	—
2-OH, 5-NO_2	$C_{10}H_{21}$	−0.51	2.79	—	—
2-OH, 5-NO_2	$C_{12}H_{25}$	0.49	2.58	2.70	—
3-Cl, 4-Cl	C_8H_{17}	0.38	2.92	2.92	—
3-Cl, 4-Cl	$C_{10}H_{21}$	1.38	3.85	3.79	—
3-Cl, 4-Cl	$C_{12}H_{25}$	2.38	4.25	4.36	—
3-Cl, 4-Cl	$C_{14}H_{29}$	3.38	4.11	4.04	—
3-Cl, 4-Cl	$C_{16}H_{33}$	4.38	3.39	3.39	—
3-Cl, 4-Cl	$C_{18}H_{37}$	5.38	3.08	3.11	—
3-OCH_3, 4-OCH_3	$C_{12}H_{25}$	1.00	3.67	3.71	—
3-OCH_3, 4-OCH_3	$C_{14}H_{29}$	2.00	4.20	4.11	—
3-OCH_3, 4-OCH_3	$C_{16}H_{33}$	3.00	3.95	3.41	—
3-OCH_3, 4-OCH_3	$C_{18}H_{37}$	4.00	3.47	—	—
3,4-(OCH_2O)	C_8H_{17}	−1.13	2.04	2.04	—
3,4-(OCH_2O)	$C_{10}H_{21}$	−0.13	2.92	3.08	—
3,4-(OCH_2O)	$C_{12}H_{25}$	0.87	3.85	4.00	—
3,4-(OCH_2O)	$C_{14}H_{29}$	1.87	4.17	4.23	—
3,4-(OCH_2O)	$C_{16}H_{33}$	2.87	4.00	4.20	—
3,4-(OCH_2O)	$C_{18}H_{37}$	3.87	3.36	3.23	—

(*continued*)

Table III—(*Continued*)



R	R′	log *P*	III-48 pC Obs.	III-49 pC Obs.	III-50 pC Obs.	III-51 pC Obs.	III-52 pC Obs.
Methyl	$CH_3CHC(CH_3)$	0.65	—	—	2.64	—	—
Methyl	$CH_2C(CH_3)$	0.15	—	—	2.12	—	—
Ethyl	Ethyl	0.65[a]	2.87	3.09	—	2.91	1.32
Ethyl	Isopropyl	0.95[a]	3.00	3.30	—	3.34	1.89
Ethyl	Butyl	1.89[a]	3.33	3.72	—	3.53	2.80
Ethyl	Isobutyl	1.69[a]	3.25	3.63	—	—	—
Ethyl	*sec*-Butyl	1.69[a]	3.03	3.63	—	—	—
Ethyl	*sec*-Pentyl	2.07	—	—	—	—	3.07
Ethyl	Isoamyl	2.07[a]	3.12	3.75	—	3.59	3.12
Ethyl	Hexyl	2.77	—	—	—	—	3.40
Ethyl	Allyl	0.85	—	—	—	3.28	—
Ethyl	$CH_2C(CH_3)$	0.65	—	—	2.91	—	—
Ethyl	$CH_3CHC(CH_3)$	1.15	—	—	3.15	—	—
Ethyl	Phenyl	1.42[a]	3.19	3.46	—	—	2.36
Propyl	Propyl	1.65	2.98	3.55	—	—	—
Propyl	Isopropyl	1.45	3.15	3.63	—	—	—
Propyl	Isoamyl	2.57	3.04	3.48	—	—	—
Propyl	$CH_3CHC(CH_3)$	1.65	—	—	3.29	—	—
Propyl	$CH_2C(CH_3)$	1.15	—	—	3.04	—	—
Propyl	Allyl	1.35	—	—	—	3.47	—
Propyl	Benzyl	3.08	2.76	—	—	—	—
Isopropyl	Butyl	2.07	—	—	—	3.49	—
Isopropyl	Allyl	1.15	—	—	—	3.60	—
Isopropyl	Benzyl	2.88	2.87	—	—	—	—
Butyl	Butyl	2.89	—	—	—	3.08	—
Butyl	Allyl	1.85	—	—	—	3.47	—
Butyl	$CH_3CHC(CH_3)$	2.15	—	—	3.36	—	—
Butyl	$CH_2C(CH_3)$	1.65	—	—	3.33	—	—
Isobutyl	Allyl	1.65	—	—	—	3.63	2.80
Isobutyl	$CH_2C(CH_3)$	1.45	—	—	3.27	—	—
sec-Butyl	Allyl	1.65	—	—	—	3.78	—
Amyl	$CH_2C(CH_3)$	2.15	—	—	3.32	—	—
Isoamyl	Allyl	2.15	—	—	—	3.45	—
Isoamyl	$CH_2C(CH_3)$	1.95	—	—	3.26	—	—
Allyl	*sec*-Pentyl	2.15[a]	—	—	—	—	3.19
Allyl	Cyclopentenyl	1.69	—	—	—	—	2.90
Allyl	Allyl	1.05	—	—	—	3.54	—
Allyl	$CH_3CHC(CH_3)$	1.35	—	—	3.39	—	—

$R_3SnOCOCH_3$			
R	log *P*	III-53 pC Obs.	III-54 pC Obs.
Methyl	−1.32	3.05	3.05
Ethyl	0.18	4.72	5.12
Propyl	1.68[a]	5.49	5.49
Butyl	3.18	5.84	5.84
Hexyl	6.18	4.34	3.64
Phenyl	3.57	5.61	—

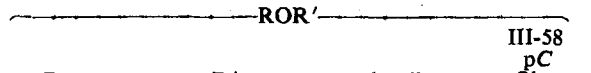
$R\overset{+}{N}(CH_3)_3$			
R	log *P*	III-55 pC Obs.	III-56 pC Obs.
C_6H_{13}	−2.07	0.53	—
C_8H_{17}	−1.07[a]	1.28	0.88
$C_{12}H_{25}$	0.84[a]	3.44	3.09
$C_{14}H_{29}$	1.84	4.08	4.11
$C_{16}H_{33}$	2.84	4.16	4.46
$C_{17}H_{35}$	3.54	3.97	4.25
$C_{17}H_{37}$	3.84	3.50	4.40

4-R-Lincomycin		
R	log *P*	III-57 RBR Obs.
H	−0.95	−1.60
Ethyl	0.05	−0.52
Propyl	0.55[a]	0.00
Butyl	1.05	0.32
Amyl	1.55	0.53
Hexyl	2.05	0.56

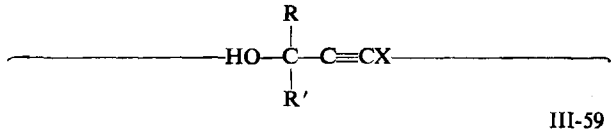
4-R-Lincomycin		
R	log *P*	III-57 RBR Obs.
Heptyl	2.55	0.18
Octyl	3.05	0.00

ROR′			
R	R′	log *P*	III-58 pC Obs.
Methyl	Methyl	−0.23	1.43
Methyl	Ethyl	0.27	1.74
Methyl	Propyl	0.77	2.45
Methyl	Isopropyl	0.57	2.26
Methyl	Cyclopropyl	0.48	2.75
Methyl	Butyl	1.27	2.70
Methyl	Isobutyl	1.08	2.79
Methyl	*sec*-Butyl	1.04	2.79
Methyl	*tert*-Butyl	0.80	2.79
Methyl	Amyl	2.03	2.88
Ethyl	Ethyl	0.77[a]	2.22
Ethyl	Propyl	1.27	2.60
Ethyl	Isopropyl	1.07	2.60
Ethyl	Cyclopropyl	0.98	3.00
Ethyl	Butyl	2.03[a]	2.82
Ethyl	Isobutyl	1.83	2.82
Ethyl	*sec*-Butyl	1.80	2.85
Ethyl	*tert*-Butyl	1.56	2.92
Ethyl	Isoamyl	2.35	3.00
Ethyl	*tert*-Amyl	2.08	3.15
Ethyl	Vinyl	0.47	2.34
Propyl	Propyl	2.03[a]	2.79
Propyl	Isopropyl	1.83	2.82

Table III—(*Continued*)

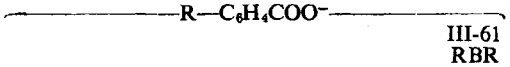


R	R′	log *P*	III-58 p*C* Obs.
Isopropyl	Isopropyl	1.63	2.82
Vinyl	Vinyl	0.17	2.33



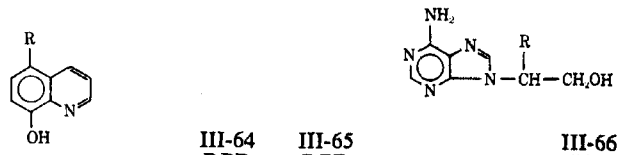
R	R′	X	log *P*	III-59 p*C* Obs.
Methyl	Ethyl	H	1.18	2.59
Methyl	Ethyl	Cl	1.51	2.94
Methyl	Vinyl	H	0.88	2.41
Methyl	ClCH=CH	H	1.50	2.94
Ethyl	Vinyl	H	1.38	2.79
Ethyl	ClCH=CH	H	2.00	3.20
Propyl	ClCH=CH	H	2.50	2.90
Isopropyl	Vinyl	H	1.68	2.92
Isopropyl	ClCH=CH	H	2.30	3.17

Compound	log *P*	III-60 p*C* Obs.
4-OCH_3-Aniline	0.78	3.39
4-OC_2H_5-Aniline	1.28	4.44
4-OC_4H_9-Aniline	2.28	5.42
4-OC_5H_{11}-Aniline	2.78	5.45
4-OC_6H_{13}-Aniline	3.28	5.80
4-OC_8H_{17}-Aniline	4.28	3.44
2-OCH_3-3-NH_2-Pyridine	0.09	2.59
2-OC_2H_5-3-NH_2-Pyridine	0.59	3.54
2-OC_3H_7-3-NH_2-Pyridine	1.09	4.79
2-*iso*-OC_4H_9-3-NH_2-Pyridine	1.39	4.52
2-OC_5H_{11}-3-NH_2-Pyridine	2.09	5.76
2-(3-OC_5H_{11})-3-NH_2-Pyridine	1.89	5.46
2-OC_7H_{15}-3-NH_2-Pyridine	3.09	4.62
2-OC_8H_{17}-3-NH_2-Pyridine	3.59	3.75
2-$OC_{10}H_{21}$-3-NH_2-Pyridine	4.59	3.19
4-OC_4H_9-3-NH_2-Pyridine	1.59	5.73
4-OC_6H_{13}-3-NH_2-Pyridine	2.59	5.80
2-OC_4H_9-5-NH_2-Pyrimidine	1.26	5.13
2-OC_6H_{13}-5-NH_2-Pyrimidine	2.26	5.49
4-OC_4H_9-1-Naphthylamine	3.63	4.03

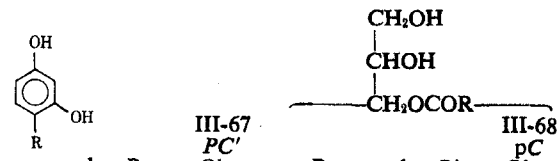


R	log *P*	III-61 RBR Obs.
H	1.87[a]	1.92
4-Cl	2.65[a]	1.93
4-F	2.06[a]	1.90
4-CH_3	2.29[a]	1.79
4-I	3.01[a]	1.76
4-OCH_3	1.95[a]	1.63
4-CN	1.56[a]	1.54
4-$NHCOCH_3$	1.08	0.74

R	log *P*	III-62 p*C* Obs.	III-63 p*C* Obs.
C_8H_{17}	−0.95[a]	1.14	0.84
$C_{12}H_{25}$	1.05	3.15	3.73
$C_{14}H_{29}$	2.05	4.12	4.33
$C_{16}H_{33}$	3.05	4.21	4.43
$C_{18}H_{37}$	4.05	3.98	4.20
3-$OC_{12}H_{25}$-3-OH-Propyl	1.66	4.00	3.76

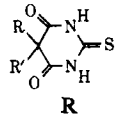


R	log *P*	III-64 RBR Obs.	III-65 RBR Obs.	R	log *P*	III-66 $[I/S]_{0.5}$ Obs.
H	2.02[a]	0.14	−0.12	CH_3	−0.37	−0.08
CH_3	2.52	0.45	—	C_2H_5	0.14[a]	0.31
C_2H_5	3.02	0.49	—	C_3H_7	0.66[a]	1.15
C_3H_7	3.52	0.61	0.62	C_4H_9	1.16[a]	1.48
C_4H_9	4.02	1.01	0.99	C_5H_{11}	1.67	1.82
C_5H_{11}	4.52	1.05	1.07	C_6H_{13}	2.18	2.21
C_6H_{13}	5.02	1.03	1.07	C_7H_{15}	2.69	2.33
C_7H_{15}	5.52	0.98	1.06	C_8H_{17}	3.20	2.41
C_8H_{17}	6.02	0.81	0.90	C_9H_{19}	3.71	2.52
C_9H_{19}	6.52	0.63	0.83			
$C_{10}H_{21}$	7.02	0.27	0.48			

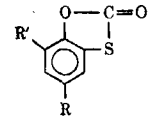


R	log *P*	III-67 *PC′* Obs.	R	log *P′*	III-68 p*C* Obs.
H	0.80[a]	−0.33	C_8H_{17}	1.83	3.00
C_4H_9	2.80	1.59	C_9H_{19}	2.33	3.48
iso-C_4H_9	2.60	1.42	$C_{10}H_{21}$	2.83	3.84
C_5H_{11}	3.30	1.80	$C_{11}H_{23}$	3.33	4.18
iso-C_5H_{11}	3.10	1.66	$C_{12}H_{25}$	3.83	4.34
C_6H_{13}	3.80	2.02	$C_{14}H_{29}$	4.83	4.25
iso-C_6H_{13}	3.60	1.75	$C_{16}H_{33}$	5.83	3.45
C_7H_{15}	4.30	1.82	$C_{18}H_{37}$	6.83	2.70

R	R′	log *P*	III-69 p*C* Obs.
Cyclohexylidine	Ethyl	3.10	2.68
Isopropylidine	Propyl	2.50	2.46
1-Methylhexylidine	Propyl	4.50	3.38
1-Methylheptylidine	Propyl	5.00	3.06
1-Phenylethylidine	Propyl	4.13	3.18
1,2-Methylpropylidine	Propyl	3.30	3.00
1,3-Methylbutylidine	Propyl	3.80	3.28
1-Methyl-4-pentenylidine	Propyl	3.70	3.18
Isopropylidine	Butyl	3.00	2.71



R	R′	log *P*	III-70 p*C* Obs.
Ethyl	Ethyl	1.70	3.35
Ethyl	Isoamyl	3.00[a]	4.12
Ethyl	1-Methylbutyl	3.00	4.25
Ethyl	Hexyl	3.70	3.97
Isopropyl	Allyl	2.20	3.92
sec-Butyl	Allyl	2.70	4.12



R	R′	log *P*	III-71 p*C* Obs.
CH_3	H	2.75	4.04
OCH_3	H	2.21	3.77

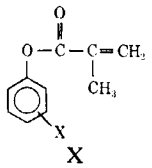
(*continued*)

Table III—(*Continued*)

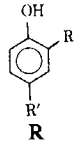
R	R′	log *P*	III-71 p*C* Obs.
Cl	H	3.01	3.78
Br	H	3.19	3.88
tert-C_4H_9	H	4.43	3.23
OH	H	1.64	2.84
COC_2H_5	H	2.20	3.22
CH_3	CH_3	3.25[a]	3.77
CH_3	Br	3.50	4.20

RSCN

R	log *P*[a]	III-72 p*C* Obs.
C_6H_{13}	3.03	2.17
C_8H_{17}	4.03	2.60
$C_{10}H_{21}$	5.03	2.75
$C_{12}H_{25}$	6.03	2.82
$C_{14}H_{29}$	7.03	2.84
$C_{16}H_{33}$	8.03	2.66



X	log *P*	III-73 p*C* Obs.
H	1.99	2.89
2-Cl	2.75	3.08
4-Cl	2.69	3.25
2-Cl, 4-Cl	3.45	3.49
2-Cl, 4-Cl, 5-Cl	4.21	3.84
2-Cl, 4-Cl, 6-Cl	4.21	3.76
2-Cl, 4-Cl, 5-Cl, 6-Cl	4.97	3.97
Pentabromo	6.74	3.64



R	R′	log *P*	III-74 p*C*′ Obs.
H	Cl	2.39[a]	0.81
Methyl	Cl	2.89	1.34
Ethyl	Cl	3.39	1.73
Propyl	Cl	3.89	2.26
Butyl	Cl	4.39	2.52
Amyl	Cl	4.89	2.63
sec-Amyl	Cl	4.69	2.23
Cyclohexyl	Cl	4.90	2.25
Heptyl	Cl	5.89	2.51
Octyl	Cl	6.39	1.83
Cl	H	2.15[a]	0.50
Cl	Methyl	2.65	0.91
Cl	Ethyl	3.15	1.35
Cl	Propyl	3.65	1.86
Cl	Butyl	4.15	2.20
Cl	Amyl	4.65	2.23
Cl	*tert*-Amyl	4.33	2.00

[a] Experimentally determined value of log *P*. All other values of log *P* were calculated according to additivity principles outlined in *References 1* and *6*. [b] Based on measured value of −0.62 for α-hydroxypropionic acid. [c] Based on measured value of 0.37 for iproniazid. [d] Based on measured value of −3.18 for α-bromopropionic acid. [e] Based on measured value of −0.16 for *N,N*-dimethyldecylammonium bromide. [f] Based on measured value of −0.17 for monobutyrin. [g] Based on measured value of 2.03 for butylthiocyanate.

each grouping is essentially constant (−0.50 to −0.10) for all groups. In addition, there is significant variation in the ranges of the constants of regression (*c*) within each group when compared between groups. Also of interest is the observation that the ranges of the individual log *P* values represented in the data used to derive the equations vary noticeably between groups.

Of the eight equations in Table I, Part A, five describe enzyme systems. Of the 58 equations in Table I, Part B, 36 are derived from data involving bacterial systems. In addition, 14 of the 27 equations in Table I, Part C, were derived from bacterial systems while nine describe hemolysis data. From the entire series of 100 equations, it appears that the coefficient of the linear term in the equation describing a bacterial system most often lies between 0.50 and 1.50. In addition, most of the equations involving hemolysis data contain coefficients of the linear term between 0.75 and 1.75.

Of the compounds used to derive these equations, the largest single grouping consists of those that are ionic. Of the eight equations in Table I, Part A, six were derived from ionic compounds. Also, 35 of the 58 equations in Table I, Part B, consist of ionic compounds, while 17 of the 27 equations in Table I, Part C, were derived from data composed of ionic compounds. From these data, it appears that most of the equations derived from these compounds contain coefficients of the linear term between 0.5 and 1.5.

The second best set of 67 equations (listed in Table II) was selected according to less stringent statistical criteria and might, therefore, be considered a slightly less reliable basis set than those given in Table I. Specifically, requirements for inclusion in this set included an *F* ratio showing the parabolic equation to be more significant than the corresponding linear equation at the 95–99% level and an *r* value greater than 0.80. In addition, the plot of log *P* values *versus* biological activity for each equation appeared unquestionably parabolic.

A summary of the results of the equations listed in Table II is given in Table IV. Of the 67 equations in Table II, the distribution among the four subsets was markedly different from that for the 100 equations in Table I. In this set the equations are essentially equally distributed among the four groups. The range of log P_0 varies in this set from −1.37 to 12.03, a range double that for the data in Table I.

However, the ranges of the coefficients of the linear term for the data in Table II are similar to those for Table I. Also very similar to the data in Table I are the ranges of the values of the coefficients of the parabolic terms in Table II. On the other hand, the ranges of the constants of regression for the equations in Table II vary drastically between groups, very much like the data in Table I.

Again similar to the data in Table I, the most common biological system type appearing in Table II is bacterial in nature. Of the 67 equations, 37 (55%) describe bacterial systems. Of the 16 equations in Table II, Part A, 10 equations (63%) involve bacterial systems, as do four of the 17 equations (23%) in Table II, Part B, 10 of the 15 equations (67%) in Table II, Part C, and 13 of the 19 equations (68%) in Table II, Part D. In addition, 40% of the equations contained in Table II were derived from ionic compounds. Of the 16 equations in Table II, Part A, 12 involve ionic compounds while eight of the 17 equations in Table II, Part B, six of the 15 equations in Table II, Part C, and one of the

Table IV—Summary of Comparison of Results

Values Compared	Equations in Table I	Equations in Table II
A. Distribution of log P_0 values		
<1.5	8%	25%
1.5–3.0	58%	24%
3.0–5.0	27%	22%
>5.0	7%	29%
Range	−0.40–6.26	−1.37–12.03
B. Range of values of b		
Group A	−0.53–1.23	−0.34–1.06
Group B	0.33–3.72	0.13–3.68
Group C	0.71–2.95	0.45–8.07
Group D	0.80–2.45	0.69–2.32
Average	0.33–2.59	0.23–3.78
C. Range of values of a		
Group A	−0.77–−0.10	−0.55–−0.05
Group B	−0.69–−0.09	−0.72–−0.02
Group C	−0.48–−0.09	−0.88–−0.05
Group D	−0.24–−0.06	−0.21–−0.04
Average	−0.54–−0.08	−0.59–−0.04
D. Range of values of c		
Group A	2.77–8.14	0.10–7.06
Group B	−1.78–6.33	−1.57–5.58
Group C	−1.84–3.84	−13.32–4.16
Group D	−3.47–1.37	−5.61–2.51
Average	−1.08–4.92	−5.10–4.82
E. Range of values of log P		
Group A	−4.38–3.80	−4.70–5.03
Group B	−3.34–6.32	−4.34–4.40
Group C	−2.22–6.32	−3.70–5.63
Group D	1.53–9.53	−3.70–10.07
Average	−2.10–6.49	−4.11–6.28

19 equations in Table II, Part D, also describe data from ionic compounds.

DISCUSSION

By what ways can the parabolic relationship between log $1/C$ and log P be explained? There are, of course, a variety of possible explanations, any one or a combination of which might be involved in a given problem. If the partition coefficient is defined as P = concentration in fatty phase/concentration in aqueous phase, one can reason that if P for a drug approaches zero, the drug will be so insoluble in fatty phases that it will not cross a lipid membrane and will remain localized in the first aqueous phase it contacts. Conversely, as P approaches infinity, the drug will be so insoluble in water that it will remain localized in fatty tissue. Somewhere between the value of zero and infinity there will be an optimum P value (termed P_0) such that those drugs possessing this value will be least inhibited in their movement through the aqueous and lipophilic phases of living tissue. Intuitively, it was felt that a parabola would approximate the relationship between the concentration of drug administered and the concentration at the active site (after a certain fixed time interval) under nonequilibrium conditions (39, 126). By definition, it is impossible to attain true equilibrium with a living system. Under certain conditions, with cells or isolated tissue, it may be possible to reach a pseudoequilibrium.

The finding of active sites by drugs can be regarded as a random walk process in which drug molecules must cross many membranes. This partitioning process is much like that of the drug's partitioning on and off of lipophilic macromolecules (Eqs. 2–4). An astronomical number of such events must occur with each drug molecule before it ultimately hits its final target. The progress a drug molecule makes in running this gantlet of aqueous and lipophilic phases is heavily dependent on its hydrophilic–lipophilic balance.

After the drug reaches the active site, it must partition onto it. This may be a much more specific kind of partitioning in which the steric and electronic characteristics of the drug may play rate-limiting roles. The rate of response can be formulated as:

$$\frac{d\ \text{response}}{dt} = Ak_XC \qquad \text{(Eq. 174)}$$

where A is the probability a drug molecule will reach the active site in the time Δt allotted for the test, C is the molar concentration of applied drug, and k_X is a rate or equilibrium constant for the combination of drug and receptor. In the first attempt to treat the problem mathematically (127), the assumption was made that A would be normally distributed with respect to log P:

$$A = ae^{-(\log P - \log P_0)^2/b} \qquad \text{(Eq. 175)}$$

For a fixed time interval of testing, d response/dt is constant so that Eq. 174 can be written as:

$$k_1 = ae^{-(\log P - \log P_0)^2/b} \cdot k_X \cdot C \qquad \text{(Eq. 176)}$$

Taking the logarithm of Eq. 176, collecting constants (bearing in mind that P_0 is a constant), and rearranging give:

$$\log 1/C = -k_2(\log P)^2 + k_3 \log P + k_4k_X + k_5 \qquad \text{(Eq. 177)}$$

In general, one might expect to correlate k_X *via* the linear combination of steric, electronic, and hydrophobic terms as in Eq. 178:

$$k_X = a \log P + b\sigma + cE_s + d \qquad \text{(Eq. 178)}$$

However, for the present review, data were selected to avoid cases where significant electronic and steric effects were involved so that it is assumed that log k_X is linearly related to log P. Substituting this into Eq. 177 yields:

$$\log 1/C = -k_2(\log P)^2 + k_3 \log P + k_6 \log P + k_7 \qquad \text{(Eq. 179)}$$

or:

$$\log 1/C = -k_2(\log P)^2 + k_8 \log P + k_7 \qquad \text{(Eq. 180)}$$

Four important parameters are associated with Eq. 180: k_2, k_8, k_7, and log P_0. The first three are obtained by fitting experimental data to Eq. 180. Log P_0 is found by setting $(d \log 1/C)/d \log P$ equal to zero and solving for log P. Since k_8 is the sum of k_3 and k_6, its value depends in part on the random walk process and in part on the hydrophobic interaction of the drug and the active site. The value of log P_0 also depends on the resultant sum of these two processes. This can be better visualized (40) by taking the derivative of Eq. 179, setting it equal to zero, and solving for log P:

$$\log P_0 = \frac{k_3}{2k_2} + \frac{k_6}{2k_2} \qquad \text{(Eq. 181)}$$

The first term on the left of Eq. 181 relates the localization rate at the sites of action to log P. Since there is reason to believe that this might be rather constant for certain types of systems (*e.g.*, mammalian), it could be defined as log P_i in the following equation:

$$\log P_0 = \log P_i + \frac{k_6}{2k_2} \qquad \text{(Eq. 182)}$$

The above equations, of course, rest on the Meyer–Overton assumption that partition coefficients between a fatty solvent and water serve to model partitioning between the lipophilic and aqueous phases of biological material; that is, Eq. 1 must hold where P_2 is from a reference system such as octanol-water and P_1 is a kind of average partition coefficient for the heterogeneous phases of biological tissue. Equation 1, first suggested by Collander (128), was shown to have certain but not unlimited generality (129). Not every solvent system serves as a suitable reference system. Recently, Seeman *et al.* (130) measured the partition coefficients for a series of alcohols between red cell ghosts and water. These were correlated (1) with octanol–water values in Eq. 183:

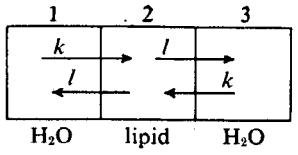
$$\log P_{\text{ghosts}} = 1.00 \log P - 0.88 \qquad \begin{matrix} n & r & s \\ 5 & 0.998 & 0.082 \end{matrix} \qquad \text{(Eq. 183)}$$

The slope of 1 in Eq. 183 indicates a 1:1 correspondence in the two processes. The negative intercept indicates that it is about seven times more difficult for an alcohol molecule to move into the ghost membrane than into octanol. Equation 183 does suggest that octanol–water is a good reference system to model partitioning in and out of membranes, while Eq. 2 and others of its kind (1, 5) show that octanol–water serves to model partitioning between an aqueous phase and proteins.

The many excellent linear correlations between log P values and various equilibrium and rate constants that are heavily dependent on partitioning processes (1, 5) emphasize that membranes and proteins in an aqueous environment are much more fluid than was indicated by the ideas developed up to 1960. The fluid mosaic model (131) of membranes developed by Singer suggests an ever changing, loose association of the lipids in which other large molecules may be rather loosely held. Branton (132) aptly described this model as: "a sea of lipid in which other molecules swim." Many enzymes and proteins must have a similar fluidity; otherwise, the kind of structure–activity correlations obtained using log P or π would not be possible. There are now over 1000 such correlations in the authors' data base alone.

The "parabolic" relationship between log $1/C$ and log P can be rationalized in a number of mechanistic ways. The following nine seem most important.

1. The kinetic model (34) is possibly the general explanation for truly complex systems such as whole animals. To formulate this model, assume a simple fluid membrane as depicted in Scheme I, where k is the rate constant for passage from the aqueous to the lipid phase, and l is the rate constant for the reverse passage. Compartment 1 has a given volume, V_1, and a given concentration of solute, A_1, at zero time. The other compartments have corresponding values. The



Scheme I

surface area between compartments is assumed to be the same for all. It is assumed that in living tissue, one is considering a "stirred" solution. The differential equations governing solute concentrations in the three compartments are:

$$\frac{dA_1}{dt} = \frac{S}{V_1}(lA_2 - kA_1) \qquad \text{(Eq. 184}a\text{)}$$

$$\frac{dA_2}{dt} = \frac{S}{V_2}(kA_1 - 2lA_2 + kA_3) \qquad \text{(Eq. 184}b\text{)}$$

$$\frac{dA_3}{dt} = \frac{S}{V_3}(lA_2 - kA_3) \qquad \text{(Eq. 184}c\text{)}$$

For cells of uniform volume and surface, $S/V_1 = S/V_2 = S/V_3 =$ constant.

In the general model, it was assumed that the solute was bound in the final phase with a rate constant m. The general set of differential equations is then:

$$\frac{dA_1}{dt} = -kA_1 + lA_2 \qquad \text{(Eq. 185}a\text{)}$$

$$\frac{dA_{2i}}{dt} = -2lA_{2i} + k(A_{2i-1} + A_{2i+1}) \qquad \text{(Eq. 185}b\text{)}$$

$$\frac{dA_{2i+1}}{dt} = -2kA_{2i+1} + l(A_{2i} + A_{2i+2}) \qquad \text{(Eq. 185}c\text{)}$$

$$\frac{dA_{n-1}}{dt} = -(l + m)A_{n-1} + kA_{n-2} \qquad n = \text{odd} \qquad \text{(Eq. 185}d\text{)}$$

$$= -(k + m)A_{n-1} + lA_{n-2} \qquad n = \text{even} \qquad \text{(Eq. 185}e\text{)}$$

$$\frac{dA_n}{dt} = mA_{n-1} \qquad \text{(Eq. 185}f\text{)}$$

In these equations, A_i represents the concentration in the ith phase and A_n that in the last phase. Since A_1/A_n does not depend on A_1^0, an arbitrary initial concentration such as 1.0 can be used. For a specific value of n, the partition coefficient ($P = k/l$) can be varied over an interval to obtain a series of solutions to the set of equations by integrating over time t. Values of k and l were chosen so that $k \times l = 1$; that is, it is assumed that there is a reciprocal relation between hydrophobic

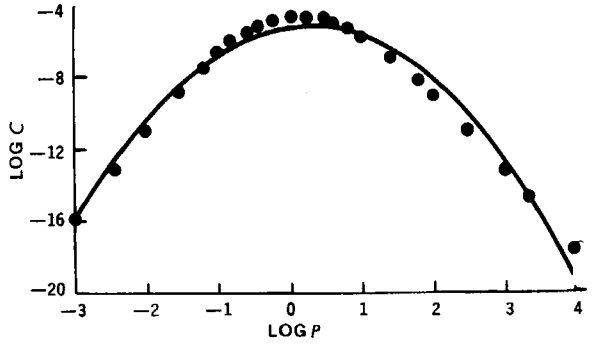


Figure 7—*Concentration in 20th compartment as a function of log* P *when* t = *10 and* m = *1. The curve is a parabola fitted to the calculated points by the method of least squares.*

character and hydrophilic character. The points in Fig. 7 show the concentration in the last compartment as a function of log P for a 20-barrier model when $t = 10$ and $m = 1$. The least-squares line in Fig. 7 results from fitting these points to Eq. 186:

$$\log A_n = a(\log P)^2 + b \log P + c \qquad \text{(Eq. 186)}$$

The fact that the points fit the line quite well justifies the postulate of Eq. 175.

The use of Eq. 180 for structure-activity correlations was also justified by McFarland (133) using a strictly probabilistic approach, which is, in effect, a kinetic justification.

As already considered, the parabolic relationship between log $1/C$ and log P has been rationalized in kinetic terms for systems not at or near equilibrium. The observed biological response is quite time dependent, and the parameters of Eq. 180, including log P_0, are at least in part determined by the time span allotted between the introduction of the drug and the "reading" of the biological response. For practical studies that one hopes to correlate *via* regression analysis, it is most important to achieve a sharp definition of Δt for the biological test.

2. The thermodynamic model (134) considers the case where, under certain conditions (for example, in a closed system of isolated tissue *in vitro*), one may approach rather close to equilibrium between drug in solution and drug on the sites of action. Generally, under such conditions (1) one can expect to find a high log P_0 (4–6) with a "linear" relationship between log $1/C$ and log P. However, Higuchi and Davis (134) showed that even under equilibrium conditions, one can expect to find "parabolic" relationships between log $1/C$ and log P. This time-independent model assumes that equilibrium or better quasiequilibrium conditions obtain (by definition, living systems are never at equilibrium). Their model is developed as follows:

a. The test system can be represented by the following compartments: w, 1, 2, 3, ... t, and r, where w represents the water phase and r the receptor. All the phases except w (1, 2, 3, *etc.*) are lipophilic. The effective volume of each compartment is V_w, V_1, V_2, *etc.*

b. Thermodynamic equilibrium is essentially reached so that, for all practical purposes, the activity of drug, inhibitor, or substrate is the same in each phase and all can be related to a standard reference state. The drug is distributed to all compartments according to Nernst's distribution law.

c. Biological or biochemical response is proportional to the fraction of active sites occupied by the substrates or inhibitors.

d. A relatively small amount (S) of the applied drug is attached to the receptor, the rest being in phases w, 1, 2, 3, ... t; that is:

$$S = C_wV_w + C_1V_1 + C_2V_2 + \ldots + C_iV_i \qquad \text{(Eq. 187)}$$

In Eq. 187, the C's refer to the effective concentration in each accessible phase. By assuming that drug distribution between the aqueous phase and each biophase follows a linear partition isotherm, the partition coefficient can be defined as:

$$K_i = \frac{C_i}{C_w} \qquad \text{(Eq. 188}a\text{)}$$

and:

$$S = C_w\left(V_w + \sum_{i=1}^{i=t} K_iV_i\right) \qquad \text{(Eq. 188}b\text{)}$$

The effective concentration of small molecules on the receptor is:

$$C_r = K_rC_w = \frac{SK_r}{V_w + \sum_{i=1}^{i=t} K_iV_i} \qquad \text{(Eq. 189)}$$

or:

$$E = \frac{C_r}{S} = \frac{K_r}{V_w + \sum_{i=1}^{i=t} K_iV_i} \qquad \text{(Eq. 190)}$$

It is assumed that relative biochemical response is proportional to E.

In a system where $V_w \gg \Sigma_{i=1}^{i=t}K_iV_i$, Eq. 190 reduces to:

$$E = \frac{K_r}{\text{constant}} \qquad \text{(Eq. 191)}$$

Increasing the partition coefficient results in increased activity up to the point set by bulk tolerance or micelle formation or to the point where $\Sigma_{i=1}^{i=t}K_iV_i > V_w$. This eventually occurs if there are compartments whose K_i's are much greater than K_r.

For the case where $V_w < \Sigma_{i=1}^{i=t}K_iV_i$, an increase in lipophilic character can yield a less active congener since now:

$$E \cong \frac{K_r}{K_iV_i} \qquad \text{(Eq. 192)}$$

For the comparison of relative activity of derivatives with a parent compound, Higuchi and Davis (134) defined the function R:

$$R = \frac{E}{E^*} = \frac{K_r\left(V_w + \sum_{i=1}^{i=t} K_i^*V_i\right)}{K_r^*\left(V_w + \sum_{i=1}^{i=t} K_iV_i\right)} \qquad \text{(Eq. 193)}$$

By the proper choice of parameters in Eq. 193, one can calculate various sets of R values, which Higuchi and Davis plotted against increasing numbers of carbon atoms in, for example, side chains. In this way, one obtains whole families of curves varying all the way from linear relations that level off at a limiting value to symmetrical parabolas.

3. The principle of bulk tolerance (135) could also lead to a nonlinear relationship between log $1/C$ and log P. In general, an increase in log P means an increase in the size of the drug. In going to larger members of a series of congeners, a point is reached where it becomes more and more difficult for each successively larger derivative to fit into or onto the active site.

4. Conformational distortion of the active site can also result in nonlinear relationships which may be

"parabolic" in certain instances. As members of a congeneric series become more hydrophobic, they produce greater distortions in a critical enzyme or membrane. This effect could account for the gradual change from agonist to antagonist often observed in the study of homologous series (136). Such distortions could be considered as overinduced fits. Koshland (137) showed that conformational changes in enzymes caused by the substrate induce the proper arrangement of enzyme components for catalytic activity. No doubt the hydrophobic portions of the substrate play an important role in inducing the proper fit. Such an induction could be overdone, with the resultant mismatching of parts producing less than optimal activity.

5. Metabolism could also be responsible for a biphasic relationship between log $1/C$ and log P. Since Brodie *et al.* (138) pointed out that there appears to be a direct relationship between the rate of microsomal metabolism and the lipophilic character of drugs, evidence has been found that this phenomenon can be quantitatively correlated using the log P scale (139, 140). As the members of a congeneric series become more lipophilic, other factors being equal, they are more rapidly destroyed by microsomal metabolism.

6. Micelle formation may, under certain conditions, account for a break in the linear relationship between activity and log P. Micelles can trap drug molecules (141). It is hard to imagine that drugs injected into whole animals could remain in micellar form when Eqs. 2–4 and many others of this type (1) indicate that organic compounds bind hydrophobically with so many of the macromolecules of living systems. However, in simpler systems such as isolated enzymes, micelle formation could be important. Even when working with drugs at concentrations below the CMC, it is possible that micelle-like clumps of molecules could form on enzyme (27) surfaces. These islands could function as a second compartment and produce a parabolic relationship *via* mechanism 2 above.

7. The limited solubility of the higher members of a congeneric series can, in principle, cause a "cutoff" in linear correlation between activity and lipophilic character. Ferguson (36, 37) demonstrated this, but it seems unlikely that this is a generally important mechanism because of the reasons discussed in connection with Eqs. 2–4.

8. Poisoning of an enzyme by a reaction product could also result in a biphasic relationship between log $1/C$ and log P. For example, consider a hydrolytic process in which an increase in log P results in better binding between enzyme and substrate. As log $1/K_m$ increases, overall hydrolysis goes more rapidly; but as log P for one of the hydrolysis products increases, desorption of this from the enzyme may become increasingly more difficult to the point where this step becomes rate controlling. It was shown (7) that the coefficient with π for enzyme–substrate complex formation is positive; but for the catalytic step, the coefficient for this term is negative.

9. Finally, the linear relation between log k and log P cannot prevail past the point where insufficient drug molecules are present to activate the minimum number of sites necessary to produce the standard biological response.

There are such a variety of reasons to expect parabolic relationships that it is extremely difficult or impossible to deduce in any given situation which mechanism or combination of mechanisms is responsible for the final result. What is most important to establish at this time is whether or not Eq. 180 can be employed to delineate the role of hydrophobic forces in the structure–activity relationship for a set of congeneric drugs. Even though, because of the variety of the discussed mechanisms, one cannot expect Eq. 180 to describe lipophilic effects perfectly and invariably, it will be enormously helpful in regression analysis if it can account for most of the variance in the hydrophobic effects. Only after these effects have been more or less separated can one begin to assign electronic and steric roles to the structural modifications present in a set of congeners.

The examples in Figs. 1–6 were selected to show the variation in types of parabolas as well as the variation in types of systems and drugs. While these examples and all of the others in Tables I and II are very well fit by symmetrical parabolas, this does not mean that other functions of log P would not give as good or even better correlations. For example, in Fig. 5 the results could also be interpreted to imply that activity increases linearly and levels off in a rather flat fashion. One might want to interpret Figs. 1 and 2 as being best described by two straight lines. Figure 2 is a very broad parabola, while Fig. 5 is more pointed. Plotting the data is helpful in understanding the variation in the linear terms (b) in Tables I and II. Since the constraint that the "best" symmetrical curve be drawn through the points is employed, a single very bad point on the right-hand side of the parabola can have a large influence on the value of b. Since these points are the most difficult to determine experimentally, caution must be used in interpreting the value of b. Only when a good spread in data points on both sides of the apex is present can one make significant comparisons with other equations.

The equations in Table I have first been categorized by log P_0, and within these sets they have been ordered on the slope of the linear term (b). One of the first points of interest is that the sets having the highest log P_0 values are composed of neutral compounds. Of the seven sets in Table I, Part D, only number 104 contains drugs ionized at pH 7. In this example, log P values were used for the neutral amines because log P ion is not available. Since these compounds are almost completely ionized at pH 7, log P_0 should be 3–4 units lower than the listed value of 5.8. This set might better be placed in Table I, Part B.

The largest number of log P_0 values in Table I falls in the 1.5–3.0 range. Many of those in Table I, Part C, are near 3 or have confidence intervals considerably below 3.

It is harder to generalize about log P_0 from Table II because of the wider confidence limits on the values of log P_0 in this set. In Table II the distribution of log P_0 values is more evenly spread. The most general statement that can be made about log P_0 is that values below 1 and above 4 are less common. Negative log P_0

values are rare. Out of 167 examples in Tables I and II, only four having negative signs occur. In this connection, it is interesting to point out that anticancer alkylating agents have negative log P_0 values (142).

It is clear from Tables I and II that the charge on a set of congeners has an important part in setting the value of log P_0. As mentioned previously, properly there are no uncharged molecules in Table I, Part D, and only one set in Table II, Part D. Since the apex of the parabola occurs at a lower value when either a positive or negative charge is present on a set of congeners, this suggests that the apolar portion of a molecule may exert a considerable drag on the molecule in its movement to the site of action, regardless of the fact that overall the molecule is relatively hydrophilic. On the other hand, it may be that the charge or a combination of the charge and the apolar moiety acting together causes the drag effect which results in a lower log P_0 for sets of ions.

In Table I there are 27 data sets where cationic drugs (the positive charge being on the organic ion) are acting on microorganisms. The mean value and standard deviation for log P_0 for these are 2.51 ± 0.43. Considering the great variety of organisms (Gram positive, Gram negative, and fungi) and the variety of drugs employed, this is a relatively sharp constant.

The results with anionic drugs are not as sharp. Omitting Eqs. 9 and 10, there are 16 examples that have a mean value of 2.34 ± 0.68. While the mean value is close to that of the cationic drugs, the standard deviation is much larger and would be even greater if the two data sets omitted were included. There are relatively few sets of cationic drugs acting on microorganisms among the less good correlations of Table II, while there are a good many sets of anionic compounds. Cationic drugs apparently show a more limited range of specificity and give more precise correlations with log P.

The log P_0 for charged compounds acting on microorganisms can be compared with log P_0 for neutral compounds. It was shown (58) that the log P_0 for neutral compounds acting *in vitro* on Gram-negative organisms is about 4, and for Gram-positive organisms it is about 6. The fact that it is possible to go to higher log P values in a congeneric series before reaching log P_0 may mean that these compounds are less hindered in their movement and that one can approach equilibrium in a shorter time.

In Table I there are very few examples of log P_0 in whole animals outside of the 1.5–3.0 range. For a wide variety of hypnotics acting in various whole animals, log P_0 of about 2 was observed (40, 143). No doubt, in these systems nothing approaching an equilibrium between drug in the open system (whole animal) and drug on the receptor sites occurs. The mean log P_0 of about 2.5 for charged drugs acting in closed *in vitro* systems against microorganisms may result from equilibrium not being reached because of the additional drag placed on drug movement by the positive or negative charge. Localization of the drug in the first lipophilic material it encounters appears to become severe as log P approaches 2–2.5.

Most equations in Tables I and II are based on log $1/C$ data; one can, therefore, compare intrinsic activities by comparing intercepts (listed under c). The value of the intercept is determined by the sensitivity of the system and the intrinsic activity of the pharmacophoric function in the set of congeners (32, 55). Comparing intercepts (other factors being equal) means comparing sets of congeners under isolipophilic conditions (log P = 0). If the systems have the same sensitivity, then differences in intercept represent differences in the stereoelectronic character of the pharmacophoric function common to the members of the set. The diversity of systems is so great in Tables I and II that not much in the way of useful generalization is possible. The mean intercept of cationic drugs (except guanidines) acting on microorganisms is about 3; this is close to the 3.2 value previously found for fungi (55). Neutral nonspecific compounds such as phenols and alcohols have low values (<1); RSCN, for example (Eq. 111), has a value of 3, showing a specificity at least two orders of magnitude above phenols, alcohols, and thioureas (Eq. 150).

In summary, it can be said that the present review provides a large amount of support for the thought embodied in Eq. 177; that is, if one can assume that the relationship between log $1/C$ and log P is well approximated by a parabola, then the role of the hydrophobic character of drugs can be at least roughly separated from the electronic and steric characteristics of drugs. This should be of great help in drug design. The many good correlations and the general agreement among log P_0 and intercept values for sets of charged congeners provide further support for the utility of log P values from the octanol–water system as an operational definition of relative lipophilic character.

Finally, it is hoped that this summary of equations will prove useful for comparison with the results of future work.

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