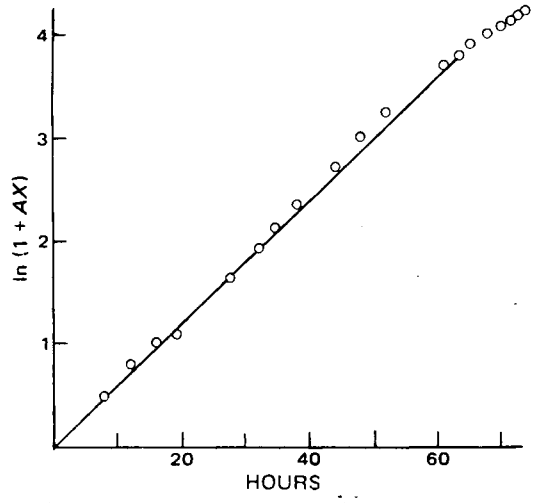

Figure 2—*Data from Fig. 1 treated according to Eq. 3* (A = 70).

The data treatment (3–6) of the curve is as follows. If the amount is n moles and if there are x moles decomposed at time t, then x is present as liquid. If the solubility of parent compound in the liquid is S moles of RCOOH/mole of RH, then the amount of solid present is $n - x - Sx$; the rate equation then is:

$$dx/dt = -k_s(n - X - Sx) - k_lSx \qquad \text{(Eq. 1)}$$

where k_s and k_l are solid and liquid first-order rate constants, respectively. If the mole fraction $X = x/n$ is used in place of moles decomposed, the equation becomes:

$$dX/dt = -k_s(1 - x - SX) - k_lSX \qquad \text{(Eq. 2)}$$

By integration:

$$\ln(1 + AX) = -\alpha t \qquad \text{(Eq. 3)}$$

where $A = \alpha/k_s$ and $\alpha = k_lS - k_sS - k_s$. The value of A is found by iteration, and linearization according to Eq. 3 is shown in Fig. 2. Once all solid has disappeared, the model no longer holds and simply reverts to solution kinetics as pointed out by Carstensen and Musa (3).

The values at four temperatures are shown in Table I. The least-squares fit for the Arrhenius plot (Fig. 3) is:

$$\ln k_s = (-38{,}650/R)(1/T) + 46.25 \qquad \text{(Eq. 4)}$$

with a correlation coefficient of −0.992. The activation

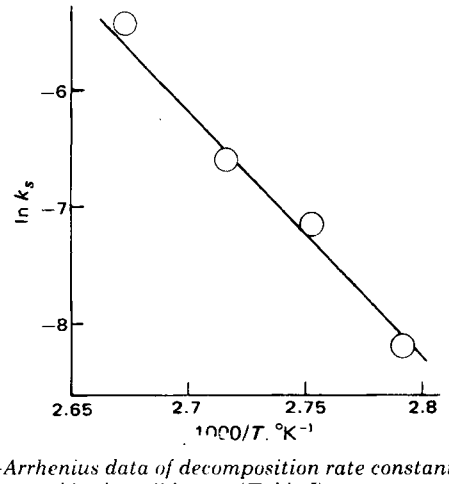

Figure 3—*Arrhenius data of decomposition rate constants,* k_s, *of the parent compound in the solid state (Table I).*

Table I—Parameter Values at Different Temperatures

Temperature	1000/T	A^a	α^b, hr^{-1}	$k_s{}^c$, hr^{-1}	ln k_s
85°	2.792	28	0.0070	0.00025	−8.094
90°	2.754	70	0.0594	0.00085	−7.070
95°	2.716	110	0.116	0.00151	−6.496
101°	2.673	175	0.571	0.00327	−5.723

[a] The A denotes the iteration constant in Eq. 3. [b] The α denotes the slope of the line according to Eq. 3. [c] The k_s is the solid-state decomposition constant.

energy for k_s is high compared to usual solution kinetics (although within range) but is lower than that for, for instance, the solid-state decomposition of substituted benzoic (3) or salicylic (6) acids. Solid-state activation energies are extremely high (3–7, 9–13). When they are wholly dictated by physical propagation (type I), the energy of activation supersedes the normal range for solution kinetics by a factor of two to three. Type II reactions usually have intermediate activation energies.

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Structure–Activity Analysis of Hydrazide Monoamine Oxidase Inhibitors Using Molecular Connectivity

Keyphrases □ Molecular connectivity analysis—hydrazide monoamine oxidase inhibitors, structure–activity relationships □ Structure–activity relationships—hydrazide monoamine oxidase inhibitors, molecular connectivity analysis □ Monoamine oxidase inhibitors—hydrazides, structure–activity relationships, molecular connectivity analysis

To the Editor:

Fulcrand *et al.* (1) recently analyzed a series of monoamine oxidase inhibitors and found good correlations between pI_{50} values and electronic and steric parameters for 24 compounds. The methods of Hansch *et al.* (2) and Free and Wilson (3), as employed by Fulcrand *et al.* (1), were equally successful in correlating physical properties with

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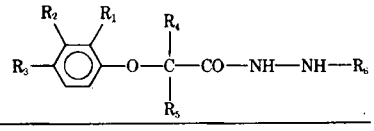

Table I—Hydrazide Monoamine Oxidase Inhibitors

Compound	R_1	R_2	R_3	R_4	R_5	R_6	E	pI_{50}
I	H	H	H	H	H	$CH(CH_3)_2$	−0.4310	5.42
II	Cl	H	H	H	H	$CH(CH_3)_2$	−0.4425	5.60
III	H	Cl	H	H	H	$CH(CH_3)_2$	−0.4368	5.40
IV	H	H	Cl	H	H	$CH(CH_3)_2$	−0.4433	5.96
V	CH_3	H	H	H	H	$CH(CH_3)_2$	−0.4390	5.54
VI	H	CH_3	H	H	H	$CH(CH_3)_2$	−0.4333	5.05
VII	H	H	CH_3	H	H	$CH(CH_3)_2$	−0.4355	5.40
VIII	OCH_3	H	H	H	H	$CH(CH_3)_2$	−0.4365	5.62
IX	H	OCH_3	H	H	H	$CH(CH_3)_2$	−0.4365	5.42
X	H	H	OCH_3	H	H	$CH(CH_3)_2$	−0.4353	5.52
XI	H	H	H	H	CH_3	$CH(CH_3)_2$	−0.4125	5.00
XII	Cl	H	H	H	CH_3	$CH(CH_3)_2$	−0.4148	5.16
XIII	H	Cl	H	H	CH_3	$CH(CH_3)_2$	−0.4118	4.96
XIV	H	H	Cl	H	CH_3	$CH(CH_3)_2$	−0.4155	5.00
XV	H	H	H	CH_3	CH_3	$CH(CH_3)_2$	−0.4025	4.34
XVI	H	H	Cl	CH_3	CH_3	$CH(CH_3)_2$	−0.4133	4.80
XVII	H	CH_3	H	H	CH_3	$CH(CH_3)_2$	−0.4115	4.90
XVIII	H	H	H	H	H	C_2H_5	−0.4232	5.82
XIX	H	H	Cl	H	H	C_2H_5	−0.4262	6.00
XX	H	H	H	H	H	$CH_2C_6H_5$	−0.4448	6.14
XXI	H	H	H	H	H	$CH(CH_3)C_6H_5$	−0.4340	5.70
XXII	H	H	CH_3	H	H	$CH(CH_3)C_6H_5$	−0.4340	6.05
XXIII	H	H	OCH_3	H	H	$CH(CH_3)C_6H_5$	−0.4368	6.00
XXIV	H	H	Cl	H	H	$CH_2C_6H_5$	−0.4560	6.96

the activity of the molecules whose structures are shown in Table I. Electronic effects, reflected in polarographic half-wave potentials, and steric effects were the most important parameters examined in the correlations. It was concluded that the monoamine oxidase inhibitory activity of the series was due to the hydrazide group, which could form an unstable diazene with the monoamine oxidase flavine coenzyme before rearrangement to bind on the enzyme.

An alternative approach to determining structure–activity relationships and to improving the understanding of the mechanism of action of a series of compounds evolved from the work of Kier and Hall (4, 5) and has been used extensively in structure–activity analyses (6–8). This approach, the molecular connectivity method, has its roots in the topology of the molecules, from which a set of indexes may be calculated. These indexes encode molecular structural information into the regression analysis. The indexes may be used alone or in conjunction with other physical parameters to discover correlations concerning biological or chemical activity within a series of molecules.

Molecular connectivity indexes were calculated for the monoamine oxidase inhibitors of Fulcrand *et al.* (1). Linear regression analysis by computer search for the three variables that gave the best correlation with activity as monoamine oxidase inhibitors yielded:

$$pI_{50} = -5.2 - 29E - 0.82\,{}^2\chi + 1.8\,{}^3\chi_p^v \qquad \text{(Eq. 1)}$$
$$n = 24 \quad r = 0.941 \quad s = 0.201 \quad F = 52$$

where E represents the half-wave potential; the other indexes calculated for the molecules were shown previously (4). This equation clearly indicates that electronic effects contribute to the monoamine oxidase inhibitor activity of the hydrazides, in agreement with Fulcrand *et al.* (1). The ${}^2\chi$ index gives weight to structural features of two-bond lengths in the molecules, whereas the ${}^3\chi_p^v$ index represents three-bond path lengths within the molecules and also emphasizes the importance of the heteroatoms in the substituents.

To gain further insight into structural influences on the interaction between the inhibitors and the active enzyme site, regression analyses were run on a subseries of molecules formed by the deletion of certain substituent groups. In particular, the nitrogen substituent (R_6) was kept constant with the isopropyl group to determine if this substituent was governing the inhibitory potency. This subset of 17 molecules correlates with pI_{50}:

$$pI_{50} = -4.1 + 0.59\,{}^0\chi^2 - 0.94\,{}^2\chi - 23E \qquad \text{(Eq. 2)}$$
$$n = 17 \quad r = 0.951 \quad s = 0.134 \quad F = 41$$

Again, E and ${}^2\chi$ emerge as significant parameters, but ${}^3\chi_p^v$ is replaced by ${}^0\chi^v$. However, this new valency chi index retains an indication of a contribution of heteroatoms in the substituents to activity. If the R_4 and R_5 substituents are limited to hydrogen while R_6 is kept as isopropyl, then only 10 molecules remain and the correlation is:

$$pI_{50} = -34 - 94E - 2.6\,{}^4\chi_{pc}^v \qquad \text{(Eq. 3)}$$
$$n = 10 \quad r = 0.923 \quad s = 0.100 \quad F = 20$$

Electronic effects again contribute to the relationship. The ${}^4\chi_{pc}^v$ index relates well to systems where ring substitutions have been made and indicates that monoamine oxidase inhibitor activity of the hydrazides is related to the ring in some fashion, perhaps indirectly through its effects on the neighboring ether linkage. A further argument can be made for this point if all substituents from R_1 through R_5 are restricted to hydrogen and R_6 is varied. Only four molecules remain in the set, but there is no hint of correlation with electronic or chi parameters to the monoamine oxidase inhibitor activity.

Although the R_6 substituents certainly must affect the hydrazide, these observations would clearly argue against the hydrazide moiety as the sole contributor to biological activity. Therefore, it may be concluded that monoamine oxidase inhibitor activity of these hydrazides depends

largely on the nature of the ring substitution as well as on the half-wave reduction potential of the ring, its substituents, or the ether oxygen.

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Calculation of Cutaneous Metabolic Rate Constant from Diffusion Model

Keyphrases □ Rotating disk—analysis, cutaneous metabolism of vidarabine, guinea pig, *in vitro* study □ Skin—metabolism of vidarabine, rotating-disk method, guinea pig, *in vitro* study □ Antiviral agents—vidarabine, cutaneous metabolism, rotating-disk method, guinea pig, *in vitro* study □ Vidarabine—cutaneous metabolism, analysis by rotating-disk method, guinea pig, *in vitro* study

To the Editor:

A method for the determination of the cutaneous metabolic rate constant for vidarabine (I) from a rotating-disk diffusion model was reported recently by Leung and Ando (1). They calculated the enzyme rate constant from the observed flux using:

$$k_m = 1 \Big/ \left[\frac{C_A(h)}{-F_A} - \frac{h}{D_{aqA}}\right](m) \qquad \text{(Eq. 1)}$$

where k_m is the first-order enzyme rate constant, $C_A(h)$ is the initial substrate concentration, F_A is the flux of the substrate in the system, h is the aqueous diffusion layer thickness, D_{aqA} is the aqueous diffusion coefficient, and m is the membrane thickness. Equation 1 was derived from Eq. 25 of a previous publication by Ando *et al.* (2) by taking the limit of $\theta \to 0$ such that $\tanh \theta \to \theta$:

$$\frac{1}{\kappa} = C_1 \tanh \kappa m \qquad \text{(Eq. 2)}$$

where:

$$\kappa = \sqrt{k_m/D_A}$$

$$C_1 = D_A\left[\frac{C_A(h)}{-F_A} - \frac{h}{D_{aqA}}\right]$$

$$\theta = \kappa m$$

and D_A is the diffusion coefficient of the substrate for the cutaneous tissue.

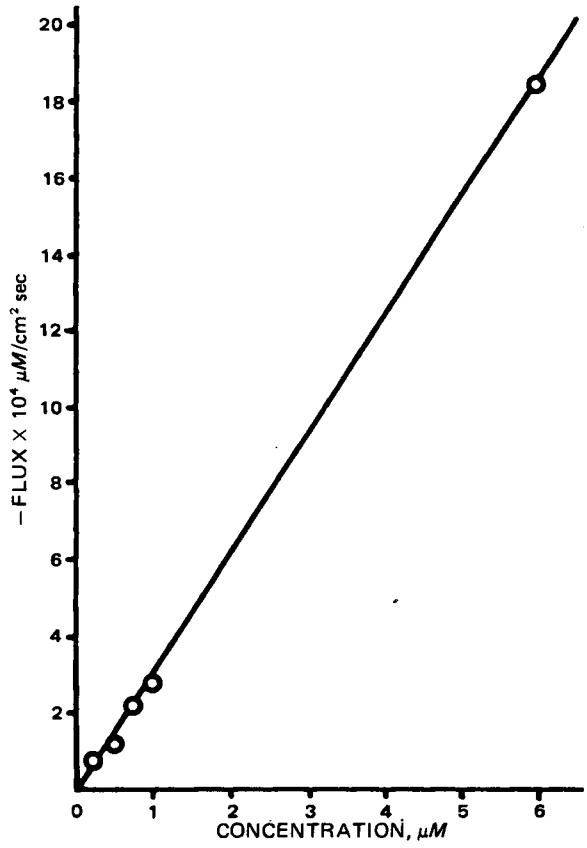

Figure 1—*Plot of flux* versus *substrate concentration. The slope of the linear regression line is 3.11 × 10⁻⁴ cm⁻² sec⁻¹ (r = 0.9997).*

The k_m of the deaminase enzyme in guinea pig epidermis was calculated to be 0.156 sec^{-1}, which contradicts the $\theta \to 0$ assumption by giving θ values of 0.25 and 24.9 for D_A values of 1.0×10^{-5} and 1.0×10^{-9} cm^2/sec, respectively. Obviously, the validity of Eq. 1 is questionable when D_A is smaller than 1.0×10^{-5} cm^2/sec. Strictly speaking, the $\theta \to 0$ assumption should never be valid because it leads to either $D_A \to \infty$, *i.e.*, no diffusional barrier exists, or $m \to 0$, *i.e.*, no membrane exists, since k_m is finite. In neither case will the simultaneous diffusion and metabolism theory

Table I—Fluxes [a] of I at Different Concentrations

Concentration, μM	Flux, %/cm^2 min	Mean Flux %/cm^2 min	Mean Flux $\mu M/cm^2$ sec
0.25	1.630 1.956 1.892	1.826	7.61×10^{-5}
0.50	1.888 0.797 1.164	1.283	1.07×10^{-4}
0.75	1.662 1.713 1.717	1.679	2.10×10^{-4}
1.0	1.691 1.921 1.230	1.616	2.69×10^{-4}
6.0	1.568 1.787 2.144	1.839	1.84×10^{-3}
600.0	0.388 0.399 0.346	0.378	3.78×10^{-2}

[a] Negative signs for all flux values, which indicate directions of the fluxes, are omitted in this table.

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