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The Structure–Activity Relationship in Barbiturates and Its Similarity to That in Other Narcotics[1]

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From a study of the structure–activity relationship of barbiturates in four biochemical systems, inhibition of *Arbacia* egg cell division, inhibition of rat brain oxygen consumption, hypnotic activity, and inhibition of NADH oxidation, it is found that very good structure–activity correlations can be obtained considering only the relative hydrophobic character of the various derivatives. Steric and electronic effects play a minor role. Comparison of the structural requirements for activity of the barbiturates with inhibitors of bacterial luminescence, paramecium mobility, lung oxygen consumption, gut contractility, histamine release, narcotic action on frog heart and muscle, and narcotic action on tadpoles and C-mitosis indicates a very similar structure–activity relationship for a great variety of molecules in a variety of processes. The value of a single mathematical reference system for comparison of experimental systems and results carried out originally for different purposes is stressed. It is suggested that interference with electron transport may be a common mechanism of action for the different compounds in the various systems. The results of our analysis also constitute further evidence for the additive-constitutive nature of octanol–water partition coefficients and illustrate the application of this principle to problems of interest to the medicinal chemist.

Recently[3–6] we have been attempting to place the discussion of structure–activity relationships of biologically active compounds on a mathematical basis. To this end we have developed an expression for the correlation of the change of biological response for a set of congeners with extrathermodynamically related[6] substituent contants. Assuming that an equivalent biological response for a series of drugs can be related to their effects on one rate-controlling reaction whose rate or equilibrium constant is represented by k_X, we can write[4] eq 1. In eq 1, relative biological response is

$$k(1/C_X) = A_X k_X \quad (1)$$

defined in terms of the applied molar concentration ($1/C$ biological response) of drug X producing a standard response in a constant time interval. A_X is the probability of drug X reaching the site of action during the test time. We have assumed[4] that A is a function of the logarithm of the partition coefficient of the drug (thus it is related to its free energy of transfer from phase to phase) and A has the form of a normal distribution. In eq 2, a and b are constants and P

$$A_X = a \exp[-(\log P_X - \log P_{0X})^2/b] \quad (2)$$

is the partition coefficient. We have normally used 1-octanol–water to represent the aqueous and lipid phases of the cell. Substituting eq 2 into eq 1, taking logarithms, and collecting constants, we obtain, remembering that P_0 is a constant for a given system

$$\log (1/C_X) = -k(\log P_X)^2 + k' \log P_X + \log k_X + k'' \quad (3)$$

The first two terms on the right of eq 3 take into account the differences in drug activity due to differences in the random-walk process by which drugs find the active sites. They may not find the receptor sites during the time of test because of being localized in lipophilic pools, metabolic destruction, or elimination. All of these processes appear to be highly dependent on $\log P$. The effect of structure variation on k_X can be treated by the technique of linear combination of free-energy-based substituent constants.[5,6] We have normally replaced $\log k_X$ in eq 3 using expressions such as eq 4. The constants a, b, c are different from those

$$\log k_X = a \log P_X + \rho\sigma + bE_s + c \quad (4)$$

in the previous equations. In eq 4, $a \log P_X$ accounts for the free-energy change in the hydrophobic binding of the drug to a critical enzyme or protein.[7] The usual Hammett[8] significance is attached to $\rho\sigma$ and E_s is the Taft steric parameter.

It is possible to formulate a higher order approximation as suggested by Miller.[9] This can be done utilizing eq 23 of Miller's paper. Recasting his equation in terms of $\log k_X$, $\log P_X$, σ, and E_s instead of his parameters

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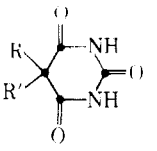
TABLE I

BARBITURATE INHIBITION OF DIVISION OF *Arbacia* EGG CELLS



No.	R	R'	log P	ΔpK_a[a,b]	−Log (1/C)− Obsd[b]	Calcd[c]	Δ log (1/C)[d]
1	Ethyl	2-Ethylhexyl	3.45	0.75	3.70	3.868	0.17
2	Allyl	1-Methylbutyl	2.15	0.92	3.62	2.878	0.74
3	Benzyl	Isopropyl	2.64	0.82	3.40	3.240	0.16
4	Allyl	Benzyl	2.54	0.06	2.82	2.844	0.02
5	Ethyl	1-Methyl-2-butenyl	1.65	0.78	3.30	2.431	0.87
6	Ethyl	Hexyl	2.65	0.66	3.12	3.182	0.06
7	2-Methyladlyl	1-Methylbutyl	2.45	0.80	3.17	3.078	0.09
8	Ethyl	Isoamyl	1.95	0.78	2.82	2.664	0.16
9	Ethyl	1-Methylbutyl	1.95	1.02	2.92	2.764	0.16
10	Ethyl	1-Ethylpropyl	1.95	0.89	2.85	2.710	0.14
11	Ethyl	Amyl	2.15	0.82	2.82	2.843	0.02
12	Ethyl	2-Phenylethyl	2.80	0.74	2.66	3.328	0.67
13	Ethyl	1,3-Dimethylbutyl	2.25	0.99	2.82	2.995	0.18
14	Ethyl	Cyclopentenyl	0.79	0.98	2.77	1.820	0.95
15	Allyl	Isobutyl	1.65	0.54	2.41	2.322	0.09
16	Ethyl	Cyclohexenyl	1.20[e]	0.36	2.24	2.085	0.16
17	Isobutyl	2-Methyladlyl	1.95	0.62	2.40	2.598	0.20
18	Ethyl	Butyl	1.65	0.76	2.40	2.413	0.01
19	Ethyl	Phenyl	1.42[e]	0.26	2.02	2.019	0.00
20	Allyl	Isopropyl	1.15	0.73	2.01	1.935	0.02
21	Allyl	Allyl	1.05	0.62	1.79	1.868	0.08
22	Ethyl	Isopropyl	0.95	0.90	1.79	1.993	0.11
23	Ethyl	Ethyl	0.65[e]	0.75	1.49	1.598	0.11

[a] ΔpK_a represents $(pK_a - 7)$. [b] From ref 12. C is concentration causing 50% inhibition at pH 8. [c] Calculated using eq 10. [d] Difference between observed and calculated log (1/C). [e] Experimentally determined values; all other values calculated.

TABLE II

BARBITURATE INHIBITION OF RAT BRAIN OXYGEN CONSUMPTION

No.	R	R'	Log P	ΔpK_a[a]	−Log (1/C)− Obsd[b]	Calcd[c]	Δ log (1/C)
24	Ethyl	Ethyl	0.65[e]	0.75	1.32	1.370	0.05
25	Ethyl	Isopropyl	0.95	0.90	1.89	1.890	0.00
26	Ethyl	Butyl	1.65	0.76	2.80	2.806	0.01
27	Ethyl	1-Methylbutyl	1.95	1.02	3.07	3.071	0.00
28	Ethyl	Isoamyl	1.95	0.78	3.12	3.071	0.05
29	Ethyl	Hexyl	2.65	0.66	3.40	3.393	0.01
30	Ethyl	Phenyl	1.42[e]	0.26	2.36	2.551	0.19
31	Allyl	Isopropyl	1.15	0.73	2.41	2.194	0.22
32	Allyl	Isobutyl	1.65	0.54	2.80	2.806	0.01
33	Allyl	1-Methylbutyl	2.15	0.92	3.19	3.205	0.02
34	Allyl	Cyclopentenyl[d]	0.93	...	2.90	1.954	0.95

[a] From ref 12. [b] From ref 18. [c] Calcd using eq 16. [d] Data for this compound were not used in the regression analysis since a value for pK_a was not available. [e] Experimentally determined values; all other values calculated.

TABLE III

HYPNOTIC ACTIVITY OF 5,5-BARBITURATES

No.	R	R'	Log P	σ^{*}[a]	−Log (1/C)− Obsd[b]	Calcd[c]	Δ log (1/C)
35	Ethyl	Ethyl	0.65[d]	−0.20	3.09	3.012	0.08
36	Propyl	Propyl	1.65	−0.24	3.55	3.656	0.11
37	Propyl	Isopropyl	1.45	−0.31	3.63	3.628	00
38	Butyl	Butyl	2.65	−0.26	2.84	3.040	0.20
39	Ethyl	Isopropyl	0.95	−0.29	3.30	3.338	0.04
40	Ethyl	Isobutyl	1.45	−0.23	3.63	3.628	00
41	Ethyl	Butyl	1.65	−0.23	3.72	3.656	0.06
42	Ethyl	Isoamyl	1.95	−0.23	3.75	3.604	0.15
43	Propyl	Isoamyl	2.45	−0.25	3.48	3.264	0.22
44	Ethyl	Phenyl	1.42[d]	0.50	3.46	3.620	0.16
45	Ethyl	*sec*-Butyl	1.45	−0.31	3.63	3.628	00

[a] From ref 6. [b] From ref 19. [c] Calculated using eq 22. [d] Experimentally determined values; all other values calculated.

y, x, z, and w, we obtain eq 5. Substitution of eq 5

$$\log k_X = a \log P_X + \rho\sigma + bE_s + c(\log P_X)\sigma + d(\log P_X)E_s + e\sigma E_s + f(\log P_X)\sigma E_s + g \quad (5)$$

into eq 3 yields an expression (eq 6) which, if the dependence of log k_X on log P, σ, and E_s is strictly linear, should give a better correlation than our previously formulated expression. The difficulty, of course, with eq 6 is that one does not often have sufficient data to statistically validate the nine constants, k–k_7 and ρ. However, often it is unnecessary to include E_s and eq 6 then reduces to eq 7. For the work in this paper we

$$\log (1/C_X) = -k(\log P_X)^2 + k_1 \log P_X + \rho\sigma + k_2E_s + k_3(\log P_X)\sigma + k_4(\log P_X)E_s + k_5\sigma E_s + k_6(\log P_X)\sigma E_s + k_7 \quad (6)$$

$$\log (1/C_X) = -k(\log P_X)^2 + k_1 \log P_X + \rho\sigma + k_3(\log P_X)\sigma + k_7 \quad (7)$$

have fitted those data in Tables I–X to eq 7 and its simpler forms.

Over the years much work has centered on the relation of the degree of ionization of drugs to their biological activity.[10] Fujita[11] has recently analyzed the advantages to be gained in correcting for ionization in structure–activity correlations where there is considerable variance in ionization. In this paper we are concerned in assessing the relative importance of the degree of ionization of the barbiturates and their lipophilic character. Considerable interest has centered on the correlation of barbiturate activity with degree of ionization.[12,13] It has also been recognized that the activity of these drugs is dependent upon their lipophilic character.[14]

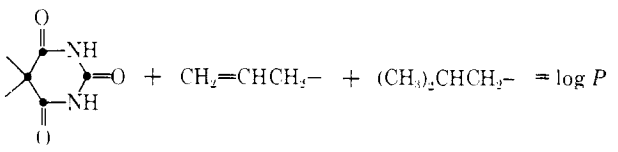
Methods

In our preliminary report on barbiturates[15] we correlated substituent effects for a single series of barbiturates using π values for substituents and log P for barbituric acid as our base of reference. Barbituric acid is not the best reference molecule to use to correlate 5,5-disubstituted barbiturates. Disubstitution shields hydrophobic and hydrophilic interactions of the 5-carbon atom and groups adjacent to it. In this work we have used 5,5-diethylbarbituric acid (log P = 0.65 ± 0.02) as our reference molecule. We have also determined log P (octanol–water) for the ethylphenylbarbituric acid (1.42 ± 0.01) and barbituric acid (−1.47 ± 0.03). The value of barbituric acid is more accurate than our previously reported value.[15]

The shielding around the 5-carbon atom by two alkyl groups can be estimated as follows. The calculated value of diethylbarbituric acid, assuming simple additivity, is

$$\pi(2\text{Et}) + \log P \text{ (barbituric acid)} = 2.00 - 1.47 = 0.53$$

The difference between this and the experimental value (0.65 − 0.53 = 0.12) represents the increase in partition coefficient due to shielding by disubstitution. No doubt this will vary somewhat with the size of large substituents; however, this will not be significant for our purposes. Random errors in the biological tests are much larger. The values for log P for the compounds in Tables I–IV were found by adding the proper π value for the alkyl groups to −1.35 (−1.47 + 0.12). For example, in Table I, **15** was calculated as follows.



$$-1.35 + 1.20 + 1.80 = 1.65$$

The value of 1.20 for allyl was obtained by subtracting 0.3 from 1.50 for n-propyl. The figure of 0.3 was obtained by subtracting π for ethyl from π for vinyl.[16] The value of isobutyl comes from subtracting 0.2 from n-butyl.

Log P for 5-ethyl-5-cyclopentenyl barbituric acid was estimated by subtracting 0.41 from the ethylcyclohexenyl derivative. The value of 0.41 is an average

TABLE IV

50% INHIBITION OF NADH OXIDATION BY BARBITURATES

No.	R	R′	Log P	Log (1/C) Obsd[a]	Log (1/C) Calcd[b]	Δ log (1/C)
46	Ethyl	Phenyl	1.42[c]	2.96	2.810	0.15
47	Ethyl	Isoamyl	1.95	3.52	3.397	0.12
48	Ethyl	1-Methylbutyl	1.95	3.51	3.397	0.11
49	Ethyl	Cyclohexenyl	1.20	2.64	2.566	0.07
50	Ethyl	Butyl	1.65	2.60	3.064	0.46
51	Ethyl	Ethyl	0.65[c]	1.96	1.957	0.00

[a] From ref 20. [b] Calculated using eq 25. [c] Experimentally determined values; all other values calculated.

TABLE V

INHIBITION OF BACTERIAL LUMINESCENCE BY ALCOHOLS AND URETHANS

Alcohol	Log P	Log (1/C) Obsd[a]	Log (1/C) Calcd[b]	Δ log (1/C)
Methanol	−0.66[f]	−0.44	−0.550	0.11
Ethanol	−0.16	0.05	0.036	0.01
Propanol	0.34[f]	0.60	0.621	0.02
Butanol	0.84	1.12	1.207	0.09
Pentanol	1.34	1.72	1.793	0.07
Hexanol	1.84	2.25	2.379	0.13
Heptanol	2.34	3.04	2.964	0.08
Octanol	2.84	3.66	3.550	0.11

Urethan	log P	Log (1/C) Obsd[c]	Log (1/C) Obsd[d]	Log (1/C) Calcd[e]	Δ log (1/C)
Methyl	−0.65	0.50	0.06	0.517	0.02
Ethyl	−0.15[f]	1.15	0.48	1.137	0.01
Propyl	0.35	1.70	1.05	1.756	0.06
Butyl	0.85	2.30	1.54	2.376	0.08
Isoamyl	1.15	3.00	2.25	2.748	0.25
Hexyl	1.85	3.50		3.616	0.12

[a] From ref 21. [b] Calculated using eq 27. [c] From ref 22. The authors included the octyl derivative as well. It was not used in our calculations since log P for this derivative was high enough so that departure from the linear relationship was apparent. [d] From ref 21. The difference in value for log (1/C) for the two sets of inhibition were used as reference points. [e] Calculated using eq 29. [f] Experimentally determined values; all other values calculated.

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TABLE VI

50% INHIBITION OF MISCELLANEOUS BIOLOGICAL FUNCTIONS BY ALCOHOLS[a]

		Obsd log (1/C)			
Compd	Log P	Gut contractility	Paramecium mobility	Lung O_2 consumption	Histamine release
Methanol	−0.66[b]	0.09	−0.20	−0.40	0.64
Ethanol	−0.16	0.32	0.14	−0.12	0.92
Propanol	0.34[b]	0.83	0.52	0.53	1.25
Butanol	0.84	1.57	1.09	0.92	1.58
Pentanol	1.34	2.05	1.66	1.46	2.02
Hexanol	1.84	2.60	2.12	1.92	2.46
Heptanol	2.34	3.15	2.64	2.15	2.72
Octanol	2.84	3.60	2.98		2.66

[a] Data from ref 23. [b] Experimentally determined values; all other values calculated.

TABLE VII

NARCOTIC ACTION ON FROG HEART

		Log (1/C)		Δ log (1/C)
Compd	Log P	Obsd[a]	Calcd[b]	
Methanol	−0.66[c]	−0.57	−0.508	0.06
Ethanol	−0.16	−0.08	0.041	0.04
Propanol	0.34[c]	0.43	0.425	0.01
2-Propanol	0.14	0.18	0.239	0.06
Butanol	0.84	0.96	0.892	0.07
Isobutyl alcohol	0.64	0.87	0.705	0.17
t-Butyl alcohol	0.37[c]	0.20	0.453	0.25
t-Pentyl alcohol	0.89[c]	0.74	0.939	0.20
Isopentyl alcohol	1.14	1.41	1.172	0.24
Heptanol	2.34	2.52	2.291	0.23
Acetone	−0.21	−0.04	−0.088	0.05
Ether	0.77[c]	0.53	0.827	0.30
Methyl acetate	0.23	0.59	0.323	0.27
Ethyl acetate	0.73[c]	0.89	0.789	0.10
Propyl acetate	1.23	1.46	1.256	0.20
Isopropyl acetate	1.03	1.21	1.069	0.14
Isobutyl acetate	1.53	1.82	1.536	0.28
Barbital	0.65[c]	1.57	0.714	0.86
Benzene	2.13[c]	1.96	2.096	0.14
Chloroform	1.97[c]	2.15	1.946	0.20
Methyl iodide	1.50	1.19	1.509	0.32
Ethyl chloride	1.39	1.34	1.405	0.07
Ethyl bromide	1.60	1.48	1.601	0.12
Ethyl iodide	2.00[c]	1.92	1.974	0.05
Propyl chloride	1.89	1.77	1.872	0.10
Propyl bromide	2.10[c]	2.10	2.068	0.03
Isopropyl bromide	1.90	2.00	1.881	0.12
Propyl iodide	2.50	2.30	2.441	0.14
Ethylene chloride	1.78	1.51	1.769	0.26

[a] From ref 24. [b] Calculated using eq 34. Barbital was not used in deriving eq 34. [c] Experimentally determined values; all other values calculated.

of several estimations. Dividing the π values from the phenoxyacetic acid series[17a] for cyclohexyl (2.51) and cyclopentyl (2.14) by 6 and 5, respectively, gives 0.42 and 0.43. Subtracting log P 0.29 for ethyl methyl ketone from log P 1.50 for methyl 2-cyclopropyl ketone[16] gives the value of 1.21 for cyclopropyl; dividing by 3 yields 0.40. The π value for cyclohexyl can also be calculated from log P cyclohexanol (1.23) and the π value for aliphatic[17b] OH (−1.16). Dividing this value of 2.39 by 6 yields 0.40 for the cyclic CH_2 unit. Thus the value of 0.41 seems like a reasonable compromise.

For the benzyl function in **3** and **4** we have used log P for toluene (2.69) and for the phenylethyl group in **12** we have used the log P figure for ethylbenzene (3.15).[16] For each double bond we have subtracted 0.3 from the *n*-alkyl group.

Table I contains data on the inhibition of cell division in *Arbacia* eggs.[12] Table II gives data on the inhibition

TABLE VIII

NARCOTIC ACTION ON FROG MUSCLE

		Log (1/C)		Δ log (1/C)
Compd	Log P	Obsd[a]	Calcd[b]	
Methanol	−0.66[d]	−0.09	0.066	0.16
Ethanol	−0.16	0.25	0.517	0.27
Acetone	−0.21	0.40	0.472	0.07
2-Propanol	0.14	0.45	0.788	0.34
Propanol	0.34[d]	0.60	0.969	0.37
Urethan	−0.15[d]	1.00	0.526	0.47
Ethyl ether	0.77[d]	1.07	1.357	0.29
Butanol	0.84	1.22	1.420	0.20
Antipyrine	0.23[d]	1.22	0.869	0.35
Pyridine	0.65[d]	1.23	1.248	0.02
Hydroquinone	0.59[d]	1.60	1.194	0.41
Aniline	0.90[d]	1.70	1.474	0.23
Benzyl alcohol	1.10[d]	1.70	1.655	0.05
Acetanilide	1.16[d]	1.83	1.709	0.12
Pentanol	1.34	1.80	1.871	0.07
Phenol	1.46[d]	2.00	1.980	0.02
Hexanol	1.84	2.44	2.323	0.12
Nitrobenzene	1.85[d]	2.53	2.332	0.20
Quinoline	2.03[d]	2.70	2.494	0.21
Heptanol	2.34	2.80	2.774	0.03
2-Naphthol	2.84[d]	3.00	3.225	0.23
Octanol	2.84	3.16	3.225	0.07
Thymol	3.30[d]	3.52	3.641	0.12
Toluene[c]	2.69[d]	2.00	3.031	1.03
Chloroform[c]	1.97[d]	1.50	2.441	0.94

[a] From ref 25. [b] Calculated using eq 36. [c] Toluene and chloroform were not used in deriving eq 36. [d] Experimentally determined values; all other values calculated.

TABLE IX

NARCOTIC ACTION ON TADPOLES

		Log (1/C)		Δ log (1/C)
Coopd	Log P	Obsd[a]	Calcd[b]	
Ethyl acetate	0.73[d]	1.41	1.541	0.13
Ethyl propionate	1.23	2.10	2.127	0.03
Ethyl butyrate	1.73	2.62	2.713	0.09
Ethyl valerate	2.23	3.05	3.299	0.25
Acetone	−0.21	0.49	0.439	0.05
2-Butanone	0.29[d]	1.02	1.025	0.01
2-Pentanone	0.79	1.57	1.611	0.04
Chloroform	1.97[d]	3.12	2.904	0.13
Nitromethane	−0.33[d]	0.85	0.298	0.55
Ethyl ether	0.77[d]	1.35	1.588	0.24
Methanol	−0.66[d]	−0.19	−0.089	0.10
Ethanol	−0.16	0.26	0.498	0.24
Propanol	0.34[d]	0.98	1.084	0.10
Butanol	0.84	1.77	1.670	0.10
Hexanol	1.84	3.03	2.842	0.19
Heptanol	2.34	3.60	3.428	0.17
Octanol	2.84	4.05	4.014	0.04
Methyl carbamate	−0.65	0.50	0.738[c]	0.15
Ethyl carbamate	−0.15[d]	1.46	1.410[c]	0.05
Propyl carbamate	0.35	2.33	2.081[c]	0.25
Isobutyl carbamate	0.65	2.49	2.484[c]	0.01
Isoamyl carbamate	1.15	3.00	3.156[c]	0.16

[a] From ref 26. Tadpoles of various ages were used in the tests. The esters were tested on 3-day tadpoles, the ketones on 7-day, the group from chloroform to ether on 6-day, the alcohols on 6-day, and the carbamates on 8-day. [b] Calculated using eq 37. [c] Calculated using eq 38. [d] Experimentally determined values; all other values calculated.

(17) (a) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964); (b) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

TABLE X
INDUCTION OF C-MITOSIS IN ALLIUM ROOT TIPS

Compd	Log P	Log $(1/C)$ Obsd[a]	Log $(1/C)$ Calcd[b]	Δ log $(1/C)$
Ethanol	−0.16	0.12	0.407	0.29
Propanol	0.34[c]	0.73	0.887	0.16
Butanol	0.84	1.33	1.367	0.04
Isobutyl alcohol	0.64	1.03	1.175	0.15
t-Butyl alcohol	0.37[c]	0.73	0.916	0.19
Isopentyl alcohol	1.14	1.43	1.656	0.23
t-Pentyl alcohol	0.89[c]	0.73	1.415	0.69
Octanol	2.84	3.43	3.289	0.14
Acetone	−0.21	0.43	0.359	0.07
Ethyl ether	0.77[c]	1.03	1.300	0.27
Acetamide	−1.20	0.12	−0.592	0.71
Ethyl carbamate	−0.15	0.60	0.416	0.18
Chloroform	1.97[c]	2.19	2.453	0.26
Benzene	2.13[c]	2.60	2.607	0.01
Xylene	3.13	3.52	3.567	0.05
Naphthalene	3.37	4.24	3.798	0.44
Anisole	2.11[c]	2.49	2.587	0.10
Acetanilide	1.16[c]	2.12	1.675	0.45
Acetophenone	1.58[c]	2.49	2.078	0.41
Barbital	0.65[c]	1.52	1.185	0.34

[a] From ref 27. Two concentration points were determined: the concentration just causing C-mitosis and the highest concentration not causing C-mitosis. We have used the average of the two in calculating log $(1/C)$. [b] Calculated using eq 39. Barbital was not used in deriving eq 39. [c] Experimentally determined values; all other values calculated.

of oxygen consumption by rat brain.[18] Table III presents data on the hypnotic action of barbiturates.[19] Although there are several good series of barbiturates which have been carefully tested for hypnotic activity, we have used this set because polar substituent constants were available for these relatively simple alkyl substituents. Table IV contains the data for the inhibition of NADH oxidation by barbiturates,[20] Table V summarizes the data on bacterial luminescence by alcohols and urethans,[21,22] Table VI those on inhibition of four biological processes by alcohols,[23] Table VII contains data on narcosis of frog heart,[24] Table VIII lists recent data on narcosis of frog muscle,[25] Table IX presents data on the narcosis of tadpoles,[26] and Table X has information on colchine-like mitosis (C-mitosis) in onions.[27]

Results

Using the method of least squares we have derived eq 8–12 from the data on the inhibition of cell division of *Arbacia* eggs. In the equations, n is the number of points used in finding the constants. In deriving these equations we have omitted using data from **2**, **5**, **12**, and **14** since the compounds were poorly fit by all of

	n	r	s	
$\log(1/C) = 0.801 \log P + 1.076$	19	0.960	0.171	(8)
$\log(1/C) = 0.504\Delta pK_a + 2.230$	19	0.209	0.594	(9)
$\log(1/C) = 0.793 \log P + 0.356\Delta pK_a + 0.845$	19	0.971	0.151	(10)
$\log(1/C) = 0.547 \log P - 0.354\Delta pK_a + 0.356(\log P)\Delta pK_a + 1.331$	19	0.974	0.146	(11)
$\log(1/C) = -0.082(\log P)^2 + 0.880 \log P - 0.320\Delta pK_a + 0.338(\log P)\Delta pK_a + 1.034$	19	0.978	0.140	(12)

the equations, even eq 12. This does not change the essential shapes of the curves, but it does improve the correlation. The multiple correlation coefficient is represented by r, s is the standard deviation, and C is the molar concentration of drug producing the standard inhibition.

Equations 8 and 9 represent the two simplest hypotheses; that is, the inhibiting power of the drugs is directly proportional to their lipophilic character (eq 8) or direcly proportional to ΔpK_a (eq 9). The correlation with eq 8 is extremely good while that of eq 9 is very low. Combining log P and ΔpK_a, we obtain eq 10 which accounts for 94.2% of the variance in the data *vs.* 92.6% accounted for by eq 8. Although this is a small difference, it is statistically significant ($F_{1,16} = 5.96$). F tests indicate that eq 11 is not significant at the 0.90 level when compared with eq 10. Equation 12 is significant at the 0.90 level when compared with eq 10. For all practical purposes eq 10 gives the best fit. While the squared term in eq 12 is significant, it is not important unless one were to consider more lipophilic molecules. Equation 10 does establish the fact that a very small amount of the variance in biological activity can probably be attributed to differences in the degree of ionization.

Equations 13–18 result from the data on oxygen consumption of Table II. Again, comparison of the two monoparameter equations reveals that log P is the parameter of overwhelming significance. Adding two additional terms, as in eq 15, does not result in a reduction in variance (compare values of s). In eq 16 and 17 we have examined the use of squared terms for the two parameters. Equation 16 results in a statistically significant improvement in correlation ($F_{1,7} = 19.1$) over the simple linear relation. The correlation with eq 17 is meaningless. The highest order approximation, eq 18, is not a significant improvement over eq 16 ($F_{2,5} = 1.23$). These results clearly indicate that small changes in the degree of ionization of the barbiturates have no bearing on their inhibition of oxygen consumption. This does not imply that ΔpK_a could be neglected

	n	r	s	
$\log(1/C) = 1.037 \log P + 0.959$	10	0.956	0.203	(13)
$\log(1/C) = 0.367\Delta pK_a + 2.367$	10	0.122	0.683	(14)
$\log(1/C) = 0.334 \log P - 1.335\Delta pK_a + 0.920(\log P)\Delta pK_a + 1.975$	10	0.962	0.218	(15)
$\log(1/C) = -0.424(\log P)^2 + 2.411 \log P + 0.017$	10	0.988	0.112	(16)
$\log(1/C) = 0.429(\Delta pK_a)^2 - 0.181\Delta pK_a + 2.521$	10	0.127	0.729	(17)
$\log(1/C) = -0.494(\log P)^2 + 3.066 \log P + 1.136\Delta pK_a - 0.572(\log P)\Delta pK_a - 1.020$	10	0.992	0.109	(18)

(18) F. A. Fuhrman and J. Field, *J. Pharmacol. Exptl. Therap.*, **77**, 392 (1943).
(19) H. A. Shonle and A. Moment, *J. Am. Chem. Soc.*, **45**, 243 (1923).
(20) A. Giuditta and G. Di Prisco, *Biochim. Biophys. Acta*, **77**, 394 (1963).
(21) G. W. Taylor, *J. Cellular Comp. Physiol.*, **4**, 329 (1934).
(22) F. H. Johnson, E. A. Flagler, R. Simpson, and K. McGeer, *ibid.*, **37**, 1 (1951).
(23) H. P. Rang, *Brit. J. Pharmacol.*, **15**, 185 (1960).
(24) H. Führer, *Biochem. Z.*, **120**, 143 (1921).
(25) D. Agin, L. Hersh, and D. Holtzman, *Proc. Natl. Acad. Sci. U. S.*, **53**, 952 (1965).
(26) H. M. Vernon, *J. Physiol.* (London), **47**, 15 (1913).
(27) G. Östergren, "Mecanisme De La Narcose," Centre National de la Research Scientifique, Paris, 1950, p 77.

for large changes.[11] Equation 13 rationalizes 91% of the variance in the data, and eq 16 accounts for 98%. Compound **34** was not used in the regression analysis because no ΔpK_a value was available. Its calculated log (1/C) (Table II) is not in very good agreement with the experimental value. The cyclopentenyl group is also not well predicted in Table I. This may be due to our method of estimating log P or some steric factor may be involved.

From the data in Table III on the hypnotic action of barbiturates, we have formulated eq 19–24. Neither

	n	r	s	
$\log (1/C) = -0.040 \log P + 3.527$	11	0.085	0.296	(19)
$\log (1/C) = -0.023\sigma^* + 3.457$	11	0.027	0.297	(20)
$\log (1/C) = 2.801 \log P - 16.496\sigma^* + 11.594(\log P)\sigma^* - 0.485$	11	0.593	0.271	(21)
$\log (1/C) = -0.630(\log P)^2 + 2.092 \log P + 1.918$	11	0.986	0.139	(22)
$\log (1/C) = 1.140(\sigma^*)^2 - 0.280\sigma^* + 3.315$	11	0.111	0.313	(23)
$\log (1/C) = -0.657(\log P)^2 + 2.099 \log P + 0.203\sigma^* - 0.305(\log \sigma^*) \log P + 1.933$	11	0.912	0.149	(24)

of the simple linear equations, 19 and 20, result in significant correlations. Even the three-parameter equation, 21, accounts for only 35% of the variance in the data. Comparing eq 22 and 23 with 19 and 20 shows a very high degree of dependence of hypnotic activity on log P and essentially no dependence on σ^*. Equation 24 does not offer an improvement over eq 22 (compare s values). For these equations we have had to employ the polar substituent constant σ^* instead of ΔpK_a since pK_a values were not available for many of these barbiturates. Within the limits of this approximation, hypnotic activity appears not to be dependent on the degree of ionization. As is usually the case[4,28] for the action of drugs in whole organisms, we find a strong dependence of activity on $(\log P)^2$.

The dependence of the inhibition of NADH oxidation of barbiturates on their lipophilic character is summarized in eq 25 and 26 obtained from data in Table IV. Again it is seen that the addition of the ionization-related term in eq 26 does not result in an improved correlation. Thus, the relative biochemical activity in the above four quite different tests is shown to depend almost entirely on their relative lipophilic character.

	n	r	s	
$\log (1/C) = 1.107 \log P + 1.237$	6	0.921	0.261	(25)
$\log (1/C) = 1.154 \log P - 0.208\Delta pK_a + 1.305$	6	0.926	0.293	(26)

Discussion

The results embodied in eq 8–26 bring out clearly the great practical importance of the additive character of log P and π. Of the 27 different barbiturates, we have measured partition coefficients for only three for our regression analyses (the value for barbituric acid is not essential). The others were estimated in a few minutes with pencil and paper. This represents a great saving in time and money. Probably the chief reason greater follow up of the work of Meyer and Overton has not been made is the expense of determining the many partition coefficients necessary for a thorough study. Sufficient evidence[6,29–33] for the additive character of log P is now in hand to justify the effort of theoretical studies such as the present.

To the best of our knowledge, all of the biochemical studies of the 5,5-disubstituted barbiturates use derivatives such as those represented in Tables I–IV where either simple or complex alkyl or alkenyl functions do not result in sets of congeners having much spread in their degree of ionization. Our results show that attempts to rationalize even a small fraction of variance in activity with degree of ionization are likely to be unprofitable.

In none of the equations formulated in this paper have we attempted to account for highly specific steric restrictions on the interactions of the barbiturates with the biochemical material through which they mediate a given biological response. The high correlations obtained without the use of such parameters indicates that "lock and key theory" is of little use in explaining their mode of action. In this respect, it is of interest to consider the four poorly fit molecules (**2**, **5**, **12**, and **14**) of Table I. With the possible exception of **12**, they do not contain unusually bulky groups. There is nothing outstanding about **2** and **5** to explain their poor fit. In any case, steric factors do not seem to be responsible. This result is most likely to be found in the measurement of the biochemical response or the calculated log P or in a combination of the two.

In one sense, the most interesting aspect of the quantitative approach to structure–activity studies is to find those molecules which do give the unexpected result. The use of regression analysis enables the researchers to quickly spot in a mass of data the unusual molecules from which the next advances in the understanding of the terribly complex pharmacological problems can be made.

One of the advantages of formulating results of structure–activity studies in the form of equations is that it greatly facilitates comparisons of results by different research groups on different systems. While a great many studies attempting to relate biochemical activity to partition coefficients or other physical parameters have been made, there has been relatively little work done using any particular reference systems. McGowan's[34] and Zahradnik's[35] studies are notable exceptions.

This comparative approach to pharmacodynamics is illustrated in the following summary of the linear relation between structure and activity in the barbiturates. The figures in parentheses are the 90% confidence intervals. Although $(\log P)^2$ was statistically significant in two of the above studies, the difference from the simple linear one-parameter equation was so slight that we can ignore these effects for the molecules under

(28) C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacol.*, **1**, 205 (1965).

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

(30) D. J. Cloetie, C. E. Keogh, R. F. Silver, and H. L. Hobbes, *Can. J. Chem.*, **44**, 1035 (1966).

(31) C. Hansch, Proceedings of the International Congress on Pharmacology, Sao Paulo, 1966.

(32) C. Hansch and S. M. Anderson, unpublished results.

(33) P. Bracha and R. D. O'Brien, *J. Econ. Entomol.*, **59**, 1253 (1966).

(34) J. C. McGowan, *J. Appl. Chem.*, **4**, 41 (1951).

(35) R. Zahradnik, *Arch. Intern. Pharmacodyn.*, **135**, 311 (1962).

50% inhibition of *Arbacia* egg cell division

$$\log (1/C) = \underset{(\pm 0.10)}{0.801} \log P + \underset{(\pm 0.20)}{1.076} \quad (8)$$

50% inhibition of rat brain oxygen consumption

$$\log (1/C) = \underset{(\pm 0.21)}{1.037} \log P + \underset{(\pm 0.36)}{0.959} \quad (13)$$

50% inhibition of NADH oxidation

$$\log (1/C) = \underset{(\pm 0.50)}{1.107} \log P + \underset{(\pm 0.77)}{1.237} \quad (25)$$

consideration. The very small role of ionization in the egg cell division study can also be neglected. This study was made at pH 8. This alkaline pH would exaggerate the effects due to ionization. The studies on brain tissue were made between pH 7.3 and 8 so that they are not too different from the cell division study. The lack of more precise pH control in this study may account for the apparent independence of eq 13–18 on ΔpK_a. Neglecting these two factors, one is struck by the close correspondence of the constants in eq 8 and 13. Both the slopes and intercepts of the two equations fall in the range covered by the confidence intervals. The fact that the intercepts are the same could be more fortuitous since this constant would be so dependent on experimental conditions. However, in this connection it is of interest to note that it was the point of 50% inhibition which was measured in each system. Moreover, it was observed that when the egg cell division was reduced by 50%, respiration wa reduced 30%. Thus it seems very likely that the same enzyme system is being acted on in each case.

Giuditta and Di Prisca[20] measured the inhibition of NADH oxidation in beef heart mitochondria by barbiturates. Although the correlation is not as sharp as with the other two systems, the slopes and intercepts of eq 25 are very close to those of eq 8 and 13. In summary, studies from three distinctly different biological systems using different kinds and numbers of barbiturate derivatives yield equations having slopes and intercepts which are almost identical. It is apparent that the structural feature of overwhelming importance in the above barbiturate studies is the lipophilic character.

The close agreement among the three barbiturate studies, as well as many good correlations in other systems,[3-5] encouraged us to use our octanol–water reference system for the comparison of barbiturates with other narcotics which might also inhibit oxidative processes such as that represented in eq 25. For this purpose we have selected studies in which rather large numbers of compounds were tested in situations which might be comparable to those of the barbiturates.

A biochemical system in which it has been possible to make careful quantitative measurements is that of bacterial luminescence.[21,22] It is also known that barbiturates and other hypnotics inhibit this phenomenon.[36]

From the data in Table V we have derived eq 27–29 for the inhibition of luminescence by alcohols and urethans. For the three sets of data we find extremely good correlations between inhibition and lipophilic character. The slopes of the equations are all close to 1 as found for the barbiturates.

(36) W. D. McElroy, *J. Cellular Comp. Physiol.*, **21**, 95 (1943).

In a recent study, Rang[23] investigated the 50% inhibition of four biochemical processes by alcohols. Equations 30–33 are derived from his data in Table VI. Again we find extremely high dependence between biological action and lipophilic character and, with the exception of inhibition of histamine release, the slopes are essentially 1. The histamine inhibition by alcohols also seems distinctly different from the other alcohol inhibitions because of its much greater intercept. For three of the five alcohol inhibitions (inhibition of luminescence, paramecium mobility, lung oxygen consumption), the intercepts as well as the slopes are essentially the same. This strongly suggests that the same mechanism of action is involved. In the fourth example, that of gut contractility, the intercept is slightly higher. However, this difference is small considering the disparity in the nature of the tests.

	n	r	s	
alcohol inhibition of luminescence[21]				
$\log (1/C) = \underset{(\pm 0.06)}{1.171} \log P + \underset{(\pm 0.10)}{0.223}$	8	0.998	0.100	(27)
urethan inhibition of luminescence[21]				
$\log (1/C) = \underset{(\pm 0.27)}{1.116} \log P + \underset{(\pm 0.20)}{0.175}$	5	0.986	0.168	(28)
urethan 50% inhibition of luminescence[22]				
$\log (1/C) = \underset{(\pm 0.16)}{1.240} \log P + \underset{(\pm 0.16)}{1.323}$	6	0.993	0.147	(29)
alcohol 50% inhibition of paramecium mobility[23]				
$\log (1/C) = \underset{(\pm 0.05)}{0.955} \log P + \underset{(\pm 0.08)}{0.327}$	8	0.998	0.086	(30)
alcohol 50% inhibition of lung O_2 consumption[23]				
$\log (1/C) = \underset{(\pm 0.08)}{0.904} \log P + \underset{(\pm 0.11)}{0.163}$	7	0.995	0.106	(31)
alcohol 50% inhibition of gut contractility[23]				
$\log (1/C) = \underset{(\pm 0.07)}{1.060} \log P + \underset{(\pm 0.11)}{0.621}$	8	0.997	0.113	(32)
alcohol 50% inhibition of histamine release[23]				
$\log (1/C) = \underset{(\pm 0.05)}{0.721} \log P + \underset{(\pm 0.06)}{1.050}$	7	0.997	0.063	(33)

It is of interest to compare the above equations for closely related sets of congeners with more complex mixed sets. Equation 34 is derived from Führer's data in Table VII on the inhibition of frog heart action, eq 35 comes from the data of Overton on the narcosis of tadpoles, eq 36 comes from the data in Table VIII on the narcosis of frog muscle, eq 37 and 38 are derived from Table IX for tadpoles, and eq 39 comes from the data in Table X on the induction of C-mitosis in onions.

The slopes for eq 34–39 are very close to those for eq 8, 13, and 25–33 indicating quantitatively the similarity of mechanism of action as defined by the octanol–water reference system. Equation 35 has been rederived using improved log P values,[32] and a slightly better correlation than our previous one[16] is obtained. The average value and the standard deviation for the slopes for the above 11 equations (omitting eq 33 and 38) is 1.03 ± 0.13. The good correlations and the consistent value of 1 for the slope in the 11 examples is evidence that the octanol–water model is a satisfactory one to represent the aqueous and lipophilic biophases.

The meaning of the intercept is hard to interpret.

	n	r	s	
narcotic action of miscellaneous aliphatic compounds on frog heart[25]				
$\log (1/C) = 0.933 \log P + 0.108$ (± 0.07) (± 0.10)	28	0.975	0.182	(34)
narcotic action on tadpoles[15]				
$\log (1/C) = 0.875 \log P + 0.797$ (± 0.061) (± 0.08)	28	0.979	0.169	(35)
narcotic action of aromatic and aliphatic compounds on frog muscle				
$\log (1/C) = 0.903 \log P + 0.662$ (± 0.08) (± 0.15)	23	0.972	0.242	(36)
narcosis of tadpoles[26]				
$\log (1/C) = 1.172 \log P + 0.685$ (± 0.09) (± 0.12)	17	0.987	0.204	(37)
narcosis of tadpoles by carbamates[26]				
$\log (1/C) = 1.343 \log P + 1.611$ (± 0.32) (± 0.22)	5	0.985	0.192	(38)
C-mitosis in allium root tips[27]				
$\log (1/C) = 0.961 \log P + 0.560$ (± 0.11) (± 0.19)	19	0.963	0.340	(39)

Comparing intercepts means comparing congeners whose octanol-water partition coefficients are 1 (*i.e.*, $\log P = 0$). Hence, *test systems being equal*, the larger the intercept, the more active the set of congeners (assuming the slopes are the same). For example, comparing eq 34 and 35 where the slopes are the same, we find two different intercepts. Since such a miscellaneous group of compounds was covered in each test, it seems unreasonable to say that one set is basically more active than the other. The more logical rationalization is that the tadpole test is more sensitive than the frog heart test. The barbiturates are more potent inhibitors by this test, being roughly five times stronger than the alcohols. That is, the average intercept for the three equations 8, 13, and 25 is 1.09. The average intercept for the alcohols in eq 27 and 30–32 is 0.333. The antilog of the difference is about 5. The value of $\log (1/C)$ for diethylbarbituric acid was measured on the frog heart test and found to be 1.57 (Table VII). Log $(1/C)$ for this molecule in Tables I, II, and IV is 1.49, 1.32, and 1.96 (av = 1.59). This molecule does indicate the mechanism of action to be the same in the heart as in the other systems.

Comparison of the intercepts of eq 37 and 38 indicates that the carbamates, like the barbiturates, are more potent narcotics when one compares them with isolipophilic congeners such as alcohols, esters, hydrocarbons, alkyl halides, etc.

Equation 39 correlates the activity of organic compounds in causing colchicine-like mitosis in plants. Östergren and others[27] have pointed out the great similarity between the compounds causing such mitosis and the nonspecific narcotics. Equation 39 makes quantitative comparison possible. The similarity of slope and intercept is indeed very striking. Diethylbarbituric acid is about two times more active in C-mitotic induction than the average molecule in Table X. Ethyl carbamate is only slightly more active.

Anderson[37] has recently made an extensive survey of the relation between CNS depressants and C-mitotic agents emphasizing the similarity pointed out by Östergren. Anderson concludes that narcotic and C-mitotic agents may both interfere with electron-transport systems in aerobic metabolism.

(37) N. B. Anderson, *Acta Anesthesiol. Scand. Suppl.*, **22**, 3 (1966).

The narcotic response may be brought about by molecular interaction of narcotics with proteins or lipoprotein complexes. Again, the octanol–water reference system can be of help in making distinctions by allowing a comparison of the dependence of narcotic action on $\log P$ with the dependence of the binding of organic compounds to proteins on $\log P$. We have shown[31] that the 1:1 binding of barbiturates with bovine serum albumin (BSA) is well correlated with $\log P$ according to eq 40. The slope of eq 40 is close

	n	r	s	
$\log (1/C) = 0.58 \log P + 2.40$	4	0.961	0.137	(40)

to that of 0.68 found for the binding of phenols to BSA and 0.67 found for the binding of miscellaneous organic compounds to bovine hemoglobin.[38]

Goldbaum and Smith,[39] from whose work eq 36 stems, also studied the binding of barbiturates to a variety of rabbit tissues. From $\log P$ values from Table I for allyl-1-methylbutyl-, ethyl-1-methylbutyl-, ethylphenyl-, and diethylbarbituric acids and from the log (% bound) data[39] we have derived eq 41–49 in Table XI for the dependence of tissue binding on $\log P$.

TABLE XI

BINDING OF BARBITURATES BY RABBIT TISSUE HOMOGENATES

Type of tissue	Log (% bound)	n	r	s	
Undiluted plasma	$0.392 \log P + 0.978$ (± 0.16) (± 0.26)	4	0.981	0.063	(41)
Red cells	$0.490 \log P + 0.402$ (± 0.12) (± 0.20)	4	0.993	0.048	(42)
Liver	$0.441 \log P + 0.792$ (± 0.19) (± 0.32)	4	0.978	0.077	(43)
Muscle	$0.459 \log P + 0.504$ (± 0.24) (± 0.40)	4	0.969	0.010	(44)
Brain	$0.526 \log P + 0.467$ (± 0.14) (± 0.23)	4	0.992	0.056	(45)
Diluted plasma	$0.527 \log P + 0.544$ (± 0.19) (± 0.31)	4	0.986	0.074	(46)
Kidney	$0.544 \log P + 0.468$ (± 0.21) (± 0.35)	4	0.983	0.084	(47)
Lung	$0.601 \log P + 0.350$ (± 0.20) (± 0.33)	4	0.987	0.080	(48)
Heart	$0.648 \log P + 0.358$ (± 0.36) (± 0.59)	4	0.966	0.142	(49)

The correlations between binding and lipophilic character are quite good as measured by r. However, because of the few points and the experimental error, the confidence intervals are broad enough so that they all overlap the average slope of 0.51. Except for the undiluted plasma, the confidence intervals on the intercepts all overlap the average value of 0.54. Although the data are not strictly comparable, it is notable that the average slope of 0.51 agrees closely with that of 0.58 in eq 40. The results embodied in eq 41–49 indicate the binding of barbiturates to miscellaneous proteinaceous material has about the same dependence on $\log P$ as the binding to pure BSA. Also, the type of binding is very close to that which we have found for neutral compounds with BSA and hemoglobin. The adsorption of neutral organic compounds to proteins

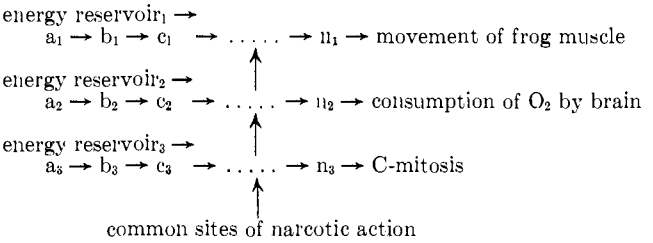
(38) K. Kiehs, C. Hansch, and L. Moore, *Biochemistry*, **5**, 2602 (1966).

(39) L. R. Goldbaum and P. K. Smith, *J. Pharmacol. Exptl. Therap.*, **111**, 197 (1954).

is a surprisingly uniform process with the slopes of dependence on log P falling in the range of 0.5–0.7 for those systems so far studied. This is quite a different dependence on hydrophobic character than we find in eq 8, 13, 25, and 27–39 and *suggests* that the simple adsorption of narcotics onto proteins is not the cause of narcotic action. It does not eliminate the possibility that perturbation of a protein by hydrophobic bonding is the cause of narcosis.

From the above studies as well as our previous ones, sufficient data have accumulated to show that the octanol–water model suggested from the work of Collander is a very useful reference system with which to study the interaction of organic compounds with biochemical systems. The exact meaning of such correlations is not clear. There are at least two important aspects. No doubt increasing lipophilic character, up to a point,[28] facilitates movement of the narcotics through lipophilic biophases onto the sites of action. However, the ultimate measured response is most likely brought about by interaction with an enzyme or lipoprotein membrane which might or might not be supporting enzymes. In such material, hydrophobic interactions could easily produce conformational perturbations[40] which could disrupt cellular processes. The great variety of saturated and unsaturated, aliphatic and aromatic molecules in Tables I–X have nothing in common except relative lipophilic character. It is difficult to imagine a common mechanism of action other than solution in a lipoidal membrane. The slopes of essentially 1 in the 14 above examples in which the measured responses are so extremely different imply that a common rate-limiting step is being influenced. The fact that so many different processes have the same dependence on log P and, except for the slightly greater activity of barbiturates and carbamates, the same concentration of isolipophilic compounds produce the same response would indicate that the mechanism of interference in the biophase is exactly like the transfer of the compound from water to octanol. All of the processes being inhibited are energy-requiring processes and we might illustrate the problem in the following diagrammatic way. Certainly all of the steps a → n in the energetic processes shown cannot be the same. The observer watching egg cell division, DPNH

(40) B. Belleau, *J. Med. Chem.*, **7**, 776 (1964).



oxidation, etc., categorizes each molecule's activity on the basis of an ultimate response very likely many steps removed from the site of inhibition.

Considerable evidence has accumulated to indicate that narcotics and C-mitotic agents inhibit oxidative metabolism through interference with electron transport.[20,37,41–44] This appears to us to be a most attractive working hypothesis for the mechanism of narcotic action. Such interference could easily be the result of slight conformational changes in a membrane which would, to varying degrees, disrupt the flow of electrons. The lipoidal material would seem to be rather loosely structured and very similar in nature or else one would not always get the same change in response for a given $\Delta(\log P)$.

To account for the difference in intrinsic activity of the barbiturates or the carbamates, one would assume that a more specific interaction of these functions with polar counterparts in a lipoprotein matrix would give leverage to the hydrophobic interactions so that a greater conformational change would be produced by molecules with no more hydrophobic bonding power (as defined by log P).

In summary, we can say that the use of a standard set of substituent constants allows us to make precise comparisons between different drugs acting in the same system and the same drugs acting in different systems. As more such correlations are made, they should form the basis for a quantitative approach to pharmacodynamics.

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(42) J. H. Quastel, *Pharmacol. Rev.*, **17**, 198 (1965).
(43) W. N. Aldridge and V. H. Parker, *Biochem. J.*, **76**, 47 (1960).
(44) B. Chance and G. Hollunger, *J. Biol. Chem.*, **238**, 419 (1963).