$CHCl_3$. The organic layers were combined, dried, and evapd *in vacuo*. The product was recrystd from a C_6H_6–hexane solvent mixture to give 174.9 g (72%), mp 117–118°.

Methyl 2-Phenoxathiinyl Ketone 10-Oxide (9).—A solution of *m*-chloroperbenzoic acid (5.3 g, 0.026 mol) in 25 ml of CH_2Cl_2 was added to 5.0 g (0.026 mol) of **7** dissolved in 100 ml of CH_2Cl_2. This was maintained at −70° for 30 min. The reaction mixture was washed with aq $NaHCO_3$, and the solvent was evapd *in vacuo*. Tlc of the residue indicated a mixture of sulfoxide and sulfone. The components were separated by chromatography over silica gel. The sulfone was eluted with 4:1 C_6H_6–EtOAc, and the desired sulfoxide with EtOAc alone. The column afforded 3.3 g (49.3%) of the sulfoxide, mp 128–130°.

Methyl 2-Phenoxathiinyl Ketone 10,10-Dioxide (10).—To compd **7** (24.2 g, 0.1 mol) in 250 ml of glacial AcOH at 60° was added, rapidly, with stirring, 30% H_2O_2 (24 ml, 0.24 mol). This was heated at 80° for 4 hr. Upon cooling, the product crystallized from AcOH. After filtration and drying, 24.5 g (89.5%) of the product was obtained, mp 168–170°.

2-(1-Methoxyethyl)phenoxathiin (20).—In a flame-dried apparatus under N_2, 50% NaH in oil suspension (1.0 g, 0.0204 mol) was added to 24 ml of PhMe. A soln of 1 (5.0 g, 0.0204 mol) in 100 ml of PhMe was added. The reaction mixture was refluxed for 2 hr and then cooled to room temp. MeI (3.0 g, 0.0204 mol) was added dropwise with stirring. The reaction mixture was washed with H_2O to remove the NaI formed, dried, filtered, and evapd *in vacuo*. The residue proved to be two-spot material by tlc. The residue was dissolved in C_6H_6–EtOAc and passed over 300 g of silica gel. Short-path distillation of the eluate from the column yielded 2.9 g (54.6%) of 2-(1-methoxyethyl)phenoxathiin.

2-(Methylcarbamate-1-ethyl)phenoxathiin (21).—A mixture of 1 (6.8 g, 0.028 mol), K_2CO_3 (0.83 g, 0.006 mol), CH_2Cl_2 (20 ml), 1 drop of H_2O, 1 drop of MeOH, and MeNCO (1.87 g, 0.033 mol) was refluxed overnight. The solvent was removed *in vacuo*, and the crude product was recrystd from Me_2CO–hexane to give 5.1 g (60.8%), mp 124–126°.

2-(1-Acetoxyethyl)phenoxathiin (23).—By the method of Fritz and Schenk[13] a soln of 2 *M* Ac_2O in EtOAc was made. To 5.0 g (0.0204 mol) of 1 was added 33 ml of 2 *M* Ac_2O at 5°. This was stirred for 10 min. The soln was washed with satd $NaHCO_3$, dried, filtered, and evapd *in vacuo*. The crude product was short-path distd to give 5.8 g of product (97.6%).

Acknowledgment.—We wish to thank Dr. C. E. Redman for statistical analysis of biological data.

(13) J. S. Fritz and G. H. Schenk, *Anal. Chem.*, **31**, 1808 (1959).

Structure–Activity Correlations for the Central Nervous System Depressant 2-Imidazolidinones

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The CNS depressant activities of a series of substituted 2-imidazolidinones are found to be highly dependent on the log of the octanol–water partition coefficient. Chlorpromazine fits the same regression lines. Exceptions to this dependence on the lipohydrophilic character are discussed in terms of steric factors.

The dependence of biological activity in a set of congeneric drugs on lipohydrophilic character has been shown in many types of drug action.[2] In particular, a study by Hansch and his coworkers[2a] pointed out that variation in the CNS depression activity of several types of hypnotics depends parabolically upon the relative lipohydrophilic character as represented by the 1-octanol–water partition coefficient (log *P*). The hypnotics reported included barbiturates, thiobarbiturates, tertiary alcohols, carbamates, substituted amides, and *N,N'*-diacylureas. In all of these compounds a value of 2 was found for log *P* for maximum activity (log P_0). Similar log P_0 values for this wide range of structurally dissimilar compounds are taken as a strong indication that these compounds have the same rate-determining step in producing CNS depression. This step may lie in the penetration of the inter- and/or intracellular membranes or one of the prior barriers such as the blood–brain barrier.

As an extension of this type of study, interesting and ample biological data published by Wright, *et al.*,[3] were analyzed by regression analysis.

Methods

The set of congeners analyzed was a series of substituted 2-imidazolidinones (ethyleneurea derivatives). Chlorpromazine was included for comparison (see Table I and Figure 1). To place the drugs on a common basis for quantitation the biological activity, given originally in milligrams per kilogram, was converted into log $1/c$ where c is the effective concentration in moles per kilogram.

Three different measurements of CNS depression were used by Wright, *et al.*,[3] (1) reduction of motor activity of mice by 50% as measured by an actophotometer (MDD_{50}), (2) inhibition of 50% of the test group of mice to walk from the midpoint of a horizontal steel rod to a platform at the ends (RWD_{50}), and (3) inability of 50% of the test mice to remain on a 60° inclined screen (ISD_{50}). All injections were intraperitoneal.

The log *P* values were calculated from the experimental value of 1-(2-dimethylaminoethyl)-3-(*m*-methoxyphenyl)-2-imidazolidinone and the π constants reported by Hansch and his coworkers[2,4] (see Table II).

The Hammett's σ constant, a measure of the electronic effect of a substituent, was given adequate analysis, and the steric effect was not considered quantitatively. σ values were included only for the substituents on the phenyl ring. Since the alkyl sub-

(1) (a) To whom requests for reprints should be addressed; (b) R. M. and J. L. Converse Fund Fellow; (c) NSF–URP participant, summer, 1969, GY-5829.

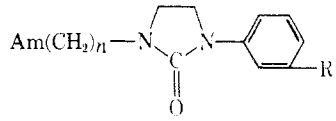
(2) (a) C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *J. Med. Chem.*, **11**, 1 (1968); (b) E. J. Lien, C. Hansch, and S. M. Anderson, *ibid.*, **11**, 430 (1968); (c) E. J. Lien, *J. Agr. Food Chem.*, **17**, 1265 (1969); (d) E. J. Lien, Symposium on Fungitoxic Action, 61st Annual Meeting of American Phytopathological Society, August 19, 1969, Spokane, Washington.

(3) W. B. Wright, Jr., H. J. Brabander, R. Hardy, and A. C. Osterberg, *J. Med. Chem.*, **9**, 852 (1966).

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

TABLE I

THE CNS DEPRESSION ACTIVITY OF 2-IMIDAZOLIDINONES AND THE PHYSICOCHEMICAL CONSTANTS USED IN THE REGRESSION ANALYSIS



No.	Am	n	R	log P	σ	log 1/c MDD$_{50}$ Obsd	MDD$_{50}$ Calcd[a]	RWD$_{50}$ Obsd	RWD$_{50}$ Calcd[b]	ISD$_{50}$ Obsd	ISD$_{50}$ Calcd[c]
1	Pyrrolidinyl	2	Br	3.50	0.38	5.63	5.41	4.19	4.07		
2	Pyrrolidinyl	2	Cl	3.32	0.37	5.47	5.36	3.92	4.00	3.52	3.65
3	Pyrrolidinyl	2	H	2.56	0.00	5.01	5.06	3.72	3.69	3.30	3.40
4	Et_2N	2	Br	3.58	0.38	5.42	5.42	4.19	4.10		
5	Et_2N	2	Cl	3.40	0.37	5.33	5.38	4.39	4.03	3.82	3.68
6	EtMeN	2	Cl	2.90	0.37	5.37	5.21	3.81	3.83	3.45	3.51
7	EtMeN	2	H	2.14	0.00	5.09	4.86	3.92	3.52	3.44	3.26
8	EtMeN	2	Br	3.08	0.38	5.43	5.28	3.78	3.90		
9	Me_2N	2	Cl	2.40	0.37	5.03	4.96	3.65	3.63	3.41	3.35
10	Me_2N	2	Br	2.58	0.38	4.89	5.06	3.72	3.70	3.37	3.41
11	Me_2N	2	SCH_3	2.26	0.15	4.67	4.88	3.65	3.57	3.31	3.30
12	Me_2N	2	OCH_3	1.76[d]	0.10	4.64	4.53	3.42	3.37	3.20	3.14
13	Me_2N	2	CH_3	2.15	0.06	4.44	4.81	3.38	3.53		
14	Me_2N	2	OH	1.15	0.17	4.05	3.99	2.96	3.13	2.95	2.93
15	Me_2N	2	H	1.64	0.00	3.84		3.97		3.13	3.10
16	Me_2N	3	Br	3.08	0.38	4.12		3.64		3.34	3.37
17	Me_2N	3	Cl	2.90	0.37	3.89		3.76		3.25	3.31
19	Piperidinyl	2	H	3.06	0.00	4.23		3.53	3.93	3.44	3.57
20	Morpholinyl	2	Cl	1.89	0.37	4.07		3.31	3.42	3.37	3.18
21	Chlorpromazine			5.35		5.20	5.25	4.72	4.82	4.50	4.33

[a] Calculated from eq 1d. [b] Calculated from eq 2b. [c] Calculated from eq 3. [d] Experimental value determined in this study.

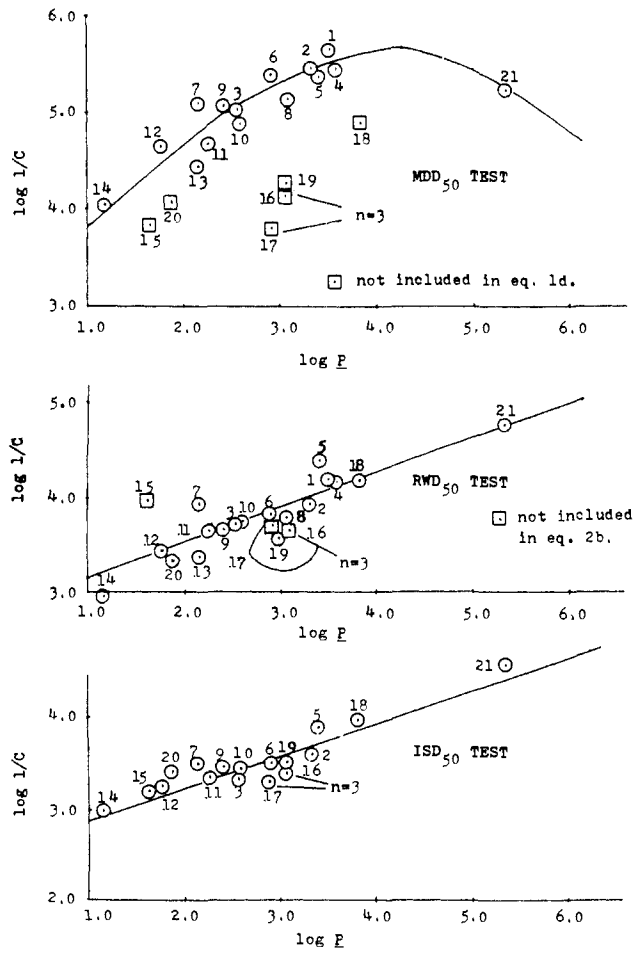
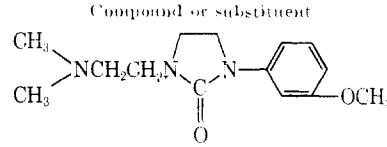


Figure 1.—Dependence of CNS depressant activity on log P.

TABLE II

LOG P AND π VALUES USED IN THE CORRELATIONS



Compound or substituent	log P or π
m-Br	0.94[b]
m-Cl	0.76[b]
m-CH_3	0.50[c]
m-SCH_3	0.62[b]
m-OH	−0.49[b]
Morpholine	−1.08[c]
Piperidine	0.85[c]
Pyrrolidinyl	0.35[d]
Et_2NH	0.43[c]
Chloropromazine	5.35[c]

[a] Standard deviation from three separate measurements using a Cary 14 spectrophotometer. [b] From T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964). [c] Private communication from Professor C. Hansch. [d] Calculated value (0.85–0.50).

stituents are insulated from the polar urea linkage by at least two methylene groups, varying them would not significantly affect the electronic distribution of the polar urea grouping. σ values obtained from Jaffé[5] are listed along with log P values in Table I.

The biological activity, log 1/c, was correlated with log P, σ, and (log P)^2 separately and simultaneously by an IBM 360/65 computer using the method of least squares. Only those equations having correlation coefficients of at least 0.90 were considered significant.

(5) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

Table III
Summary of Equations Correlating CNS Depressant Activity with log P

Equation	Test	n	r	s	log P_0	No.
$\log 1/c = -0.096 (\log P)^2 + 0.933 \log P + 3.001$	MDD_{50}	21	0.58	0.49	4.85	1a
$\log 1/c = -0.152 (\log P)^2 + 1.307 \log P + 2.547$	MDD_{50}	19	0.77	0.36	4.30	1b
$\log 1/c = -0.163 (\log P)^2 + 1.354 \log P + 2.584$	MDD_{50}	17	0.84	0.27	4.16 (3.63–5.96)[a]	1c
$\log 1/c = -0.163 (\log P)^2 + 1.359 \log P + 2.638$	MDD_{50}	15	0.91	0.19	4.17 (3.75–5.11)[a]	1d
$\log 1/c = 0.354 \log P + 2.813$	RWD_{50}	21	0.83	0.23		2a
$\log 1/c = 0.403 \log P + 2.662$	RWD_{50}	18	0.91	0.19		2b
$\log 1/c = 0.331 \log P + 2.552$	ISD_{50}	17	0.92	0.14		3

[a] 95% confidence interval.

Results

The equations obtained from the regression are summarized in Table III, where n is the number of data points used, r is the correlation coefficient, and s is the standard deviation. The dependence of the CNS depressant activity on log P is also presented in Figure 1. More scattering in the log $1/c$ *vs.* log P plot for the MDD_{50} test is observed than in the other two tests. Nevertheless, the $(\log P)^2$ term in equations 1c and 1d is significant at the 99.5 percentile level. The ideal log P value for the maximum activity (log P_0) is about 4.2. In equations 1c, 1d, and 2b data points with deviations higher than or close to $2s$ were not included.

For equations 1d, 2b, and 3, more than 81% ($r^2 > 0.81$) of the variance in the data can be accounted for by these equations. For compounds with σ constants available, addition of this term does not result in improved correlations.

Discussion

Variations in log P (P = octanol–water partition coefficient) account for the relative biological activities very well. The increasing order of activity in both RWD_{50} and ISD_{50} tests of the molecules having various substituents parallels the increasing log P value (see Figure 1), while in the MDD_{50} test a parabolic dependence on log P emerges. This overall agreement is gratifying considering the wide variations resulting from biological testing and the approximations used in calculating most of the log P values.

As CNS depressants, it may be assumed that these imidazolidinones would fit into the same pattern as those reported by Hansch and his coworkers.[2a] Indeed, the urea group of the imidazolidinones is similar to that of the barbiturates and that of the diacylureas. The reason why linear equations rather than parabolic equations are obtained for the RWD_{50} and ISD_{50} tests may be due to the fact that the log P of the unprotonated forms are used, while at physiological pH the amino group will be protonated more than 99%. The protonated species will have log P several log units lower than that of the uncharged form. Another possibility is that these may be different type of sedative–hypnotics than those having log P_0 about 2. The two groups would have different rate-limiting steps and probably different mechanisms of action.

The fact that addition of σ term does not improve the correlations significantly may be due to insulation of the electronic effect of the ring substituent by the saturated carbon atoms. In other words the pk_a values of the compounds examined do not vary significantly.

Among the three tests examined, measurement of decreased motor activity (MDD_{50}) using an actophotometer appears to be the most sensitive (log $1/c$ = 3.8 to 5.6). Ataxia and paralysis tests (RWD_{50} and ISD_{50}) require higher effective dosages (log $1/c$ = 2.95 to 4.72), but the results give somewhat better correlations (see Figure 1 and eq 2a–3).

The linear equations obtained for the RWD_{50} and ISD_{50} tests suggest that the log P_0 for the maximum activity has not yet been reached and that the points examined lie on the initial linear portion of the parabola, while in the MDD_{50} test it can be seen that the curve begins to level off before chlorpromazine is reached (log P = 5.35). It is interesting to note that the slope and the intercepts of equations 2a, 2b, and 3 are very close.

While lipohydrophilic character accounts for most of the variance in the data, there are three major observations not explainable in terms of the partition coefficient. These are the systematically lower than expected activities when n is increased to three (see Figure 1), when the phenyl is *para* rather than *meta* substituted[3] and when the cyclic urea ring is unsaturated.[6]

Although no quantitative data were reported on the *para*-substituted compounds, and therefore no mathematical analysis of the steric factors is possible, the lessened activities of both the *para*-substituted and the n = 3 compounds may be explained in the following terms. It has been hypothesized that drugs of this type may bind to lipoprotein membranes through dipole–dipole interaction with the protein portion of the membranes, and hydrophobic interactions of the rest of the molecule with the lipoid portion of the membranes.[2c,7] These interactions may then change membrane conformation and alter permeability and excitability. In accordance with this, Sprites and Guth have suggested that chlorpromazine acts by decreasing mitochondrial membrane permeability.[8] Since

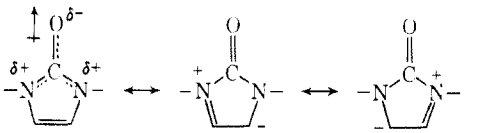
(6) W. B. Wright, Jr., H. J. Brabander, and R. H. Hardy, Jr., *J. Med. Chem.*, **9**, 858 (1966).

(7) (a) A. Shulman and G. Laycock, *Eur. J. Pharmacol.*, **1**, 295 (1967); (b) E. J. Lien and W. D. Kumler, *J. Med. Chem.*, **11**, 214 (1968).

(8) M. A. Sprites and P. S. Guth, *Nature*, **190**, 274 (1966).

present data indicate a similarity between chlorpromazine and the imidazolidinones (cyclic ureas), a similar effect on membrane permeability is possible. To account for the lower than expected activities for a number of compounds examined (see Figure 1) one may apply the classical lock and key theory. If a molecule must fit into a depression in the membrane in order for effective binding to occur, then excess lengthening of the molecule could prevent it from fitting into the receptor site and therefore inactivate it. This agrees with the finding that increasing the alkyl length from 2 to 3 C decreases activity less than changing from *meta* to *para* substitution,[3] since the three-dimensional tetrahedral bond of the CH_2 group adds less horizontal length to the molecule than the linear bond of the *p*-X-Ar substituent. Similarly, the fact that changing Me_2N to Et_2N does not lengthen the molecule too much, as shown by the activities, is also in accordance with this explanation. A conformation with a six-membered cyclic ion–dipole interaction or a seven-membered ring through the $\geqslant NH^+ \cdots {}^-O-$ bridge may be fairly stable; however, this conformation may retard the dipole–dipole interaction with the receptor. Another more probable conformation may have the protonated N and the partially positive urea N extended as far apart as possible. It is conceivable from the second conformation that by extending the alkylene side chain from 2 to 3 carbons or by putting a substituent at the *para* position of the benzene ring this molecule might be rendered too long to fit into the receptor.

The inactivity of the unsaturated imidazolin-2-ones[6] could be due either to the faster biotransformation of the double bond or to the introduction of resonance into the ring, thus altering the dipole moment of the urea grouping:[7b]



While the preceding discussion is highly speculative, it offers a seemingly viable explanation for the anomalies observed. Outside of these the lipohydrophilic character is the predominant factor controlling the relative potency for this group of CNS depressants. In the future it will be interesting to increase the partition coefficient to log P_0 and beyond to see if more potent depressants can be obtained. This might be done by adding a larger alkyl group to the 4 or 5 position of the imidazolidinone, by adding larger alkyl group to the meta position of the benzene ring, or by making α-naphthyl derivatives instead of the benzene derivatives.

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Stereochemical Studies on Medicinal Agents. VIII.[1] Absolute Stereochemistries of Isomethadol Isomers[2,3]

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The absolute stereochemistries of optically active α- and β-isomethadol diastereomers have been deduced by the asymmetric induction procedure of Prelog. The dissociation constants of the title compounds and isomethadone suggest the absence of intramolecular $+N-H\cdots O$ in aq medium. Ir data indicate that both diastereomers are internally bonded in CCl_4 and that the α isomer is more strongly H bonded. Results from nmr studies support the ir data and are consistent with conformations **11a** and **12a** in $CDCl_3$. The fact that only one isomer (3*S*,5*S*) possesses high potency suggests that the proper combination of configurations is necessary. The possible influences of conformational isomerism on analgetic activities are discussed. It is proposed that the potency differences between enantiomers are due primarily to the obstructive role of the 5- or 6-Me groups of (+)-isomethadone and (+)-methadone.

We have reported[1] previously on the absolute stereochemistries of α- and β-methadol enantiomers and have offered an explanation for the inversion of receptor stereoselectivity at the C-6 asymmetric center of these diastereomeric analgetics. As a continuation of our interest in this area, we have investigated[3] a group of closely related compounds derived from reduction of isomethadone (**1**).[5-7]

These diastereomers, commonly known as α- and β-isomethadol (**2**), have been prepared in their optically active forms by May and Eddy.[7] It is noteworthy that the analgetically active alcohol (+)-β-**2** and the more potent acetate esters [(−)-β-**3**, (+)-α-**3**] all are configurationally related at C-5 since they were derived from (−)-isomethadone (Table I).

(1) Part VII of this series: P. S. Portoghese and D. A. Williams, *J. Med. Chem.*, **12**, 839 (1969).

(2) We gratefully acknowledge support of this work by National Institute of Health Grant NS 05192.

(3) For a preliminary report on this work, see P. S. Portoghese and D. A. Williams, *Tetrahedron Lett.*, 6299 (1966).

(4) Predoctoral Fellow 5-FI-GM 20515, 1963-1966.

(5) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 663 (1948).

(6) M. Speeter, W. Byrd, L. Cheney, and S. Brinkley, *J. Amer. Chem. Soc.*, **71**, 57 (1949).

(7) E. L. May and N. B. Eddy, *J. Org. Chem.*, **17**, 1210 (1952).