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Comparative Study of Lipophilicity *versus* Topological Molecular Descriptors in Biological Correlations

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Abstract □ This paper analyzes the relative efficacies of lipophilicity *vis-à-vis* topological indices in the correlation of the biological properties of four groups of bioactive molecules: alcohols, barbiturates, triazinones, and ketobemidones. Wiener number (W), information-theoretic topological parameters (IC, SIC, CIC, I_D^w, and $\bar{I}_D^w$), and molecular connectivity indices ($^1\chi$, $^1\chi^v$) were used as the molecular descriptors. Results show that theoretical indices are comparable or superior to log P in biological correlations.

Keyphrases □ Lipophilicity—correlations with topological molecular descriptors, assessment of the biological activity of diverse molecules □ Biological activity—comparison of lipophilicity with topological molecular descriptors, diverse molecules □ Topology—molecular descriptors, comparison with lipophilicity, assessment of the biological activity of diverse molecules

In contemporary biomedicinal chemistry, quantum chemical (1–4), physicochemical (5–7), and topological (8–21) parameters have been extensively utilized in the prediction of biological activity of molecules. While quantum chemical descriptors provide the most accurate numerical information regarding molecular architecture, the complexity of many bioactive molecules precludes the possibility of the extensive use of these methods in drug design (8). The problem reaches a staggering dimension when one considers the enormous number of candidate structures derivable from a pharmacological "lead" by means of probable molecular manipulations (22).

To resolve this impasse attempts have been directed at developing methods that contribute reasonably accurate and practical information at a level less comprehensive than the quantum chemical treatment (8). The extrathermodynamic linear free energy relationship (LFER) approach, derived from physical organic chemistry, and topological indices defined on the chemical graph of the molecule, appear to provide convenient model systems in relating chemical structure to biological functions.

The LFER approach, usually termed Hansch analysis, relies on the basic premise that complex physicochemical interactions between pharmacological and biological targets under *in vitro* and *in vivo* conditions can be quantitatively expressed in terms of multiparametric regression models involving steric, electronic, hydrophobic, and other substituent constants (6, 7). The outcome of a large number of quantitative structure–activity relationship (QSAR) studies of the Hansch type indicates the predominant role of hydrophobicity (log P or π) in determining the action of a large variety of nonspecific bioactive molecules. On the other hand, stereoelectronic variables seem to be crucial for the physiological action of molecules that act *via* specialized enzyme or receptor systems (23). However, a number of studies show that steric, electronic, and hydrophobic factors have an appreciable degree of interdependence on each other. For a group of aromatic molecules, Rogers and Cammarata (24) found log P to be positively correlated with ΣS_r, the sum of the electrophilic superdelocalizabilities for the aryl atoms, and negatively correlated with $\Sigma|Q_r|$, the sum of the π-electron charge densities. Fujita (25) discussed the inherent difficulty in the complete separation of the hydrophobic and steric effects of substituents arising out of the internal correlation between these two classes of substituent constants. Van der Waals' volume (V_w), a steric factor, is well correlated with log P for a wide variety of compounds (26). Also, the different topological steric descriptors have appreciable correlation with log P (8, 15, 17, 20). These studies indicate that some common structural features affect the steric, electronic, and hydrophobic factors in an unknown manner. Moreover, it has been pointed out that although the Hansch approach is a valid QSAR model for the closely related congeners, it cannot account for the common biological properties of molecules with considerable structural diversity (27).

These considerations necessitated the development of substructural (27–29) and topological methods (8) to determine a direct relationship between chemical structure and biological action. In particular, QSAR literature of recent years shows

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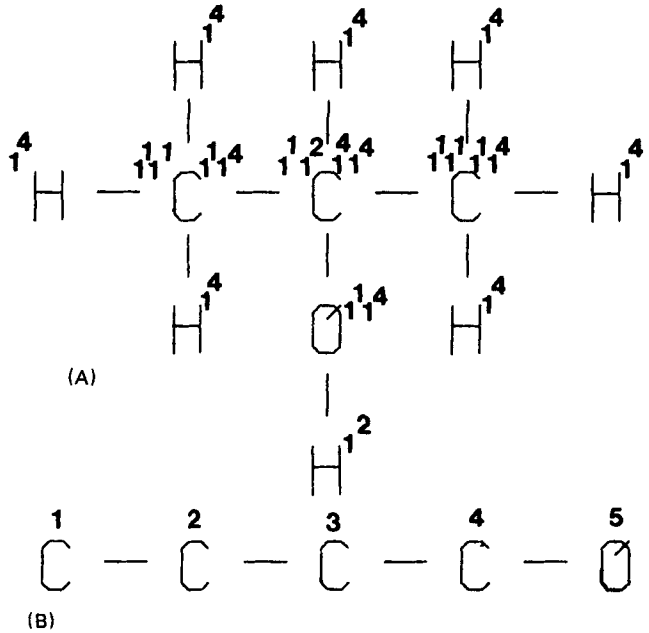


Figure 1—*(A) Coordinate-attached structure for 2-propanol. The coordinate notation $1^1 1^2 1^4 1^4$ for C-2 means that this carbon atom is singly bonded to four atoms whose valences are 1, 2, 4, and 4. (B) The labeled graph for 1-butanol.*

the progressive reliance on various topological indices as convenient structural parameters for correlational studies in chemistry (8, 30) and biology (8–21). Although a topological index is likely to be inherently steric in nature by virtue of being a numerical descriptor of molecular shape and size (8, 21), the most important progress in this area has been the development of topological structural parameters capable of expressing the electronic properties of molecules (31, 32).

One of the necessary preconditions of successful QSAR analysis is the availability of a set of parameters with minimum overlap profile (21, 33). Therefore, it seemed fitting to study the relative efficacies of lipophilicity *vis-à-vis* steric descriptors in rationalizing pharmacological and toxicological properties. With this purpose we have investigated the utility of log P (octanol-water), information-theoretic topological indices (IC, SIC, CIC, I_D^v, $\bar{I}_D^w$), Wiener number (W), and molecular connectivity indices ($^1\chi$, $^1\chi^v$) in the quantitative correlation of the toxicity of alcohols, the analgesic property of ketobemidones, Hill reaction inhibitory potencies of triazinones, and the anesthetic action of three different groups of barbiturates.

EXPERIMENTAL

Source of the Hydrophobic Parameter (log P, Octanol-Water)—Log P values for the various congeneric series were taken either from the literature or calculated according to the method of Hansch and Leo (34).

Table I—Partitioning and Calculation of Information Indices (IC, SIC, and CIC) for 2-Propanol [a]

Partition Class with Coordinate	Number of Atoms in the Partitioned Class[b] (n_i)	Probability ($p_i = n_i/n$)
I 1^4	7	7/12
II 1^2	1	1/12
III $1^1 1^4$	1	1/12
IV $1^1 1^1 1^1 1^4$	2	2/12
V $1^1 1^4 1^4 1^2$	1	1/12

[a] $IC = 7/12 \log_2(12/7) + 2/12 \log_2(12/2) + 3 \times 1/12 \log_2(12) = 1.7807$ bits; $SIC = IC/\log_2(12) = 0.4967$; $CIC = 1/12[7 \log_2(7) + 2 \log_2(2) + 1 \log_2(1)] = 1.8043$ bits. [b] Total number of atoms in the molecule (n) = 12.

Table II—Distance Matrix D(G) of the Hydrogen-Suppressed Graph G of 1-Butanol

Atom	1	2	3	4	5
1	0	1	2	3	4
2	1	0	1	2	3
3	2	1	0	1	2
4	3	2	1	0	1
5	4	3	2	1	0

Calculation of Molecular Connectivity ($^1\chi$)—To each atom of the hydrogen-suppressed molecular graph, a δ value is assigned corresponding to the number of nonhydrogen atoms bonded to it. A connectivity value for a bond C_k (connecting atoms i and j) is computed as follows (8):

$$C_k = (\delta_i \delta_j)^{-1/2} \qquad \text{(Eq. 1)}$$

And finally, $^1\chi$ is calculated as the sum of all the individual connectivity terms:

$$^1\chi = \sum_k C_k \qquad \text{(Eq. 2)}$$

Calculation of Valence Molecular Connectivity ($^1\chi^v$)—To each atom of the hydrogen-depleted molecular skeleton, a δ^v value is assigned according to the formulation:

$$\delta^v = Z_i^v - h_i \qquad \text{(Eq. 3)}$$

where Z_i^v represents the number of valence electrons and h_i denotes the number of bonded hydrogen atoms for the ith atom in the labeled graph. Thereafter, $^1\chi^v$ is calculated as in the case of $^1\chi$ by substituting δ^v for δ in Eq. 1.

Calculation of Information-Theoretic Indices from the Molecular Graph—The statistical treatment of chemical structure by means of information theory relies on the basic premise that each structure contains a finite set of elements (n) that could be decomposed into disjoint subsets n_i ($i = 1, 2, \ldots, k$) by means of selected equivalence relations defined on the set. A probability scheme may then be attached to this distribution:

$$\begin{pmatrix} n_1, n_2, \ldots, n_k \\ p_1, p_2, \ldots, p_k \end{pmatrix}$$

where $p_i = n_i/n$ is the probability that a randomly selected element will lie in the ith subset. The entropy (or complexity) of the probability distribution of the elements of the set (or structure) can then be computed by means of Shannon's formula (35):

$$\text{Information Content} = -\sum_i p_i \cdot \log_2 p_i \text{ bits} \qquad \text{(Eq. 4)}$$

where the logarithm is taken at a basis 2 in order to measure the information in bits. Following the pioneering studies of Rashevsky (36) and Trucco (37, 38) on the topological information content of chemical graphs, various authors have defined information-theoretic indices and applied them to structure-property (15, 30, 39, 40) and structure-activity (15–20, 40) correlations.

In the formalism developed by Sarker *et al.* (41), Basak *et al.* (19, 42), and Raychaudhury *et al.* (43) the total (nonhydrogen-suppressed) molecular graph is used to define the various topological indices, and the method is sufficiently general to include linear graphs as well as multigraphs. On the basis of a first-order topological neighborhood, Sarker *et al.* (41) defined an equivalence relation which decomposes the vertex set $\mathbf{X}(G)$ of the molecular graph G into disjoint subsets, whereby the information content (IC) of the graph is computed as:

$$IC(\mathbf{X}(G)) = -\sum_i p_i \cdot \log_2 p_i \text{ bits}$$

Subsequently, Basak *et al.* (42) defined another information-theoretic index, structural information content (SIC):

$$SIC(\mathbf{X}(G)) = IC/\log_2 n \qquad \text{(Eq. 5)}$$

where n is the cardinality of $\mathbf{X}(G)$. In continuation of this work Raychaudhury *et al.* (43) developed another information-theoretic topological index, *viz* complementary information content (CIC):

$$CIC(\mathbf{X}(G)) = \frac{1}{n}\sum_{i=1}^{k} n_i \cdot \log_2 n_i \text{ bits} \qquad \text{(Eq. 6)}$$

The equivalence relation is a relation (defined on a set) that has the property of being reflexive, symmetric, and transitive. Such a relation partitions a set into nonempty and disjoint subsets. The probability scheme attached to such

Table III—Hydrophobicity, Toxicity (log LC_{50}), and Molecular Descriptors for Aliphatic Alcohols

Compound	log LC_{50}	log P	IC	SIC	CIC	$^1\chi$	$^1\chi^v$	W	I_D^w	$\bar{I}_D^w$
Methanol	−0.06	−0.77	1.7925	0.6934	0.7925	1.0000	0.4472	1	0.00	0.00
Ethanol	−0.51	−0.32	1.8800	0.5931	1.2900	1.4142	1.0233	4	6.00	1.50
2-Propanol	−0.80	0.14	1.7807	0.4967	1.8043	1.7320	1.4129	9	22.53	2.50
1-Butanol	−1.63	0.88	1.8716	0.4790	2.0353	2.4142	2.0233	20	62.93	3.15
1-Hexanol	−3.02	2.03	1.7206	0.3917	2.6717	3.4142	3.0233	56	233.46	4.17
1-Octanol	−4.00	3.15	1.6069	0.3379	3.1480	4.4142	4.0233	120	590.03	4.92
1-Nonanol	−4.40	3.65	1.5615	0.3182	3.3454	4.9142	4.5233	165	862.59	5.23
1-Decanol	−4.84	4.15	1.5220	0.3017	3.5224	5.4142	5.0233	220	1211.77	5.51
1-Undecanol	−5.22	4.65	1.4874	0.2877	3.6825	5.9142	5.5233	286	1648.26	5.76
1-Dodecanol	−5.27	5.15	1.4568	0.2756	3.8286	6.4142	6.0233	364	2183.03	6.00

Table IIIa—Correlation of the log LC_{50} with log P and Topological Indices (log $LC_{50} = a + bx + cx^2$)[a]

x	a	b	c	r	s	F
IC	−23.0	12.0	—	0.94	0.75	58.8
	−40.6	33.2	−6.34	0.94	0.80	26.4
SIC	−8.75	13.8	—	0.96	0.58	104
	−15.0	43.2	−31.3	0.99	0.21	422
CIC	1.98	−1.90	—	0.99	0.32	355
	0.730	−0.601	−0.272	0.99	0.23	353
$^1\chi$	0.839	−1.03	—	0.99	0.26	551
	1.64	−1.63	0.0822	0.99	0.13	1090
$^1\chi^v$	0.398	−1.02	—	0.99	0.26	544
	0.839	−1.44	0.0650	0.99	0.19	512
W	−1.19	−1.43E-2	—	0.91	0.91	37.7
	−0.585	−3.40E-2	5.97E-5	0.98	0.43	98.7
I_D^w	−1.39	−2.32E-3	—	0.88	1.03	27.5
	−0.822	−5.78E-3	1.77E-5	0.97	0.57	54.3
$\bar{I}_D^w$	0.842	−0.986	—	0.97	0.53	128
	.00776	−0.105	−0.138	0.99	0.20	456
log P	−0.842	−0.939	—	0.99	0.21	875
	−0.826	−1.14	4.75E-2	0.99	0.14	911

[a] In all cases the number of data points = 10.

decompositions of a set is, therefore, very much dependent on the nature of the equivalence relation. So, the information indices (IC, SIC, and CIC) of a chemical graph are not unique; rather the values of such indices are dependent on the mode of partition of the vertex set $\mathbf{X}(G)$ of the corresponding molecular graph G. In this paper we have computed IC, SIC, and CIC indices from the corresponding chemical graphs using an equivalence relation which is a slightly modified form of that used by Sarkar *et al.* (41). According to the equivalence relation used in this paper, two vertices of a chemical graph are said to be equivalent if they have similar edge multiplicity and the same number of first-order neighbors that have identical degrees (valence). If x represents an arbitrary element of the vertex set $\mathbf{X}(G)$ of a molecular graph G and r is a real number satisfying the relation $1 < r \leq 2$, then the open sphere $S(x,r)$ is given by:

$$S(x,r) = (x) \cup S_x^1 \qquad \text{(Eq. 7)}$$

where $S_x^1 = \{y \epsilon \mathbf{X}(G), d(x,y) = 1\}$ and (x) is the one-point set consisting of x only. If N be a set consisting of all such open spheres $S(x,r)$, where x runs over the whole set $\mathbf{X}(G)$, then N represents a collection of the first-order neighborhoods of all the vertices belonging to $\mathbf{X}(G)$.

Two vertices x and y of the vertex set $\mathbf{X}(G)$ will be called equivalent with respect to the first-order topological neighborhood if and only if:

1. $\mathbf{O}(S_x^1) = \mathbf{O}(S_y^1)$, where $\mathbf{O}(S_x^1)$ and $\mathbf{O}(S_y^1)$ represent the cardinalities of S_x^1 and S_y^1, respectively.
2. Corresponding to each element $x^i \epsilon S_x^1$ there exists an element $y^i \epsilon S_y^1$ such that $E[x,x^i] = E[y,y^i]$, where $E[x,x^i]$ denotes the number of edges connecting x and x^i, while $E[y,y^i]$ represents the number of edges of G connecting y and y^i; and
3. x^i and y^i have the same degrees (valence) for all i.

This theoretical scheme for the realization of the partition of atoms is exemplified along with the coordinate-attached structure of 2-propanol (Fig. 1A) and the calculation of its IC, SIC, and CIC indices (Table I) from the consideration of first-order topological neighborhood.

The Wiener number (W), proposed by Wiener (44), was the first topological index and represents the sum of all possible topological distances of a hydrogen-suppressed molecular graph. W can be conveniently calculated from the distance matrix $\mathbf{D}(G)$ of any graph G. It is a square $N \times N$ matrix, where N is the number of vertices in the hydrogen-depleted graph, the entries of the matrix being $d_{ij} = d_{ji}$, d_{ij} representing the number of bonds between vertices i and j by the shortest path. Table II shows the distance matrix of the labeled graph of 1-butanol (Fig. 1B). From the distance matrix, W is computed as:

$$W = \sum_{ij} d_{ij}/2 \qquad \text{(Eq. 8)}$$

The information indices from the distance matrix arise out of the statistical treatment of the topological distances of the chemical graph through the formalism of information theory (39). The index (I_D^w) is defined as:

$$I_D^w = W \cdot \log_2 W - \sum(k_d)(d \cdot \log_2 d) \qquad \text{(Eq. 9)}$$

where the distance d appears k_d times in the partition. The mean information index ($\bar{I}_D^w$) is calculated as:

$$\bar{I}_D^w = I_D^w / W \qquad \text{(Eq. 10)}$$

Statistical Analysis—Regression analysis was carried out according to the method of Nie *et al.* (45).

RESULTS AND DISCUSSION

Toxicity of Alcohols—The characteristic toxic action of aliphatic alcohols probably is narcosis (46). Veith *et al.* (47) reported that the aquatic toxicity (96 h LC_{50}) of alkanols in *Pimephales promelas* is highly correlated with log P (octanol-water) in terms of a bilinear model (48). However, Basak and Magnuson (19) showed that CIC can account for the toxicity of alcohols in a significant manner. It was of interest, therefore, to carry out a comparative study of log P *vis-à-vis* various structural parameters in the correlation of the LC_{50} of alcohols.

Table III shows the log LC_{50}, log P, IC, SIC, CIC, $^1\chi$, $^1\chi^v$, W, I_D^w, and $\bar{I}_D^w$ values for a series of 10 alkanols; the experimental log LC_{50} values were taken from Veith *et al.* (47). Table IIIa summarizes the results of the statistical analysis in an attempt to correlate log LC_{50} with log P and the different topological indices; r is the correlation coefficient, s the standard deviation, and F the F-ratio between the variances of observed and calculated values.

It appears from the results that a nonlinear fit shows significant improvement in the correlation coefficients as compared with the linear fits. The extent of fit of log LC_{50} values with log P and other structural parameters indicate that the topological indices (SIC, CIC, $^1\chi$, $^1\chi^v$, $\bar{I}_D^w$) are capable of explaining the properties of alcohols almost as efficiently as log P.

Analgesic Property of Ketobemidones—The opiate group of drugs is thought to bring about analgesia through the perturbation of certain types of specific receptors (49). The importance of lipophilicity for analgesic action is evident from the sharp decrease in the agonistic potency concomitant with quaterni-

Table IV—Hydrophobicity, Analgesic Potency (A-ED_{50}), and Molecular Descriptors for Ketobemidones (I)

R	A-ED_{50}, mM	log P	IC	SIC	CIC	$^1\chi$	$^1\chi^v$	W	I_D^w	$\bar{I}_D^w$
Methyl[a]	2.10	1.22	2.2949	0.4179	3.1970	8.5814	7.4814	558	3950.76	7.08
Ethyl	67.20	1.76	2.2305	0.3994	3.3544	9.1194	8.0575	662	4785.09	7.23
Propyl	16.00	2.30	2.1830	0.3848	3.4894	9.6194	8.5575	785	5781.87	7.36
Butyl	4.60	2.84	2.1385	0.3716	3.6164	10.1194	9.0575	928	6954.56	7.49
Pentyl	0.78	3.38	2.0970	0.3595	3.7359	10.6194	9.5575	1092	8316.82	7.62
Hexyl	7.50	3.92	2.0581	0.3484	3.8488	11.1194	10.0575	1278	9882.44	7.73
Heptyl	9.00	4.46	2.0218	0.3382	3.9555	11.6194	10.5575	1487	11665.27	7.84
Octyl	26.50	5.00	1.9878	0.3289	4.0566	12.1194	11.0575	1720	13679.22	7.95
Nonyl[a]	Inactive	5.54	1.9558	0.3202	4.1527	12.6194	11.5575	1978	10217.71	5.16

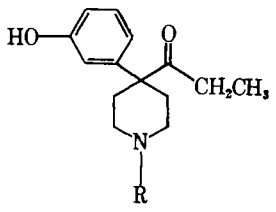
[a] Not included in the regression analysis.

Table IVa—Correlation of A-ED_{50} with log P and Topological Indices (A-$ED_{50} = a + bx + cx^2$)[a]

x	a	b	c	r	s	F
IC	$-2.54E+2$	$1.30E+2$	—	0.50	22	1.6
	$1.36E+4$	$-1.30E-4$	$3.11E+3$	0.97	7.2	29
SIC	$-1.48E+2$	$4.63E+2$	—	0.51	22	1.8
	$4.70E+3$	$-2.63E+4$	$3.67E+4$	0.97	6.5	36
CIC	$1.84E+2$	−44.5	—	0.49	22	1.6
	$5.28E+3$	$-2.80E+3$	$3.72E+2$	0.96	7.4	27
$^1\chi$	$1.20E+2$	−9.51	—	0.44	22	1.2
	$2.40E+3$	$-4.44E+2$	20.4	0.94	9.1	17
$^1\chi^v$	$1.10E+2$	−9.51	—	0.45	22	1.2
	$1.96E+3$	$-4.00E+2$	20.4	0.94	9.1	17
W	43.1	$-2.14E-2$	—	0.36	24	0.73
	$2.47E+2$	−0.400	$1.60E-4$	0.88	13	7.1
I_D^w	40.4	$-2.48E-3$	—	0.35	24	0.68
	$2.09E+2$	$-4.38E-2$	$2.25E-6$	0.88	14	6.6
$\bar{I}_D^w$	$3.42E+2$	−42.5	—	0.48	22	1.5
	$2.05E+4$	$5.35E+3$	$3.50E+2$	0.96	7.6	25
log P	48.6	−8.81	—	0.45	22	1.2
	$2.28E+2$	$-1.27E+2$	17.5	0.94	9.1	17

[a] In all cases, the number of data points = 7.

zation (50). It is proposed that hydrophobicity is critically important for the passage of opiates through the blood–brain barrier (51). In view of the fact that the mode of action for opiates is complicated by participation of various biogenic amine systems, different neuronal subpopulations, and multiple receptor types (52, 53), substituted ketobemidones (I) provide a convenient class of compounds for the study of the structure–activity relationships of opiates because the molecular manipulations within the group involve minimal alterations in the molecular electronic characteristics.



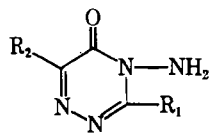
I

In an earlier study, Ray *et al.* (17) reported that SIC could correlate the analgesic potency (A-ED_{50}) of ketobemidones in mice. In view of the reportedly important role of lipophilicity in opiate pharmacology, we decided to study the relative efficacies of log P *vis-à-vis* other structural parameters in the correlation of the analgesic action of ketobemidones.

Table IV depicts the hot-plate analgesic potencies (A-ED_{50}) in mice, log P values, and the topological descriptors for a series of nine ketobemidones; the experimental A-ED_{50} values were taken from Wilson *et al.* (54). A look at the A-ED_{50} values indicates that there are two peaks of agonist activity in the series, namely when the side chain in the nitrogen atom is either methyl or amyl. Some of the higher homologues (hexyl, heptyl, and octyl) have measurable antagonist potencies (50), while the nonyl derivative has no analgesic property in the *in vivo* test. Under these circumstances we decided to delete the methyl and nonyl homologues of Table IV from the regression analysis. Table IVa represents the outcome of nonlinear regression analysis using log P as well as the topological indices. The linear correlations were not appreciable with any of the parameters. It is evident from the statistical analysis that the topological parameters IC, SIC, CIC, and $\bar{I}_D^w$ are superior to log P in the correlation of analgesic action while $^1\chi$ and $^1\chi^v$ appear to be as correlated as log P.

Herbicidal Action of Triazinones—Most herbicides are thought to exert their characteristic action through the blocking of the electron-transfer step in the oxygen-evolving photosynthesis process (55, 56). Therefore, in an attempt to design more effective herbicides, various authors have studied the effects of molecular manipulations on the Hill reaction inhibitory potencies of these compounds in isolated chloroplasts (55–59).

For a group of 1,2,4-triazinones, Hansch analysis revealed that lipophilicity (log P) alone was able to correlate the Hill reaction inhibitory potency (pI_{50}) in a significant manner (59). On the other hand, Ray *et al.* (17) reported that the information-theoretical topological index SIC could adequately account for the pI_{50} of triazinones. So it was deemed desirable to undertake a comparative study of log P and other theoretical parameters in the QSAR study of this class of herbicides.



II

The pI_{50}, log P, $^1\chi$, $^1\chi^v$, IC, SIC, CIC, W, I_D^w, and $\bar{I}_D^w$ values for a series of 11 triazinone derivatives (II) are presented in Table V; the log P and experimental pI_{50} values were taken from Draber *et al.* (59). Table Va reveals the outcome of statistical analysis in an attempt to correlate pI_{50} with log P and other descriptors. It is clear that all the parameters correlate significantly with experimental pI_{50} values. In all cases the parabolic relationship results in significant improvement in the fit with respect to the linear one. It is noteworthy that the theoretically derived indices IC, SIC, CIC, $^1\chi$, and $\bar{I}_D^w$ are almost as effective as log P in the correlation of pI_{50} values of the herbicides.

Narcotic Property of Barbiturates—Barbiturates are widely used in the treatment of several convulsive disorders (60). Although the precise mechanism of action of barbiturates is still not clear, attenuation of excitatory synaptic transmission (61, 62), potentiation of inhibitory synaptic transmission (61, 63), and blockage of electrically excitable membranes (64) are tentatively considered to be the causative factors behind the biological action of these compounds. Some recent studies, however, demonstrated the interaction of barbiturates with benzodiazepine receptors (65).

The high correlations of the physiological action of barbiturates with log P are the crucial factors for the assignment of a nonspecific mode of action to

Table V—Hydrophobicity, Hill Reaction Inhibitory Potency (pI_{50}), and Molecular Descriptors for Triazinones (II)

R_1	R_2	pI_{50}	IC	SIC	CIC	$^1\chi$	$^1\chi^v$	W	I_D^w	$\bar{I}_D^w$	log P
SCH_3	Methyl	3.88	3.2211	0.7583	1.0268	5.1639	4.1393	146	821.30	5.62	−0.16
$NHCH_3$	Isopropyl	5.79	3.0860	0.6565	1.6144	6.0746	4.0001	236	1442.11	6.11	0.30
SCH_3		5.38	3.1144	0.6347	1.7925	7.7364	6.3606	428	2868.80	6.70	0.38
SCH_3	Ethyl	5.27	3.1867	0.7146	1.2727	5.7019	7.4000	190	1115.97	5.87	0.46
SCH_3	Propyl	5.70	3.0751	0.6622	1.5688	6.2019	5.2000	246	1499.30	6.09	0.93
SCH_3	Isopropyl	6.24	3.0751	0.6622	1.5688	6.0746	5.0827	236	1442.11	6.11	1.01
SCH_3	Isobutyl	6.15	3.0567	0.6358	1.7507	5.5558	4.3356	304	1918.55	6.31	1.39
SCH_3	*tert*-Butyl	6.63	2.9583	0.6154	1.8491	6.3752	5.3893	284	1798.44	6.33	1.70
SCH_3	3-Methylbutyl	6.40	2.9767	0.6008	1.9775	7.0577	6.0558	386	2507.45	6.50	1.85
SCH_3	Cyclohexyl	6.60	2.8465	0.5693	2.1535	7.7364	6.7445	428	2868.80	6.70	2.14
SCH_3	Hexyl	6.43	2.7460	0.5398	2.3415	7.7019	6.7000	496	3302.79	6.66	2.68

Table Va—Correlation of pI_{50} with Hydrophobicity and Topological Indices ($pI_{50} = a + bx + cx^2$)[a]

x	a	b	c	r	s	F
IC	19.3	−4.42	—	0.77	0.54	13
	$-1.67E+2$	$1.21E+2$	−20.9	0.95	0.29	35
SIC	13.0	−11.1	—	0.85	0.45	23
	−12.8	69.1	−61.9	0.92	0.35	22
CIC	2.79	1.78	—	0.83	0.48	19
	−2.13	7.90	−1.81	0.91	0.38	19
$^1\chi$	2.19	0.558	—	0.60	0.68	5.2
	−31.5	10.9	−0.779	0.89	0.41	15
$^1\chi^v$	3.10	0.508	—	0.60	0.68	5.0
	−3.99	3.20	−0.249	0.64	0.69	2.9
W	4.54	$4.30E-3$	—	0.60	0.68	5.0
	0.548	$3.21E-2$	$-4.30E-5$	0.82	0.52	8.2
I_D^w	4.71	$5.85E-4$	—	0.59	0.70	4.7
	1.43	$4.26E-3$	$-8.81E-7$	0.82	0.51	8.4
$\bar{I}_D^w$	−4.31	1.62	—	0.71	0.60	9.0
	$-1.53E+2$	49.5	−3.85	0.91	0.37	19
log P	4.98	0.760	—	0.83	0.48	20
	4.58	1.97	−0.490	0.94	0.32	28

[a] In all cases the number of data points = 11.

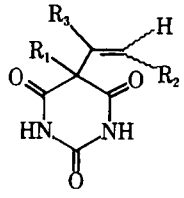
Table VI—Lipophilicity, Duration of Anesthesia (log T), Induction Time for Anesthesia (log t), and Molecular Descriptors for Barbiturates (III)

R_1	R_2	R_3	log T^a, h	log t^b, min	IC	SIC	CIC	log P	$^1\chi$	$^1\chi^v$	W	$\bar{I}_D^w$	I_D^w
Methyl	Ethyl	Methyl	0.0000	1.2041	2.8397	0.5845	2.0183	1.15	6.9238	4.5593	340	2224.00	6.5410
Ethyl	Ethyl	Methyl	−0.3979	0.9542	2.7871	0.5574	2.2129	1.65	7.4844	5.3271	398	2684.00	6.7430
Propyl	Ethyl	Methyl	−0.5229	0.8451	2.7217	0.5306	2.4076	2.15	7.9844	5.8271	472	3268.00	6.9240
Isopropyl	Ethyl	Methyl	−0.5229	0.6021	2.7648	0.5390	2.3645	1.95	7.8672	5.7098	458	3174.00	6.9300
Methyl	Methyl	Ethyl	0.0000	1.3222	2.8397	0.5845	2.0183	1.15	6.9618	4.7890	330	2164.00	6.5570
Ethyl	Methyl	Ethyl	−0.1549	1.0792	2.7871	0.5574	2.2129	1.65	7.5224	5.3497	387	2165.00	6.7570
Propyl	Methyl	Ethyl	−0.3979	0.7782	2.7271	0.5306	2.4076	2.15	8.0224	5.8497	460	3191.00	6.9360
Isopropyl	Methyl	Ethyl	−0.5229	0.6990	2.7648	0.5390	2.3645	1.95	7.9052	5.7324	446	3105.00	6.9620
Methyl	Propyl	Methyl	0.0000	0.7782	2.7871	0.5574	2.2129	1.65	8.4238	5.2664	423	2840.00	6.7130
Ethyl	Propyl	Methyl	0.0792	0.4771	2.7217	0.5306	2.4076	2.15	7.9844	5.8271	488	3374.00	6.9140
Methyl	Isopropyl	Methyl	−0.2218	0.7782	2.7482	0.5496	2.2518	1.45	7.2796	5.1391	410	2758.00	6.7270
Methyl	Butyl	Methyl	−0.3979	0.7782	2.7217	0.5306	2.4076	2.15	7.9238	5.7664	522	3588.00	6.8730
Ethyl	Butyl	Methyl	−1.0000	0.9031	2.6540	0.5057	2.5939	2.65	8.4844	6.3271	595	4197.00	7.0540
Ethyl	Ethyl	Propyl	−1.0000	0.9031	2.6540	0.5057	2.5939	2.65	8.5224	6.3877	551	3909.00	7.0950

[a] Logarithm of the duration of anesthesia in hours after intraperitoneal injection at the AD_{100} dose level. [b] Logarithm of the induction time for anesthesia in minutes after intraperitoneal injection at the AD_{100} dose level.

this class of drugs (23, 66, 67). On the other hand, Kier and Hall (8) found the action of congeneric series of barbiturates to be well correlated with connectivity-type steric parameters. Raychaudhury *et al.* (68) reported significant linear correlations of the *in vivo* stability of barbiturates with IC and SIC indices. In a further study, Basak *et al.* (20) showed that steric parameters like V_w, CIC, $^1\chi^v$, and $\bar{I}_D^w$ are superior to log P in rationalizing the duration of physiological action of the barbiturate group of drugs. The above considerations necessitate a comparative study of lipophilic and steric parameters in the quantitative prediction of the phenomenology of barbiturate action.

To illustrate the relative efficacies of log P *vis-à-vis* topological descriptors in the analysis of the narcotic action of barbiturates, a QSAR study was carried out with three different groups of barbituric acid derivatives, where the structural variations in the side chains include elongation of the carbon skeleton, branching, and unsaturation. Table VI presents the duration of anesthesia (T in hours) and the logarithm of the induction time for anesthesia (t in minutes) after administration of the drugs at AD_{100} dose levels, log P, $^1\chi$, $^1\chi^v$, IC, SIC, CIC, W, I_D^w, and $\bar{I}_D^w$ values for a series of 14 barbiturates (III) with variously modified side chains. The experimental T and t values (determined after the intraperitoneal injection of the compounds to albino mice) were taken from Cope and Hancock (69), and the log P values were taken from Hansch (23).



III

Table VIa shows the correlations of log T values with lipophilicity and the theoretically computed descriptors. None of the parameters used show excellent correlations with the T values. However, $\bar{I}_D^w$, $^1\chi$, and CIC exhibit correlations comparable or superior to that with log P values. Table VIa depicts the correlation of the induction time for anesthesia (log t) with log P and other theoretical structural parameters. It is noteworthy that the correlations of log t

Table VIa—Correlation of log T and log t with log P and Topological Indices [a]

x	a	b	c	r	s	F
			$\log T = a + bx + cx^2$			
IC	$-0.132E+02$	$0.467E+01$	—	0.77	0.23	17
	$-0.169E+03$	$0.118E+03$	$-0.207E+02$	0.80	0.22	9.8
CIC	$0.324E+01$	$-0.155E+01$	—	0.80	0.22	21
	$-0.115E+02$	$0.113E+02$	$-0.280E+01$	0.85	0.20	14
SIC	$-0.648E+01$	$0.113E+02$	—	0.79	0.22	20
	$-0.500E+02$	$0.171E+03$	$-0.147E+03$	0.84	0.21	13
W	$0.120E+01$	$-0.348E-02$	—	0.76	0.23	16
	$-0.666E+00$	$0.489E-02$	$-0.914E-05$	0.78	0.24	8.5
I_D^w	$0.925E+00$	$-0.422E-03$	—	0.76	0.23	17
	$-0.824E+00$	$0.757E-03$	$-0.191E-06$	0.80	0.23	9.6
$\bar{I}_D^w$	$0.108E+02$	$-0.163E+01$	—	0.80	0.22	21
	$-0.168E+03$	$0.508E+02$	$-0.385E+01$	0.86	0.19	16
$^1\chi$	$0.281E+01$	$-0.406E+00$	—	0.61	0.28	7.0
	$-0.468E+01$	$0.154E+01$	$-0.126E+00$	0.61	0.30	3.3
$^1\chi^v$	$0.254E+01$	$-0.522E+00$	—	0.79	0.22	20
	$-0.740E+01$	$0.313E+01$	$-0.333E+00$	0.85	0.20	14
log P	$0.724E+00$	$-0.574E+00$	—	0.78	0.22	19
	$-0.512E+00$	$0.814E+00$	$-0.367E+00$	0.82	0.21	12
			$\log t = a + bx + cx^2$			
IC	$-0.450E+01$	$0.195E+01$	—	0.49	0.20	3.8
	$0.311E+03$	$-0.228E+03$	$0.418E+02$	0.85	0.13	14
SIC	$-0.214E+01$	$0.553E+01$	—	0.59	0.19	6.4
	$0.600E+02$	$-0.223E+03$	$0.209E+03$	0.86	0.13	15
CIC	$0.262E+01$	$-0.756E+00$	—	0.59	0.19	6.5
	$0.235E+02$	$-0.190E+02$	$0.396E+01$	0.86	0.13	15
W	$0.158E+01$	$-0.161E-02$	—	0.54	0.20	4.9
	$0.661E+01$	$-0.242E-01$	$0.247E-04$	0.89	0.11	22
I_D^w	$0.148E+01$	$-0.202E-03$	—	0.56	0.19	5.4
	$0.486E+01$	$-0.248E-02$	$0.370E-06$	0.88	0.12	20
$\bar{I}_D^w$	$0.646E+01$	$-0.819E+00$	—	0.62	0.18	7.3
	$0.204E+03$	$-0.590E+02$	$0.427E+01$	0.82	0.14	11
$^1\chi$	$0.282E+01$	$-0.251E+00$	—	0.57	0.19	5.9
	$0.319E+02$	$-0.781E+01$	$0.489E+00$	0.81	0.14	10
$^1\chi^v$	$0.220E+01$	$-0.241E+00$	—	0.56	0.19	5.4
	$0.136E+02$	$-0.444E+01$	$0.383E+00$	0.77	0.16	8.0
log P	$0.134E+01$	$-0.294E+00$	—	0.52	0.20	4.5
	$0.334E+01$	$-0.250E+01$	$0.596E+00$	0.82	0.14	11

[a] In all cases, the number of data points = 14.

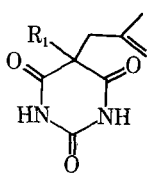
Table VII—Lipophilicity, Minimum Anesthetic Dose (MAD, log $1/c$), and Topological Descriptors for a Set of 16 Barbiturate Derivatives (IV)

R_1	log P	MAD (log $1/c$)	IC	SIC	CIC	W	I_D^w	$\bar{I}_D^w$	$^1\chi$	$^1\chi^v$
Ethyl	1.15	3.23	2.8397	0.5845	2.0183	334	2189.41	6.5551	6.9196	4.7504
Propyl	1.65	3.27	2.7871	0.5574	2.2129	402	2711.99	6.7462	7.4196	5.2504
Isopropyl	1.45	3.35	2.7482	0.5496	2.2518	389	2627.46	6.7544	7.3023	5.1331
Butyl	2.15	3.38	2.7217	0.5306	2.4076	486	3361.64	6.9170	7.9196	5.7504
Isobutyl	1.95	3.36	2.7649	0.5390	2.3644	472	3269.89	6.9277	7.7754	5.6062
sec-Butyl	1.95	3.42	2.7649	0.5390	2.3644	460	3189.83	6.9344	7.8403	5.6711
Amyl	2.65	3.26	2.6540	0.5057	2.5939	587	4151.26	7.0720	8.4196	6.2504
sec-Amyl	2.45	3.62	2.7265	0.5195	2.5214	548	3888.54	7.0959	8.3403	6.1711
2-Methylbutyl	2.45	3.34	2.7265	0.5195	2.5214	559	3964.27	7.0917	8.3134	6.1442
3-Methylbutyl	2.45	3.36	2.7265	0.5195	2.5214	572	4051.54	7.0831	8.2754	6.1062
1-Ethylpropyl	2.45	3.50	2.7265	0.5195	2.5214	535	3802.09	7.1067	8.3783	6.2091
Hexyl	3.15	3.18	2.5878	0.4830	2.7697	706	5094.11	7.2155	8.9196	6.7504
2-Ethylbutyl	2.95	3.25	6.6759	0.4995	2.6817	650	4713.39	7.2514	8.8514	6.6822
Cyclopentyl	2.29	3.40	2.8156	0.5446	2.3543	530	3763.10	7.1002	8.4641	6.2949
Allyl	1.35	3.44	2.7974	0.5701	2.1095	402	2711.99	6.7462	7.4196	4.8891
2-Methylallyl	1.65	3.37	2.7396	0.5431	2.3048	472	3269.89	6.9277	7.7754	5.2671
Phenyl	1.92	3.24	3.0659	0.5761	2.2560	726	5368.42	7.3945	9.3579	6.8696

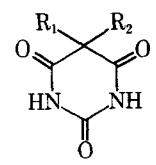
with I_D^w, $\bar{I}_D^w$, $^1\chi$, W, CIC, SIC, and IC are superior or comparable to that with log P (Table VIa).

Table VII summarizes the minimal anesthetic dose (MAD, log $1/c$) levels, log P, molecular connectivity, Wiener number, and the different information-theoretic indices for a series of 17 barbiturates (IV); the experimental MAD (log $1/c$) values were taken from Doran and Shoule (70). In an earlier study Hansch *et al.* (67) showed that log P correlates more or less satisfactorily with the experimental log $1/c$ values of this set of compounds. The results of regression analysis, depicted in Table VIIa, show that some of the topological descriptors (SIC, CIC, W, I_D^w, $\bar{I}_D^w$, $^1\chi$, and $^1\chi^v$) are superior to log P in the correlation of the anesthetic concentrations of this congeneric series of compounds.

Table VIII represents the anesthetic concentrations (AD_{50}, log $1/c$), log P,



IV



V

Table VIIa—Correlation of MAD (Rats) with log P and Molecular Descriptors, [log (1/c) = a + bx + cx²][a]

x	a	b	c	r	s	F
IC	0.348E + 01	−0.450E − 01	—	0.04	0.11	0.025
	−0.218E + 02	0.179E + 02	−0.316E + 01	0.52	0.10	2.6
SIC	0.334E + 01	0.204E − 01	—	0.005	0.11	0.00
	−0.201E + 01	0.878E + 02	−0.819E + 02	0.64	0.090	5.0
CIC	0.340E + 01	−0.218E − 01	—	0.040	0.11	0.023
	−0.392E + 01	0.613E + 01	−0.128E + 01	0.54	0.099	2.9
W	0.348E + 01	−0.251E − 03	—	0.25	0.11	1.0
	0.206E + 01	0.528E − 02	−0.518E − 05	0.68	0.086	6.0
I_D^w	0.346E + 01	−0.308E − 04	—	0.25	0.11	0.97
	0.240E + 01	0.561E − 03	−0.782E − 07	0.66	0.088	5.5
$\bar{I}_D^w$	0.357E + 01	−0.319E − 01	—	0.062	0.11	0.058
	−0.480E + 02	0.148E + 02	−0.106E + 01	0.54	0.099	2.8
$^1\chi$	0.354E + 01	−0.238E − 01	—	0.14	0.11	0.30
	−0.512E + 01	0.212E + 01	−0.132E + 00	0.59	0.095	3.7
$^1\chi^v$	0.349E + 01	−0.236E − 01	—	0.14	0.11	0.30
	−0.170E + 01	0.178E + 01	−0.155E + 00	0.57	0.096	3.4
log P	0.338E + 01	−0.148E − 01	—	0.075	0.11	0.086
	0.266E + 01	0.717E + 00	−0.172E + 00	0.53	0.099	2.7

[a] In all cases, the number of data points = 17.

Table VIII—Lipophilicity, Anesthetic Dose (AD_{50}, log 1/c), and Topological Indices for a Set of Barbituric Acid Derivatives (V)

R_1	R_2	log P	AD_{50} (log 1/c)	IC	SIC	CIC	W	I_D^w	$\bar{I}_D^w$	$^1\chi$	$^1\chi^v$
Propyl	1-Propenyl	1.35	3.12	2.7968	0.5757	2.0612	338	2215.24	6.5540	7.0637	4.8724
Isopropyl	1-Propenyl	1.15	3.28	2.7708	0.5704	2.0872	326	2139.91	6.5641	6.9464	4.7551
Butyl	1-Propenyl	1.85	3.31	2.7246	0.5449	2.2754	415	2794.55	6.7338	7.5637	5.3724
Ethyl	1-Butenyl	1.35	3.37	2.7968	0.5757	2.0612	346	2262.81	6.5399	7.0637	4.9104
Propyl	1-Butenyl	1.85	3.31	2.7246	0.5449	2.2754	415	2794.55	6.7338	7.5637	5.4104
Isopropyl	1-Butenyl	1.65	3.57	2.7871	0.5574	2.2129	402	2709.65	6.7404	7.4464	5.2931
Butyl	1-Butenyl	2.35	3.56	2.6506	0.5168	2.4787	500	3453.76	6.9075	8.0637	5.9104
Ethyl	2-Methyl-1-propenyl	1.15	2.56	2.8397	0.5845	2.0183	334	2189.41	6.5551	6.9196	4.7504
Ethyl	1-Pentenyl	1.85	3.45	2.7246	0.5449	2.2754	431	2892.67	6.7115	7.5637	5.4104
Isopropyl	1-Pentenyl	2.15	3.50	2.7433	0.5348	2.3860	494	3409.09	6.9010	7.9464	5.7931
Ethyl	3-Methyl-1-butenyl	1.65	3.51	2.7871	0.5574	2.2129	418	2811.32	6.7257	7.4196	5.2831
Propyl	3-Methyl-1-butenyl	2.15	3.32	2.7433	0.5348	2.3860	494	3413.36	6.9096	7.9196	5.7831
Isopropyl	3-Methyl-1-butenyl	1.95	3.68	2.6506	0.5168	2.4787	480	3318.94	6.9145	7.8023	5.6658

Table VIIIa—Correlation of AD_{50} (Mice) with log P and Molecular Descriptors [log (1/c) = a + bx + cx²][a]

x	a	b	c	r	s	F
IC	0.124E + 02	−0.329E + 01	—	0.65	0.22	8.2
	−0.200E + 03	0.153E + 03	−0.283E + 02	0.74	0.21	6.1
SIC	0.822E + 01	−0.885E + 01	—	0.69	0.21	10
	−0.491E + 02	0.200E + 03	−0.190E + 03	0.76	0.20	6.6
CIC	0.630E + 00	0.121E + 01	—	0.68	0.22	9.4
	−0.179E + 02	0.177E + 02	−0.367E + 01	0.73	0.21	5.8
W	0.222E + 01	0.272E − 02	—	0.62	0.23	6.9
	−0.170E + 01	0.221E − 01	−0.234E − 04	0.68	0.23	4.2
I_D^w	0.236E + 01	0.354E − 03	—	0.62	0.23	6.8
	−0.780E + 00	0.266E − 02	−0.412E − 06	0.68	0.23	4.2
$\bar{I}_D^w$	−0.375E + 01	0.120E + 01	—	0.62	0.23	7.0
	−0.173E + 03	0.511E + 02	−0.371E + 01	0.66	0.23	3.8
$^1\chi$	−0.837E − 01	0.459E + 00	—	0.64	0.23	7.6
	−0.412E + 02	0.115E + 02	−0.740E + 00	0.72	0.21	5.4
$^1\chi^v$	0.958E + 00	0.449E + 00	—	0.64	0.22	7.8
	−0.178E + 02	0.758E + 01	−0.673E + 00	0.72	0.21	5.3
log P	0.258E + 01	0.446E + 00	—	0.62	0.23	6.7
	0.670E + 00	0.280E + 01	−0.690E + 00	0.70	0.22	4.8

[a] In each case, the number of data points = 13.

$^1\chi$, $^1\chi^v$, W, I_D^w, $\bar{I}_D^w$, IC, SIC, and CIC values) for a set of 13 barbiturates (V). The experimental log 1/c data were taken from the work of Cope *et al.* (71). The outcome of regression analysis indicates that log P and the various molecular descriptors correlate significantly with the AD_{50} values of this group of analogues (Table VIIIa). It is evident from the statistical analysis that IC, SIC, CIC, and $^1\chi$ are superior and I_D^w as well as $\bar{I}_D^w$ are slightly inferior to log P in accounting for the AD_{50} values of this group of barbiturates.

CONCLUSIONS

We have analyzed the relative roles of hydrophobicity (log P, octanol–water) *vis-à-vis* several topological parameters in the QSAR study of diverse sets of bioactive molecules that vary considerably with respect to chemical structure and physiological function. While alcohols and ketobemidones are simple homologous series, triazinones and barbiturates represent considerable structural diversity. At the biochemical level, alcohols and barbiturates are thought to be narcotic agents that act through nonspecific perturbation of cellular proteins or lipoprotein complexes (46, 47, 66, 72, 73). On the other hand, triazinones and ketobemidones act *via* specific mechanisms where well-defined biotargets are involved (54, 59). Yet it is interesting to note that certain graph theoretic invariants like CIC, $^1\chi$, $^1\chi^v$, W, and $\bar{I}_D^w$ could predict these dissimilar biological phenomena as efficiently as hydrophobicity.

From QSAR studies of different series of bioactive molecules, Hansch (23) pointed out that lipophilicity alone is sufficient to account for the action of

nonspecific bioactive molecules. On the other hand, stereoelectronic factors are deemed to be critical for molecules with specialized mechanism of action at the biochemical level (23, 74). However, the results of this paper indicate that topological steric parameters can correlate the action of both specific (triazinones and ketobemidones) and nonspecific (alcohol and barbiturates) bioactive agents. These findings could be rationalized in terms of the studies of Nemethy and Scheraga (75–77) where a "steric basis of hydrophobicity" is proposed on theoretical grounds. Alternatively, some recent studies highlight that certain so called "nonspecific" compounds may have specific physiological receptors (65, 78, 79) which could conceivably be sensitive to the steric factors associated with the effector molecule.

Finally, from the QSAR of these diverse series of bioactive molecules, the easily calculable molecular descriptors like CIC, $^1\chi$, $^1\chi^v$, W, and $\bar{I}_D^w$ appear to be as effective as log P in the rationalization of biological action. Of these five topological descriptors, only CIC and $\bar{I}_D^w$ are highly correlated with biological response for all six sets of compounds tested; accordingly, either CIC or $\bar{I}_D^w$ is the best single choice for a molecular descriptor.

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Comparative Bioavailability of Two Furosemide Formulations in Humans

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Abstract □ Twelve healthy male volunteers participated in a balanced crossover comparison of a brand-name and generic furosemide formulations. Each treatment was given as a single 40-mg tablet following an overnight fast. Furosemide concentrations in plasma and urine were determined up to 24 h after treatment; urine output and urinary sodium excretion were also measured. In comparison with the brand-name tablets, generic furosemide was significantly less bioavailable. Using a 95% confidence interval approach, generic furosemide gave up to 66% lower maximum furosemide plasma levels, up to 52% less area under the plasma level curve to infinite time, and up to 37% less urinary recovery of furosemide. Comparison of the effect of the two treatments was a less sensitive measurement of bioequivalence. Confidence intervals for differences in urinary output and sodium excretion over the period of maximum effect (0–4 h) were, however, asymmetrical, and pharmacodynamic differences between treatments were significant at the 10% level.

Keyphrases □ Furosemide—comparative bioavailability, brand-name and generic formulations, humans, plasma and urine □ Bioavailability—comparative, furosemide formulations in humans, plasma and urine □ Formulations—comparative bioavailability, brand-name and generic furosemide in humans, plasma and urine

During 1979, generic formulations of furosemide tablets which were not legally marketed became available to U.S. physicians. Shortly after these tablets were introduced, reports began to appear of diuretic ineffectiveness of some of the products. The Food and Drug Administration became aware of the problem and took steps to prevent further clinical use of unauthorized furosemide tablets (1).

With the above background in mind, it was felt that it would be useful to compare the relative bioavailability of the brand-name tablet formulation of furosemide available in the United States and one of the abovementioned generic furosemide tablets. This paper presents the results of a crossover study in healthy volunteers with comparative pharmacokinetic and pharmacodynamic measurements.

EXPERIMENTAL

Subjects—Twelve healthy male volunteers aged 18–42 years, within 10% of ideal body weight, received treatment on two occasions with 1-week between doses. A comprehensive checkup, including clinical examination, clinical chemistry/hematology evaluation, and urinalysis revealed no evidence of cardiac, respiratory, hepatic, or renal disease. The project was subject to ethics review, and each subject gave his signed informed consent.

Treatment—Furosemide (40 mg) was administered as a single tablet on two occasions 1 week apart to each subject, according to a balanced crossover design. Treatments were designated product I[1] and product II[2] respectively. Product I (the brand-name tablet) contained an average of 39.6 mg of furosemide/tablet; product II (the generic tablet) contained an average of 40.3 mg of furosemide/tablet. Therapy was given by mouth with 100 mL of water following an overnight fast, 1 h before a standard tea/toast breakfast. Oral fluid supplements (150 mL of water) were given at 1, 2, 3, 4, and 6 h after treatment.

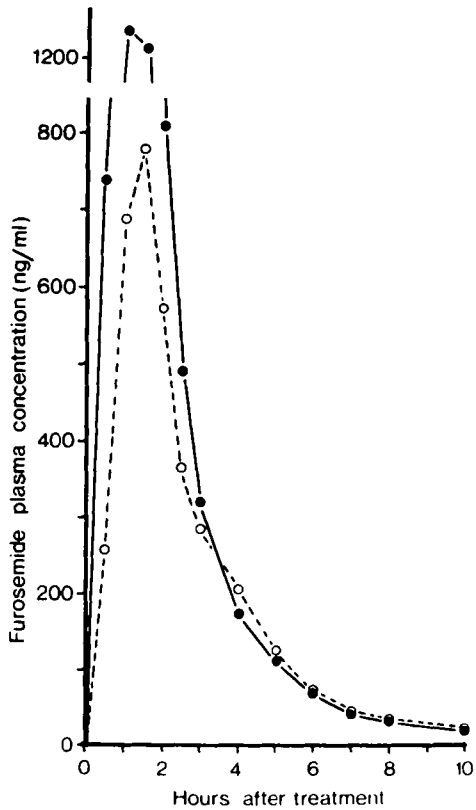

Figure 1—*Mean furosemide plasma concentration following oral treatment with product I (●) and product II (○).*

[1] Lasix, lot 600229; Hoechst-Roussel Pharmaceuticals, Inc., Somerville, N.J.
[2] Furosemide lot 8137-07; Pharmadyne Laboratories Inc., Elmwood Park, N.J.

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