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The Parabolic Dependence of Drug Action upon Lipophilic Character as Revealed by a Study of Hypnotics

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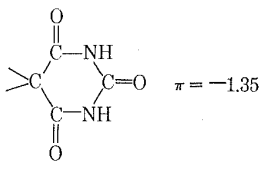
Evidence is presented that the hypnotic activity of groups of barbiturates depend almost entirely on their relative lipophilic character as defined by their octanol–water partition coefficients. Ideal lipophilic character is defined for each set by the constant log P_0. This constant for the barbiturates is about 2. It is shown that many other sets of hypnotics structurally unrelated to the barbiturates also have log P_0 values near 2. It is also shown that the rate of metabolism of barbiturates is linearly related to their partition coefficients. Certain guidelines are suggested for the design of new CNS depressants.

It has long been known that the relative activity of drugs in a series of congeners is highly dependent on their lipophilic character. It has also been appreciated tacitly that linear relations between relative activity and lipophilic character do not hold indefinitely as the latter continues to increase. However, with the exception of the efforts by Ferguson[3] to rationalize this fall of activity which inevitably occurs when derivatives of a parent drug are made sufficiently lipophilic, most workers have ignored the problem or assumed that it was too unruly to deal with in precise terms. Our working hypothesis has assumed[4–6] that such fall-off in activity was the result of the decrease in mobility of drug movement through biological material when one departed in either direction from ideal lipophilic character. That is, assuming all other factors except lipophilic character to be constant for a given set of congeners producing a specific biological reaction, there should exist for the set an ideal balance between hydrophobic and hydrophilic interactions of the drug so that those members possessing this ideal balance would find the sites of action through a random-walk process in the minimum time. Or, to put it another way, the concentrations of these drugs reaching the reaction sites in the test interval, Δt, would be maximum for the set. We have chosen 1-octanol and water to represent the two extremes of the biophase. The partition coefficient, P, is a measure of the preference of drugs for hydrophilic or lipophilic phase. Equation 1 formulates our model. In eq 1, C is the molar concentration of applied drug producing a standard biological response and k, k', and k'' are constants obtained *via* the method of least squares. Setting the derivative d log $(1/C)$/d log P equal to zero and solving the resulting equation for log P yields what we have termed log P_0, the ideal lipophilic character for the set of congeners under the specific test conditions. We have postulated[6–8] that this should be a particularly useful constant in drug research. For example, once log P_0 or π_0 is found for a group of congeners, one has a meaningful point from which to start the design of a completely new set of congeners to cause the same response. The purpose of this paper is to examine a variety of different hypnotics by fitting the experimental results to eq 1 and to compare the log P_0 values for the different sets. Hypnotics were chosen because of the large amount of experimental data in the literature. Even so, we were surprised by the paucity of examples in which sufficient spread in activity was investigated and quantitatively reported, so that log P_0 could be calculated with any degree of certainty.

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

Method

In a preliminary report on barbiturates,[7] we correlated substituent effects for a single series using π values for substituents and log P for barbituric acid as our base of reference. In a subsequent study[9] we used



$\pi = -1.35$

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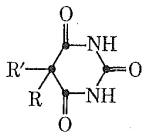
(2) Smith Kline and French Research Associate.
(3) J. Ferguson, *Proc. Roy. Soc.* (London), **B127**, 387 (1939).
(4) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963).
(5) C. Hansch and T. Fujita, *ibid.*, **86**, 1616 (1964).
(6) C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacology*, in press.
(7) C. Hansch, A. R. Steward, and J. Iwasa, *ibid.*, **1**, 87 (1965).
(8) C. Hansch, Proceedings of the International Congress on Pharmacology, Sao Paulo, Brazil, 1966.

TABLE I

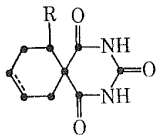
OBSERVED AND CALCULATED CONCENTRATIONS OF BARBITURATES CAUSING HYPNOSIS



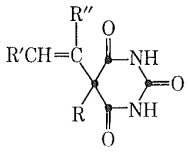
No.	R	R′	Log P	Log (1/C) Obsd[a]	Log (1/C) Calcd[b]	$\lvert\Delta$ Log (1/C)$\rvert$
1	Methyl	1-Methyl-1-propenyl	0.65	2.64	2.767	0.13
2	Ethyl	1-Methyl-1-propenyl	1.15	3.15	3.163	0.01
3	Propyl	1-Methyl-1-propenyl	1.65	3.29	3.340	0.05
4	Allyl	1-Methyl-1-propenyl	1.35	3.39	3.260	0.13
5	Butyl	1-Methyl-1-propenyl	2.15	3.36	3.298	0.06
6	Methyl	1-Methylvinyl	0.15	2.12	2.153	0.03
7	Ethyl	1-Methylvinyl	0.65	2.91	2.767	0.14
8	Propyl	1-Methylvinyl	1.15	3.04	3.163	0.12
9	Allyl	1-Methylvinyl	0.85	3.06	2.952	0.11
10	Butyl	1-Methylvinyl	1.65	3.33	3.340	0.01
11	Isobutyl	1-Methylvinyl	1.45	3.27	3.296	0.03
12	Amyl	1-Methylvinyl	2.15	3.32	3.298	0.02
13	Isoamyl	1-Methylvinyl	1.95	3.26	3.341	0.08
				Obsd[c]	Calcd[d]	
14	Ethyl	Ethyl	0.65[r]	3.09	3.012	0.08
15	Propyl	Propyl	1.65	3.55	3.656	0.11
16	Propyl	Isopropyl	1.45	3.63	3.628	0.00
17	Butyl	Butyl	2.65	2.84	3.040	0.20
18	Ethyl	Isopropyl	0.95	3.30	3.338	0.04
19	Ethyl	Isobutyl	1.45	3.63	3.628	0.00
20	Ethyl	Butyl	1.65	3.72	3.656	0.06
21	Ethyl	Isoamyl	1.95	3.75	3.604	0.15
22	Propyl	Isoamyl	2.45	3.48	3.264	0.22
23	Ethyl	Phenyl	1.42[r]	3.46	3.620	0.16
24	Ethyl	*sec*-Butyl	1.45	3.63	3.628	0.00
				Obsd[e]	Calcd[f]	
25	Ethyl	1-Methylbutyl	1.95	4.05	3.976	0.07
26	Ethyl	1-Ethylbutyl	1.95	3.95	3.976	0.03
27	Methyl	1-Methylbutyl	1.45	3.63	3.686	0.06
28	Propyl	1-Methylbutyl	2.45	3.90	4.001	0.10
29	Propyl	1-Ethylpropyl	2.45	3.78	4.001	0.22
30	Allyl	1-Methylbutyl	2.15	4.20	4.018	0.18
31	Allyl	1-Ethylpropyl	2.15	4.08	4.018	0.06
32	Butyl	1-Methylbutyl	2.95	3.86	3.763	0.10
33	Butyl	1-Ethylpropyl	2.95	3.75	3.763	0.01
				Obsd[g]	Calcd[h]	
34	Ethyl	2-Methylallyl	1.15	3.23	3.252	0.02
35	Propyl	2-Methylallyl	1.65	3.27	3.369	0.10
36	Isopropyl	2-Methylallyl	1.45	3.35	3.333	0.02
37	Butyl	2-Methylallyl	2.15	3.38	3.401	0.02
38	Isobutyl	2-Methylallyl	1.95	3.36	3.399	0.04
39	*sec*-Butyl	2-Methylallyl	1.95	3.42	3.399	0.02
40	Amyl	2-Methylallyl	2.65	3.26	3.346	0.09
41	*sec*-Amyl	2-Methylallyl	2.45	3.62	3.379	0.24
42	2-Methylbutyl	2-Methylallyl	2.45	3.34	3.379	0.04
43	3-Methylbutyl	2-Methylallyl	2.45	3.36	3.379	0.02
44	1-Ethylpropyl	2-Methylallyl	2.45	3.50	3.379	0.12
45	Hexyl	2-Methylallyl	3.15	3.18	3.205	0.03
46	2-Ethylbutyl	2-Methylallyl	2.95	3.25	3.272	0.02
47	Cyclopentyl	2-Methylallyl	2.29	3.40	3.394	0.01
48	Allyl	2-Methylallyl	1.35	3.44	3.309	0.13
49	2-Methylallyl	2-Methylallyl	1.65	3.37	3.369	0.00
50	Phenyl	2-Methylallyl	1.92	3.24	3.397	0.16
				Obsd[i]	Calcd[j]	
51	Allyl	Allyl	1.05	3.54	3.392	0.15
52	Ethyl	Allyl	0.85	3.28	3.238	0.04
53	Propyl	Allyl	1.35	3.47	3.540	0.07
54	Isopropyl	Allyl	1.15	3.60	3.452	0.15
55	Butyl	Allyl	1.85	3.47	3.570	0.10
56	Isobutyl	Allyl	1.65	3.63	3.591	0.04

TABLE I (*Continued*)

No.	R	R′	Log *P*	Log (1/*C*) Obsd[i]	Log (1/*C*) Calcd[j]	|Δ Log (1/*C*)|
58	Isoamyl	Allyl	2.15	3.45	3.457	0.01
59	Ethyl	Ethyl	0.65[r]	2.91	3.041	0.13
60	Butyl	Ethyl	1.65	3.53	3.591	0.06
61	Isopropyl	Ethyl	0.95	3.34	3.320	0.02
62	Isoamyl	Ethyl	1.95	3.59	3.543	0.05
63	Butyl	Isopropyl	1.95	3.49	3.543	0.05
64	Butyl	Butyl	2.65	3.08	3.051	0.03
65	Phenyl	Ethyl	1.42[r]	3.32	3.561	0.24
				Obsd[k]	Calcd[l]	
66	Propyl	1-Propenyl	1.35	3.12	3.191	0.07
67	Isopropyl	1-Propenyl	1.15	3.28	2.976	0.30
68	Butyl	1-Propenyl	1.85	3.31	3.485	0.18
69	Ethyl	1-Butenyl	1.35	3.37	3.191	0.18
70	Propyl	1-Butenyl	1.85	3.31	3.485	0.18
71	Isopropyl	1-Butenyl	1.65	3.57	3.409	0.16
72	Butyl	1-Butenyl	2.35	3.56	3.435	0.12
73	Ethyl	2-Methyl-1-propenyl	1.15	2.56	2.976	0.42
74	Ethyl	1-Pentenyl	1.85	3.45	3.485	0.04
75	Isopropyl	1-Pentenyl	2.15	3.50	3.497	0.00
76	Ethyl	3-Methyl-1-butenyl	1.65	3.51	3.409	0.10
77	Propyl	3-Methyl-1-butenyl	2.15	3.32	3.497	0.18
78	Isopropyl	3-Methyl-1-butenyl	1.95	3.68	3.503	0.18



No.	R	Ring	Log *P*	Log (1/*C*) Obsd[m]	Log (1/*C*) Calcd[n]	|Δ Log (1/*C*)|
79	Methyl	Unsatd[o]	0.75	2.69	2.690	0.00
80	Ethyl	Unsatd[o]	1.25	2.96	3.090	0.13
81	Propyl	Unsatd[o]	1.75	3.27	3.372	0.10
82	Isopropyl	Unsatd[o]	1.55	3.28	3.273	0.01
83	3,4,5-Trimethyl	Unsatd[o]	1.55	3.13	3.273	0.14
84	Methyl	Satd	1.05	3.06	2.944	0.12
85	Ethyl	Satd	1.55	3.33	3.273	0.06
86	Propyl	Satd	2.05	3.65	3.485	0.16
87	Isopropyl	Satd	1.85	3.55	3.414	0.14
88	Isobutyl	Satd	2.35	3.45	3.555	0.11



No.	R	R′	R″	Log *P*	Log (1/*C*) Obsd[p]	Log (1/*C*) Calcd[q]	|Δ Log (1/*C*)|
89	Methyl	Ethyl	Methyl	1.15	3.21	3.125	0.09
90	Ethyl	Ethyl	Methyl	1.65	3.65	3.439	0.21
91	Propyl	Ethyl	Methyl	2.15	3.56	3.632	0.07
92	Isopropyl	Ethyl	Methyl	1.95	3.98	3.569	0.41
93	Methyl	Methyl	Ethyl	1.15	3.06	3.125	0.07
94	Ethyl	Methyl	Ethyl	1.65	3.40	3.439	0.04
95	Propyl	Methyl	Ethyl	2.15	3.42	3.632	0.21
96	Isopropyl	Methyl	Ethyl	1.95	3.72	3.569	0.15
97	Methyl	Propyl	Methyl	1.65	3.27	3.439	0.17
98	Ethyl	Propyl	Methyl	2.15	3.64	3.632	0.01
99	Methyl	Isopropyl	Methyl	1.45	3.20	3.328	0.13
100	Methyl	Butyl	Methyl	2.15	3.38	3.632	0.25
101	Ethyl	Butyl	Methyl	2.65	3.75	3.706	0.04
102	Ethyl	Ethyl	Propyl	2.65	3.75	3.706	0.04

[a] From ref 14. [b] Calculated using eq 2. [c] From ref 15. [d] Calculated using eq 3. [e] From ref 16. [f] Calculated using eq 4. [g] From ref 17. [h] Calculated using eq 5. [i] From ref 18. [j] Calculated using eq 6. [k] From ref 19. [l] Calculated using eq 7. [m] From ref 20. [n] Calculated using eq 8. [o] Unsatd indicates that the spirane ring contains a double bond in the position indicated by the dotted line. Satd means the ring was saturated. [p] From ref 21. [q] Calculated using eq 9. [r] These values for log *P* were experimentally determined;

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