H_2O until the washings showed a negative $AgNO_3$ test for halide (150 ml). The amine was then eluted with 200 ml of 4 *N* HCl. The presence of the product in each fraction was determined by observing a yellow color after the addition of a few drops of 15% NaOH to a small aliquot. The eluent was concentrated under vacuum to give a white solid which was filtered in hot MeOH. The addition of a few drops of Et_2O led to crystallization of amine hydrochloride (2.45 g, 0.0112 mol, 47%). The analytical sample was obtained by recrystallization from 2-propanol-Et_2O: mp 226–227.5° dec; nmr (D_2O) δ 6.85 (s, Ar), 6.81 (s, Ar), 3.75 (m, CH), 2.95 (d, CH_2), 2.24 (s, $ArCH_3$), 1.42 ppm (d, CH_3); ir (KBr) 3460 (OH stretch), 3240 (OH stretch), 2970 cm^{-1} (NH_3^+); uv (absolute EtOH, 2.1 mg/100 ml) λ_{max} 296 nm (ϵ 4000), 318 (sh, 5000); uv (1 min after addition of 1 drop of 1% NaOH) λ_{max} 296, 273 nm. The absorbances indicated essentially complete conversion of **5** to **7**. A transient absorbance at 435 nm with a half-life of a few seconds was observed immediately upon addition of a drop of 1% NaOH to a solution of **5**·HCl. *Anal.* ($C_{10}H_{15}NO_2$) C, H, N.

5-Hydroxy-2,6-dimethylindole (7). A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**4**, 1.60 g, 0.00766 mol) in 10 ml of 48% HBr was held at reflux for 12 hr and then poured into 50 ml of ice H_2O. The pH of the aqueous mixture was adjusted to 9.5 by careful addition of concentrated NH_4OH. After stirring overnight in air, the crude indole was extracted with 2 × 60 ml of Et_2O; the Et_2O was dried ($MgSO_4$) and concentrated to give 1.5 g of solid. Sublimation (115–118°, 100 μ) provided 0.835 g (0.00518 mol, 68%) of a colorless solid. Recrystallization from PhH-Et_2O gave the pure product: mp 180–183° (lit.[14] mp 183–184°); nmr ($CDCl_3$) δ 7.00, 6.85, 5.92 (s, Ar), 2.35, 2.26 ppm (s, CH_3); uv (absolute EtOH, 2.30 mg/100 ml) λ_{max} 296 nm (ϵ 5700), 274 (7000); uv (30 sec after addition of 1 drop of 1% NaOH) λ_{max} 296 nm (ϵ 5200), 273 (6900).

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Quantum Statistical Calculation for the Correlation of Biological Activity and Chemical Structure. 2. Drug-Membrane Penetrations

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In part 1[1] it was shown that drug actions could be correlated in terms of drug–receptor interactions through the use of the quantum statistical concept. Infrared spectroscopic data for given functional groups were used as the independent variable in a linear regression. The theoretical background is based on the probability of binding a set of receptor sites with active centers of a drug molecule. This probability is related to the partition function of statistical mechanics, and the partition function is associated with quantum energy levels of drug molecules, which are observable by various spectral techniques. The main feature of this correlation is to avoid the tedious procedure of quantum chemical calculations, though the calculations are fascinating and interesting.

In part 1 we also discussed the variable p(Brownian) which is associated with the probability of a drug molecule's passing through biological membranes. At that time we mentioned the possibility of publishing the theoretical derivation of p(Brownian) in part 2. We now proceed to do this by identifying this variable with the lipophilic parameter[2-6] π, which is defined as log (P_x/P_h) where P_h and P_x are, respectively, the partition coefficients of the parent compound and its derivatives between the organic phase and the aqueous phase. Two variables are used for the correlation of biological activity and chemical structure. First, spectroscopic data (including uv and ir) are used to express the probability of adsorption between the receptors and the drug molecules. Second, the parameter π, the relative lipophilicity, is used as a measure of the penetration ability of the drug molecules.

Theoretical Method. The same postulate as in part 1 is made; *i.e.*, the rate of biological response is expressed in the simple form

$$\frac{d(\text{biological response})}{dt} = AC \times p^{a1}(\text{Brownian}) \times p^{a2}(\text{binding}) \quad (1)$$

where C is the drug concentration, p(Brownian) is the probability of successful penetration of a drug molecule in the Brownian-like motion (see Figure 1) through biomembranes to reach a receptor, p(binding) is the probability of a successful binding between a drug molecule and a receptor, and a1 and a2 are constants.

To derive p(Brownian) we shall assume a simple physical model which can be handled mathematically. In Figure 1 a drug molecule is moving from the origin to the receptor site, with **r** representing the position vector in two-dimensional version. A drug molecule has made M steps (the length of each step is a) from the origin in the extracellular phase to reach the receptor site which is located l units from the origin. Each step of the movement can be in the states $i = 1, 2, 3, \ldots, n$ with partition function $j_i(T)$† and length l_i. Suppose a net attraction force of the lipophilicity τ is applied in the biomembrane to pull in the drug molecule in the extracellular fluid. The partition function for this system is

$$\Delta(\tau, M, T) = \xi(\tau, T)^M \quad (2)$$

†For a similar model used in polymer chemistry see ref 7.

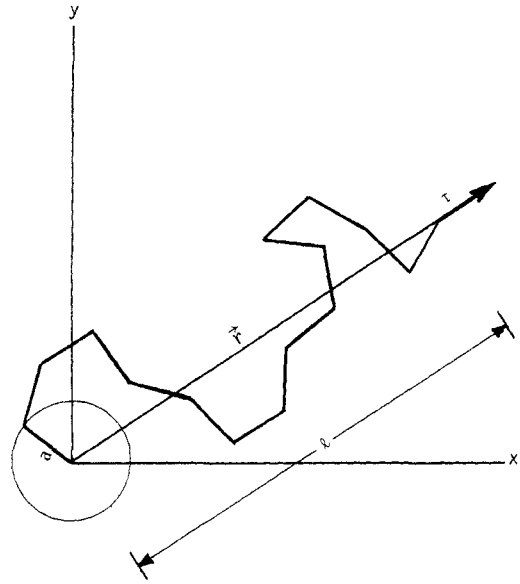

Figure 1. Two-dimensional version of the free journey movement of a drug molecule.

where

$$\xi(\tau, T) = \sum_{i=1}^{n} j_i(T) e^{\tau l_i / kT} \tag{3}$$

Now if the free journey movement is defined by starting at the origin and taking a step anywhere on the surface of a sphere with radius a, and center at the origin (see Figure 1), the end point of any step is the origin of the next step; then we can integrate along the **r** direction, obtaining

$$\xi = \int_{-a}^{a} j(T) e^{\tau l / kT} \mathrm{d}l = (2ja/t) \sinh t \tag{4}$$

where $t = \tau a/kT$. The relationship with the thermodynamic functions of interest is

$$\mathrm{d}F = -S\mathrm{d}T - \bar{l}\mathrm{d}\tau + \mu \mathrm{d}M \tag{5}$$

$$F = -kT \ln \Delta \tag{6}$$

where F is the Gibbs free energy, S is the entropy, and μ is the chemical potential. The relationship of the mean length $\bar{l}$ and lipophilicity force τ can be obtained from eq 2, 4, 5, and 6

$$\bar{l} = -\left(\frac{\partial F}{\partial \tau}\right)_{M,T} = kT\left(\frac{\partial \ln \Delta}{\partial \tau}\right)_{M,T} = MkT\left(\frac{\partial \ln \xi}{\partial \tau}\right)_{T} = MaL(t)$$

or

$$t = L^{-1}(\bar{l}/Ma) \tag{7}$$

where L is the Langevin function defined as

$$L(x) = \coth x - 1/x \tag{8}$$

The expansion of $L(x)$ about $x = 0$ is

$$L(x) = x/3 - x^3/45 + \ldots \tag{9}$$

and if L^{-1} is the inverse Langevin function, we have

$$\tau = \frac{kT}{a} L^{-1}(\bar{l}/Ma) \simeq 3kT\bar{l}/Ma^2 \tag{10}$$

provided $\bar{l} \ll Ma$, as it should be. Now, if we choose the drug which produces τ_0, the optimal attraction force of lipophilicity, at a given receptor located at the mean length $\bar{l}_0$ from the origin, then, from eq 10, we obtain

$$\tau_0 = 3kT\bar{l}_0/Ma^2 \tag{11}$$

The differential equation for the Helmholtz free energy is

$$\mathrm{d}(A - A_0) = (\tau - \tau_0)\mathrm{d}\bar{l} \tag{12}$$

Therefore

$$(A - A_0) = \int [3kT(\bar{l} - \bar{l}_0)/Ma^2]\mathrm{d}\bar{l} = 3kT(\bar{l} - \bar{l}_0)^2/2Ma^2 = -kT \ln [Q(\bar{l}, M, T)/Q(\bar{l}_0, M, T)] \tag{13}$$

where Q is the canonical ensemble partition function, which is defined as

$$Q(l, M, T) = \sum_{M} M! \prod_{i=1}^{n} \frac{j_i^{M_i}}{M_i!} \tag{14}$$

Finally, we obtain

$$p(\text{Brownian}) = VQ(\bar{l}, M, T)/Q(\bar{l}_0, M, T) = V \exp[-(A - A_0)/kT] = V \exp[-3(\bar{l} - \bar{l}_0)^2/2Ma^2] \tag{15}$$

where V is a proportionality constant. Eliminating $\bar{l}$ from eq 10, 11, and 15, we have

$$p(\text{Brownian}) = V \exp[-Ma^2(\tau - \tau_0)^2/6k^2T^2] \tag{16}$$

Since τ is associated with the attraction force of lipophilicity, the postulate may be made that

$$\tau = b\pi, \quad \tau_0 = b\pi_0 \tag{17}$$

where π is Hansch's parameter of the lipophilicity, and b is a proportionality constant, which has unit of the force. If we substitute eq 17 in eq 16 and let $c = Ma^2b^2/6k^2T^2$, then we obtain

$$p(\text{Brownian}) = V \exp[-c(\pi - \pi_0)^2] \tag{18}$$

Equation 18 is similar to Hansch's empirical equation.[2] Substituting eq 5 of part 1,[1] which is

$$p(\text{binding}) = B\lambda\xi^{-1}(\partial\xi/\partial\lambda)_T \tag{19}$$

and eq 18 in eq 1, taking logarithms on both sides, and rearranging, we obtain

$$\ln 1/C = k_1 + k_2\pi - k_3\pi^2 + k_4 \ln [B\lambda\xi^{-1}(\partial\xi/\partial\lambda)_T] \tag{20}$$

where ξ and λ are respectively given by $\xi = \Sigma_s q(s)\lambda^s$ and $\lambda = \exp(\mu/kT)$, and μ is the chemical potential. Equation 20 is the mathematical expression relating drug activity to the drug-membrane penetrations and the drug-receptor interactions. For the explicit expression of the last term of eq 20 in terms of the spectroscopic data, see ref 1.

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Quantum Statistical Calculation for the Correlation of Biological Activity and Chemical Structure. 3. Diisopyramide Phosphate and Related Compounds as Antiarrhythmic Agents

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Diisopyramide phosphate has been recognized as a new antiarrhythmic agent.[1] Our screening program for antiarrhythmic activity has generated a large amount of biological data on compounds having structural variations. We consider the data appropriate for analysis of the structure-activity relationship employing the quantum statistical concepts.[2,3] In doing this, we gain insight into the antiarrhythmic action, in the hope of predicting the drug potency before a potential antiarrhythmic agent is synthesized.

The compounds shown in Table I have the structural variations near the carbonyl group and show a wide variance in the ir absorption peak of the carbonyl group. The wave numbers ranging from as low as 1622 cm^{-1} (compound **10**) up to as high as 1735 cm^{-1} (compound **12**) represent the absorption of the fundamental vibrational transitions ($l = 0 \rightarrow l = 1$, and l is the vibrational quantum number). This difference in wave numbers measures a contribution to the variation in the drug potency.

The partition coefficients of the compounds shown in Table I were experimentally determined in an octanol-pH 7.4 phosphate buffer system[4] and found to be substantially influenced by the chemical structures. However, the partition coefficients alone did not correlate significantly with the drug potency. At this point, the lipophilicity and C=O absorption frequency are only useful correlative variables, and this study does not imply that these variables are the only variables of importance in drug-transfer and drug-receptor interaction.

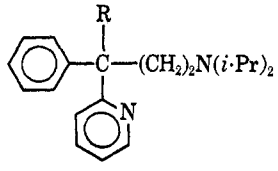
Theoretical Method. The ventricular arrhythmia induced in the unanesthetized dog by ligation of the anterior descending coronary artery was reduced by intravenous treatment with the compounds in Table I. If antiarrhythmic potency (AP) is defined as mean maximal reduction in extrasystoles per mean effective dose, eq 2 of part 1[2] must be slightly modified as

$$\mathrm{AP} = \frac{\text{mean maximal reduction in extrasystoles}}{\text{mean effective dose}} = \frac{\mathrm{d(response)}/\mathrm{d}t}{1000C} = Ap^{a1}(\text{Brownian}) \times p^{a2}(\text{binding}) \quad (1)$$

where C is the molar concentration and A is the proportionality constant, which has the same unit as d(response)/Cdt. Substituting eq 5 of part 1[2] and eq 18 of part 2[3] in eq 1, taking logarithms on both sides, and collecting constants in one term, we obtain

$$\ln \mathrm{AP} = k_1 + k_2\pi - k_3\pi^2 + k_4 \ln [\lambda\xi^{-1}(\partial\xi/\partial\lambda)_T] \quad (2)$$

Table I. Data for Observed and Calculated Antiarrhythmic Potency



Compd	R	π	Ir, cm^{-1}, $\nu_{C=O}$	Ln AP[a] Obsd	Ln AP[a] Calcd[b]	Ln AP[a] Calcd[c]
1	$-CONMeNMe_2$	0.30	1640	2.254	2.276	2.276
2	$-CONHEt$	0.21	1656	1.891	1.936	1.965
3	$-CONHNHMe$	−0.35	1645	1.711	1.601	1.649
4	$-CO_2Et$	1.11	1733	1.677	1.518	1.603
5	$-CONHNHAc$	−0.57	1624	1.715	1.738	1.769
6	$-COMe$	0.75	1712	1.403	1.527	1.604
7	$-NHAc$	0.05	1679	1.313	1.419	1.492
8	$-CONHN{=}CMe_2$	0.21	1680	1.374	1.549	1.613
9	$-CONH_2(H_3PO_4)$ (Norpace)	0.00	1682	2.195		1.405
10	$-CONHNH_2$	−0.73	1622	1.407	1.624	1.663
11	$-CONHNMe_2$ (oxalate MeOH)	−0.59	1656	1.514	1.204	1.284
12	$-CO_2Me$	0.61[d]	1735	0.910	1.028	1.148
13	$-CONHPh$ $(H_2SO_4 \cdot 0.5H_2O)$	1.65	1683	2.935	2.818	2.795
14	$-CONHMe$	−0.31[e]	1661	1.404	1.379	1.449
15	$-CONHCH_2OH$	−0.82	1657	1.085	0.977	1.073

[a] AP = 5 × MW × AR/1000, where MW is the molecular weight and AR is the activity ratio, which is described in a paper by Yen, Lowrie, and Dean (*J. Med. Chem.*, submitted for publication). [b] The values are computed from eq 9. [c] The values are computed from eq 10. [d] This value was estimated by subtracting 0.5 from compound **4**. [e] This value was estimated by subtracting 0.5 from compound **2**.