# Decomposition of Pharmacological Activity Indices into Mutually Independent Components Using Principal Component Analysis

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Various subsets of pharmacological activity indices of benzodiazepines, of 8-quinolinol derivatives, and of rifamycin B amides were decomposed into mutually independent components by using principal component analysis. The activities not included into the subset were considered as the dependent variables. In three out of the six cases with a fair correlation coefficient ($r \geq 0.9$) between pairs of primary pharamcological indices, the main component obtained by the decomposition procedure showed significantly higher correlation with the dependent variable than any of the original pharmacological activity indices. Factors, explaining a rather low portion of the total sample variance of the subset, may still account for important secondary effects.

Expected pharmacological potencies of new derivatives of a series of biologically active molecules can often be predicted by using multiple linear regression analysis. It is postulated that significant correlations should exist between parameters characteristic for the molecules and the dependent variable, the "target" activity, which is to be optimized. If such correlations exist, predictions can be made for the new derivative on the basis of multiple linear regression equations derived between these parameters and the pharmacological activity indices of the other molecules of the series.

The well-known Hansch approach[1] tries to explain the variance in the observed pharmacological activities in terms of *physical–chemical* indices. The method proposed by Free and Wilson[2] uses *codes*, representing the chemical structure of the molecules. *Biological activities* themselves can also be used to predict the pharmacological activity of a new derivative of a series of molecules. This approach is used practically in all cases where the activities of the series of molecules were determined in animals and some also in humans, and the results are to be extrapolated to the human activity index of a new derivative entering clinical examination. In this example, the dependent variable is one of the pharmacological activities, i.e., the observed potency in humans, whereas other types of pharmacological indices serve as parameters to explain the variance in the human activities of the molecules.

Serious problems may arise if there are intercorrelations between the physical–chemical indices or between the various biological activity indices. First, all possible combinations of the independent variables have to be considered[3] to ensure that the regression equation derived was the best possible. The term "best" denotes the equation with the highest multiple correlation coefficient, $R$, out of all the equations obtained by considering the same number of independent variables. Secondly, if intercorrelations exist, no unique interpretation can be given for the equations derived.

Attempts were made to use noninterrelated data sets or to construct such sets from intercorrelated ones. These include the transformation of the Hammett indices[4] $\sigma_m$ and $\sigma_p$ into the essentially independent values $\mathcal{F}$ and $\mathcal{R}$, defined by Swain and Lupton.[5] Hansch et al. grouped the similar substituents on the basis of cluster analysis.[6] Factor analysis and a subsequent multiple linear regression analysis were applied to the various activity indices of diphenylaminopropanols by Weiner and Weiner[7] to identify the essential factors influencing the pharmacological potency. Cammarata and Menon[8] performed principal component analysis for the geometric descriptor indices of weak and strong pressor agents and for the molar refractivity indices of the constituents of antihistaminics, anticholinergics, antidepressants, and antipsychotics. Dunn et al.[9,10] used principal component analysis to classify the molecules on the basis of components of the substituent constants.

The present work is an attempt to *decompose* pharmacological activity indices of drugs into mutually independent components and to test their use in quantitative predictions. The sequence of the calculations performed was as follows: (1) Groups of $n$ molecules with $k'$ pharmacological activity indices were considered ($k' < n$). Depending on the conditions, we had $k' = 4$ or 5. (2) Principal component analysis was performed using only $k$ of the original pharmacological indices per subset, where $k = k' - 1$. The omitted index was considered to be the "dependent" variable. In this way, for each series $k'$, different test cases were constructed. (3) Multiple linear regression equations were derived between the various dependent variables and the components obtained in step 2. (4) The results were compared with regression equations derived between the nontransformed (primary) pharmacological indices. (5) The results were also compared with multiple linear regression equations obtained by using the standard Hansch approach.[1] The substituent constants were *not* subjected to the decomposition procedure.

## Method of Calculation

To introduce principal component analysis, we follow the notation given by Wilks.[11] Consider a sample $x_{1\xi}, x_{2\xi}, ..., x_{k\xi}$ (where $\xi = 1, ..., n$) of size $n$, where $n$ denotes the number of compounds and $k$ ($k < n$) is the number of pharmacological tests used to determine the potencies of the drug molecules. The various experimental indices are interrelated. We may transform these activity data, denoted in compact matrix notation by $\|x_{ij}\|$ ($i$ =

(1) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964); T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964).
(2) S. M. Free and J. M. Wilson, *J. Med. Chem.*, **7**, 395 (1964).
(3) C. Hansch and C. Silipo, *J. Med. Chem.*, **17**, 661 (1974).
(4) L. P. Hammett, *Trans. Faraday Soc.*, **34**, 156 (1938).
(5) C. G. Swain and E. C. Lupton, Jr., *J. Am. Chem. Soc.*, **90**, 4328 (1968).
(6) C. Hansch, S. H. Unger, and A. B. Forsythe, *J. Med. Chem.*, **16**, 1217 (1973).
(7) M. L. Weiner and P. M. Weiner, *J. Med. Chem.*, **16**, 655 (1973).
(8) A. Cammarata and G. K. Menon, *J. Med. Chem.*, **19**, 739 (1976).
(9) W. J. Dunn III, S. Wold, and Y. C. Martin, *J. Med. Chem.*, **21**, 922 (1978).
(10) W. J. Dunn III and S. Wold, *J. Med. Chem.*, **21**, 1001 (1978).
(11) S. S. Wilks, "Mathematical Statistics", Wiley, New York, 1962, p 564.

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Table I. Experimental[a] and Predicted Activities [in −Log $C$ (mmol/kg) Units] of Benzodiazepine Derivatives (I)

| | | | | incl screen | | foot shock | | pentylene-tetrazol | | electroshock max | | electroshock min | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | X | Y | Z | obsd | pred (eq 11) | obsd | pred (eq 17) | obsd | pred (eq 23) | obsd | pred (eq 29) | obsd | pred (eq 35) |
| 1 | H | H | H | 0.20 | 0.02 | 0.37 | 0.41 | −0.53 | 0.83 | 0.90 | 0.68 | 0.50 | 0.22 |
| 2 | H | F | H | 0.23 | 0.09 | 0.41 | 0.45 | −0.50 | 0.89 | 1.04 | 0.64 | 0.41 | 0.29 |
| 3 | H | Cl | H | 0.56 | 0.63 | 1.13 | 0.95 | 1.66 | 1.94 | 1.03 | 1.38 | 0.65 | 0.15 |
| 4 | H | Br | H | 1.10 | 0.90 | 1.20 | 1.50 | 2.27 | 2.03 | 1.93 | 1.33 | 0.20 | 0.57 |
| 5 | H | $NO_2$ | H | 1.27 | 1.30 | 1.75 | 1.67 | 2.75 | 2.69 | 1.52 | 1.58 | 3.28 | 0.29 |
| 6 | H | $CF_3$ | H | 1.48 | 1.03 | 1.48 | 1.66 | 2.48 | 2.59 | 1.78 | 2.06 | 1.16 | 0.45 |
| 7 | H | $CH_3$ | H | −0.40 | −0.07 | 0.40 | 0.30 | 1.55 | 0.42 | 1.75 | 0.14 | −0.51 | −0.15 |
| 8 | H | Cl | F | 0.86 | 1.39 | 1.76 | 1.41 | 3.55 | 3.32 | 2.28 | 1.98 | 0.76 | 0.67 |
| 9 | H | Cl | Cl | 0.48 | 0.41 | 0.88 | 1.10 | 2.88 | 1.65 | 1.37 | 1.51 | 0.42 | 0.31 |
| 10 | H | Cl | $CH_3$ | 0.28 | 0.05 | 0.45 | 0.80 | 1.57 | 0.91 | 1.13 | 1.00 | 0.19 | 0.27 |
| 11 | H | Cl | $OCH_3$ | 0.00 | 0.02 | 0.48 | 0.58 | 1.60 | 1.05 | 1.00 | 1.07 | 0.35 | 0.21 |
| 12 | $CH_3$ | Cl | H | 0.98 | 1.04 | 1.45 | 1.35 | 2.31 | 2.51 | 1.65 | 1.62 | 0.65 | 0.40 |
| 13 | $CH_3$ | $NO_2$ | H | 1.47 | 1.81 | 2.07 | 1.83 | 2.69 | 3.36 | 2.29 | 1.52 | 0.19 | 0.65 |
| 14 | H | $N(CH_3)_2$ | H | −0.25 | −0.14 | 0.45 | 0.40 | 0.82 | 0.40 | −0.12 | 0.38 | −0.38 | −0.33 |
| 15 | $CH_3$ | $N(CH_3)_2$ | H | 0.29 | 0.32 | 0.87 | 0.87 | 1.70 | 1.18 | 0.50 | 0.90 | −0.06 | −0.09 |
| 16 | H | CN | H | 0.54 | 0.35 | 0.82 | 1.19 | 2.30 | 1.04 | 0.89 | 0.85 | −0.41 | 0.08 |
| 17 | $CH_3$ | CN | H | 1.14 | 1.28 | 1.74 | 1.55 | 2.36 | 2.56 | 1.29 | 1.35 | 0.14 | 0.19 |
| 18 | H | $NO_2$ | F | 1.87 | 1.66 | 2.18 | 2.10 | 2.49 | 2.90 | 1.18 | 1.53 | 0.18 | 0.07 |
| 19 | $CH_3$ | $NO_2$ | F | 2.50 | 2.08 | 2.59 | 2.71 | 3.42 | 3.31 | 1.42 | 1.73 | −0.04 | 0.11 |
| 20 | $C_2H_5$ | Cl | H | 0.60 | 0.87 | 1.17 | 1.16 | 1.87 | 1.87 | 1.56 | 0.84 | −0.30 | 0.40 |
| 21 | $C(CH_3)_3$ | Cl | H | −0.19 | −0.03 | 0.51 | 0.29 | 0.39 | 0.41 | −0.26 | 0.11 | −0.39 | −0.38 |
| 22 | $CH_3$ | Cl | Cl | 0.90 | 0.98 | 1.50 | 1.38 | 2.88 | 2.47 | 1.33 | 1.70 | 0.59 | 0.22 |

[a] The experimental data have been taken from a compilation by Sternbach (ref 13).

Table II. Benzodiazepine Derivatives (I). Physicochemical Parameters[a]

| no. | $\pi_x$ | $\pi_y$ | $\sigma_{m(y)}$ | $\mathcal{F}_y$ | $\pi_z$ | $\sigma_{m(z)}$ | $\sigma_{p(z)}$ |
|---|---|---|---|---|---|---|---|
| 1 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 2 | 0.00 | 0.14 | 0.34 | 0.43 | 0.00 | 0.00 | 0.00 |
| 3 | 0.00 | 0.71 | 0.37 | 0.41 | 0.00 | 0.00 | 0.00 |
| 4 | 0.00 | 0.86 | 0.39 | 0.44 | 0.00 | 0.00 | 0.00 |
| 5 | 0.00 | −0.28 | 0.71 | 0.67 | 0.00 | 0.00 | 0.00 |
| 6 | 0.00 | 0.88 | 0.43 | 0.38 | 0.00 | 0.00 | 0.00 |
| 7 | 0.00 | 0.56 | −0.07 | −0.04 | 0.00 | 0.00 | 0.00 |
| 8 | 0.00 | 0.71 | 0.37 | 0.41 | 0.14 | 0.34 | 0.06 |
| 9 | 0.00 | 0.71 | 0.37 | 0.41 | 0.71 | 0.37 | 0.23 |
| 10 | 0.00 | 0.71 | 0.37 | 0.41 | 0.56 | −0.07 | −0.17 |
| 11 | 0.00 | 0.71 | 0.37 | 0.41 | −0.02 | 0.12 | −0.27 |
| 12 | 0.56 | 0.71 | 0.37 | 0.41 | 0.00 | 0.00 | 0.00 |
| 13 | 0.56 | −0.28 | 0.71 | 0.67 | 0.00 | 0.00 | 0.00 |
| 14 | 0.00 | 0.18 | −0.15 | 0.10 | 0.00 | 0.00 | 0.00 |
| 15 | 0.56 | 0.18 | −0.15 | 0.10 | 0.00 | 0.00 | 0.00 |
| 16 | 0.00 | −0.57 | 0.56 | 0.51 | 0.00 | 0.00 | 0.00 |
| 17 | 0.56 | −0.57 | 0.56 | 0.51 | 0.00 | 0.00 | 0.00 |
| 18 | 0.00 | −0.28 | 0.71 | 0.67 | 0.14 | 0.34 | 0.06 |
| 19 | 0.56 | −0.28 | 0.71 | 0.67 | 0.14 | 0.34 | 0.06 |
| 20 | 1.02 | 0.71 | 0.37 | 0.41 | 0.00 | 0.00 | 0.00 |
| 21 | 1.98 | 0.71 | 0.37 | 0.41 | 0.00 | 0.00 | 0.00 |
| 22 | 0.56 | 0.71 | 0.37 | 0.41 | 0.71 | 0.37 | 0.23 |

[a] Reference 18.

1, ..., $k$; $j$ = 1, ..., $n$), into a new matrix $\|z_{p\xi}\|$ ($p$ = 1, ..., $k$; $\xi$ = 1, ..., $n$), the rows of which are *not* interrelated:

$$z_{p\xi} = \sum_{i=1}^{k} c_{ip} x_{i\xi} \qquad (1)$$

$$\xi = 1, ..., n$$

The transformation coefficients $\|c_{ip}\|$ are obtained by solving the eigenvalue equation

$$\sum_{j=1}^{k} (u_{ij} - l_p \delta_{ij}) c_{jp} = 0 \qquad (2)$$

$$i = 1, ..., k$$

where $\delta_{ij} = 1$ if $i = j$, and $\delta_{ij} = 0$ if $i \neq j$; $l_p$ ($p$ = 1, ..., $k$) denotes the $p$th root of the characteristic equation

$$|u_{ij} - l\delta_{ij}| = 0 \qquad (3)$$

where $|u_{ij} - l\delta_{ij}|$ denotes the determinant of matrix $\|u_{ij} - l\delta_{ij}\|$. The internal scatter matrix $\|u_{ij}\|$ is easily obtained from sample $\|x_{ij}\|$:

$$u_{ij} = u_{ji} = \sum_{\xi=1}^{n} (x_{i\xi} - \bar{x}_i)(x_{j\xi} - \bar{x}_j) \qquad (4)$$

$$i, j = 1, ..., k$$

where $\bar{x}_i$ and $\bar{x}_j$ denote the mean values of rows $i$ and $j$ of matrix $\|x_{ij}\|$. The diagonal element $u_{ii}$ of the internal scatter matrix, divided by $n - 1$, is equal to the sample variance $s_i^2$ of variable $i$. The eigenvalues $l_1, l_2, ..., l_k$ of matrix $\|u_{ij}\|$ divided by $n - 1$ are the *principal components* of the total sample variance (SV). The symbol $PR_p$ ($p$ = 1, ..., $k$) is used to denote row $p$ of matrix $\|z_{pq}\|$ ($q$ = 1, ..., $n$), to indicate that these indices were obtained using principal component analysis. $PR_1$ belongs to the highest eigenvalue ($l_1$), $PR_2$ to the second ($l_2$), etc. Some properties of the variables $PR_p$ are as follows: (1) The correlation coefficients $r_{ps}$ calculated between pairs of indices $PR_p$ and $PR_s$ are $r_{ps} = 0$[12] ($p$, $s$ = 1, ..., $k$). (2) The correlation coefficients $r_p$ calculated between the dependent variable $A$ and indices $PR_p$ can be used to calculate the multiple correlation coefficient $R$ between $A$ and indices $PR_p$,[20]

$$R = \sqrt{r_1^2 + r_2^2 + ... + r_k^2}$$

This property of the mutually independent components simplifies the stepwise development of multiple linear regression equations, since the order of the variables to be considered can be determined by simple inspection of the correlation coefficients $r_p$. As a consequence, consideration of all combinations in the independent variables[3] becomes unnecessary. (3) The variance $s_{PR_p}^2$ of index $PR_p$ is $s_{PR_p}^2 = l_p/(n - 1)$. (4) The sum of the variances $s_{PR_p}^2$ is the total sample variance (SV):

$$\sum_{p=1}^{k} s_{PR_p}^2 = 1/(n - 1) \sum_{p=1}^{k} l_p = \sum_{i=1}^{k} s_i^2 \qquad (5)$$

where $s_i^2$ denotes the variance of the nontransformed variable $i$, i.e., the $i$th row of matrix $\|x_{ij}\|$.

According to eq 5, the actual ratio of the total SV "explained" by component $PR_p$ is given by the formula $l_p/\Sigma l_p$. Instead of the internal scatter matrix $\|u_{ij}\|$, the matrix of the correlation coefficients $\|r_{ij}\|$ may also be used in principal component analysis. The results obtained by using these two approaches may lead to

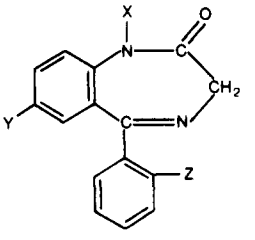
(12) T. W. Anderson, "An Introduction to Multivariate Statistical Analysis", Wiley, New York, 1958, p 272.

Table III. Regression Equations Derived for the Benzodiazepine (I) Derivatives

| type of test | equation | $n$ | $R$ | $s$ | eq no. |
|---|---|---|---|---|---|
| incl screen | $A_{IS} = 2.07(\pm0.41)\sigma_{m(y)} - 0.03$ | 22 | 0.752 | 0.48 | 6 |
| $A_{IS} = -\log C_{ED_{50}}$ | $A_{IS} = 2.06(\pm0.38)\sigma_{m(y)} - 0.11(\pm0.08)(\Sigma\pi)^2 + 0.09$ | 22 | 0.794 | 0.46 | 7 |
| | $A_{IS} = 1.01(\pm0.08)A_{FS} - 0.46$ | 22 | 0.941 | 0.25 | 8 |
| | $A_{IS} = 0.99(\pm0.08)A_{FS} + 0.15(\pm0.13)A_{E_{min}} - 0.46$ | 22 | 0.944 | 0.25 | 9 |
| | $A_{IS} = 0.40(\pm0.06)PR_1^{IS} - 0.26$ | 22 | 0.812 | 0.43 | 10 |
| | $A_{IS} = 0.40(\pm0.04)PR_1^{IS} - 0.92(\pm0.15)PR_3^{IS} - 0.53$ | 22 | 0.942 | 0.25 | 11 |
| foot shock | $A_{FS} = 1.83(\pm0.40)\sigma_{m(y)} + 0.49$ | 22 | 0.716 | 0.47 | 12 |
| $A_{FS} = -\log C_{ED_{50}}$ | $A_{FS} = 1.77(\pm0.37)\sigma_{m(y)} + 1.97(\pm0.94)\sigma_{p(z)} + 0.50$ | 22 | 0.777 | 0.44 | 13 |
| | $A_{FS} = 0.87(\pm0.07)A_{IS} + 0.53$ | 22 | 0.941 | 0.23 | 14 |
| | $A_{FS} = 0.72(\pm0.09)A_{IS} + 0.12(\pm0.06)A_{PT} + 0.42$ | 22 | 0.953 | 0.21 | 15 |
| | $A_{FS} = 0.39(\pm0.05)PR_1^{FS} + 0.27$ | 22 | 0.858 | 0.35 | 16 |
| | $A_{FS} = 0.39(\pm0.03)PR_1^{FS} + 0.65(\pm0.11)PR_3^{FS} + 0.42$ | 22 | 0.955 | 0.21 | 17 |
| pentylenetetrazol | $A_{PT} = 3.72(\pm1.06)\mathcal{F}_y + 0.35$ | 22 | 0.617 | 0.98 | 18 |
| $A_{PT} = -\log C_{ED_{50}}$ | $A_{PT} = 3.01(\pm1.00)\mathcal{F}_v + 3.11(\pm1.32)\sigma_{m(z)} + 0.38$ | 22 | 0.721 | 0.89 | 19 |
| | $A_{PT} = 1.45(\pm0.25)A_{FS} + 0.15$ | 22 | 0.788 | 0.77 | 20 |
| | $A_{PT} = 1.04(\pm0.31)A_{FS} + 0.62(\pm0.30)A_{E_{max}} - 0.10$ | 22 | 0.830 | 0.71 | 21 |
| | $A_{PT} = 0.89(\pm0.15)PR_1^{PT} + 0.28$ | 22 | 0.804 | 0.74 | 22 |
| | $A_{PT} = 0.89(\pm0.14)PR_1^{PT} + 1.40(\pm0.96)PR_4^{PT} + 0.20$ | 22 | 0.826 | 0.72 | 23 |
| electroshock max | $A_{E_{max}} = 1.54(\pm0.47)\sigma_{m(y)} + 0.61$ | 22 | 0.594 | 0.55 | 24 |
| $A_{E_{max}} = -\log C_{ED_{50}}$ | $A_{E_{max}} = 1.57(\pm0.41)\sigma_{m(y)} - 0.34(\pm0.13)\pi_x^2 + 0.71$ | 22 | 0.728 | 0.48 | 25 |
| | $A_{E_{max}} = 0.39(\pm0.09)A_{PT} + 0.46$ | 22 | 0.709 | 0.49 | 26 |
| | $A_{E_{max}} = 0.31(\pm0.07)A_{PT} + 0.66(\pm0.22)A_{E_{min}} + 0.46$ | 22 | 0.815 | 0.41 | 27 |
| | $A_{E_{max}} = 0.34(\pm0.07)PR_1^{E_{max}} + 0.40$ | 22 | 0.747 | 0.46 | 28 |
| | $A_{E_{max}} = 0.34(\pm0.06)PR_1^{E_{max}} + 0.60(\pm0.21)PR_3^{E_{max}} + 0.44$ | 22 | 0.832 | 0.39 | 29 |
| electroshock min | $A_{E_{min}} = -0.19(\pm0.11)\pi_x^2 + 0.27$ | 22 | 0.368 | 0.41 | 30 |
| $A_{E_{min}} = -\log C_{ED_{50}}$ | $A_{E_{min}} = -0.22(\pm0.10)\pi_x^2 + 0.71(\pm0.34)\pi_y^2 + 0.04$ | 22 | 0.543 | 0.38 | 31 |
| | $A_{E_{min}} = 0.40(\pm0.11)A_{E_{max}} - 0.26$ | 22 | 0.613 | 0.35 | 32 |
| | $A_{E_{min}} = 0.48(\pm0.15)A_{E_{max}} - 0.15(\pm0.15)A_{FS} - 0.20$ | 22 | 0.637 | 0.35 | 33 |
| | $A_{E_{min}} = 0.50(\pm0.19)PR_3^{E_{min}} + 0.07$ | 22 | 0.501 | 0.38 | 34 |
| | $A_{E_{min}} = 0.11(\pm0.05)PR_1^{E_{min}} + 0.50(\pm0.18)PR_3^{E_{min}} - 0.21$ | 22 | 0.634 | 0.35 | 35 |

different conclusions, if variances of some variables are significantly larger than those of others.[8] For our purposes, the original version of principal component analysis[11,12] seemed to be more appropriate. It should be noted that the variances of most activity indices do not differ essentially from each other.

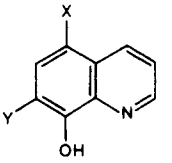
For the actual calculations, three sets of activity data have been considered. The pharmacological activities of the benzodiazepine derivatives (I) listed in Table I were taken from ref 13. The values




I

are expressed in $-\log C_{ED_{50}}$ (mmol/kg) units. The pharmacological activities determined by performing the *incl screen*, *foot shock*, *pentylenetetrazol*, *electroshock maximum*, and *electroschock minimum* tests are denoted by $A_{IS}$, $A_{FS}$, $A_{PT}$, $A_{E_{max}}$, and $A_{E_{min}}$, respectively. Principal component analysis was performed for this set five times, because the dependent activity had to be excluded from the data set used to calculate the internal scatter matrix $\|u_{ij}\|$. The index $X$ on $PR^X$ indicates which of the pharmaceutical indices has been discarded. The respective indices are $PR_p^{IS}$, $PR_p^{FS}$, $PR_p^{PT}$, $PR_p^{E_{max}}$ and $PR_p^{E_{min}}$ ($p$ = 1–4).

Similar investigations were performed for 26 derivatives of 8-quinolinol (II). The activities were determined on various




II

microbial systems (*Aspergillus niger*, *Aspergillus oryzae*, *Trichoderma viride*, *Trichophyton mentagrophytes*, and *Myrothecium verrucaria*) by Gershon et al.[14-16] and are listed in Table VI. The fungistatic activities are expressed in $-\log C$ units, where $C$ (mmol/L) denotes the minimal antifungal activity. The primary activity indices are denoted by $A_{A.n.}$, $A_{A.o.}$, $A_{T.v.}$, $A_{T.m.}$, and $A_{M.v.}$ and the transformed ones by $PR_p^{A.n.}$, $PR_p^{A.o.}$, $PR_p^{T.v.}$, $PR_p^{T.m.}$, and $PR_p^{M.v.}$ ($p$ = 1–4), respectively.

The data listed in Table XI are the activities of rifamycin B amides ($n$ = 44), which have been used by Quinn et al.[17] in a quantitative structure–activity (QSAR) study. The data given for the strains *Micrococcus aureus*, *Streptococcus faecalis*, *Streptococcus hemolyticus*, and *Bacillus subtilis* are expressed in $-\log C$ units, where $C$ ($\mu$mol/L) is defined as the lowest concentration of antibiotic that prevents visible growth after an 18-h incubation. The respective activities are denoted by $A_{M.a.}$, $A_{S.f.}$, $A_{S.h.}$, and $A_{B.s.}$; the transformed activity indices considered were $PR_p^{M.a.}$, $PR_p^{S.f.}$, $PR_p^{S.h.}$, and $PR_p^{B.s.}$ ($p$ = 1–3).

Equations involving primary activity indices only were obtained by considering all possible combinations of the independent variables.

(13) L. H. Sternbach, in "The Benzodiazepines", Raven Press, New York, 1973, p 1.

(14) H. Gershon, M. W. McNeil, R. Parmegiani, and P. K. Godfrey, *J. Med. Chem.*, 15, 987 (1972).

(15) H. Gershon, M. W. McNeil, and Y. Hinds, *J. Med. Chem.*, 12, 1115 (1969).

(16) H. Gershon, *J. Med. Chem.*, 11, 1094 (1968).

(17) F. R. Quinn, J. S. Driscoll, and C. Hansch, *J. Med. Chem.*, 18, 332 (1975).

Table IV. Benzodiazepine Derivatives (I). Mutually Independent Components of Pharmacological Activities (Table I)

| no. | $PR_1^{IS}$ | $PR_3^{IS}$ | $PR_1^{FS}$ | $PR_3^{FS}$ | $PR_1^{PT}$ | $PR_4^{PT}$ | $PR_1^{E\,max}$ | $PR_3^{E\,max}$ | $PR_1^{E\,min}$ | $PR_3^{E\,min}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.11 | 0.55 | 0.06 | −0.04 | 0.89 | 0.17 | −0.13 | 0.47 | 0.13 | 0.83 |
| 2 | 0.20 | 0.59 | 0.14 | −0.02 | 0.99 | 0.15 | −0.09 | 0.37 | 0.23 | 0.95 |
| 3 | 2.30 | 0.26 | 2.07 | −0.43 | 1.64 | 0.49 | 2.10 | 0.37 | 2.27 | 0.23 |
| 4 | 3.11 | 0.20 | 3.07 | −0.18 | 2.39 | 0.08 | 2.79 | −0.12 | 3.28 | 0.83 |
| 5 | 3.58 | 0.42 | 3.40 | −0.12 | 2.62 | 0.40 | 3.49 | −0.10 | 3.79 | 0.18 |
| 6 | 3.46 | 0.19 | 3.47 | −0.18 | 2.89 | 0.16 | 3.35 | 0.78 | 3.66 | 0.52 |
| 7 | 2.87 | 0.38 | 0.00 | −0.18 | 0.03 | 0.42 | 0.10 | −0.57 | 0.21 | 0.07 |
| 8 | 4.60 | 0.08 | 4.23 | −1.02 | 2.84 | 0.72 | 4.01 | 0.27 | 4.50 | 0.76 |
| 9 | 3.31 | −0.43 | 3.13 | −0.84 | 1.58 | 0.32 | 2.92 | 0.11 | 3.19 | 0.34 |
| 10 | 1.93 | −0.22 | 1.85 | −0.52 | 1.05 | 0.13 | 1.58 | 0.03 | 1.86 | 0.55 |
| 11 | 1.94 | −0.25 | 1.73 | −0.79 | 0.85 | 0.35 | 1.52 | 0.18 | 1.74 | 0.45 |
| 12 | 3.19 | 0.31 | 3.00 | −0.38 | 2.40 | 0.42 | 2.93 | 0.29 | 3.27 | 0.51 |
| 13 | 3.94 | 0.82 | 3.71 | −0.06 | 3.29 | 0.46 | 3.65 | −0.27 | 4.22 | 0.80 |
| 14 | 0.76 | 0.09 | 0.47 | −0.31 | −0.04 | 0.45 | 0.69 | −0.49 | 0.65 | −0.37 |
| 15 | 1.93 | 0.08 | 1.69 | −0.32 | 0.91 | 0.41 | 1.83 | −0.29 | 1.90 | −0.17 |
| 16 | 2.51 | −0.14 | 2.39 | −0.25 | 1.17 | 0.14 | 2.36 | −0.67 | 2.58 | 0.27 |
| 17 | 3.15 | 0.60 | 2.91 | −0.01 | 2.37 | 0.47 | 3.10 | −0.26 | 3.36 | 0.07 |
| 18 | 3.39 | 0.91 | 3.28 | 0.61 | 3.02 | 0.30 | 3.70 | −0.29 | 3.88 | −0.28 |
| 19 | 4.38 | 0.93 | 4.36 | 0.90 | 3.72 | 0.15 | 4.85 | −0.62 | 5.08 | −0.46 |
| 20 | 2.56 | 0.41 | 2.33 | −0.26 | 1.77 | 0.35 | 2.20 | −0.59 | 2.65 | 0.65 |
| 21 | −0.27 | 0.66 | −0.55 | 0.13 | −0.04 | 0.46 | −0.22 | −0.44 | −0.26 | −0.26 |
| 22 | 3.55 | 0.09 | 3.31 | −0.52 | 2.20 | 0.51 | 3.37 | 0.18 | 3.58 | 0.08 |

Table V. Benzodiazepine Derivatives (I). Correlations between Experimental Activities

| | $A_{FS}$ | $A_{PT}$ | $A_{E\,max}$ | $A_{E\,min}$ |
|---|---|---|---|---|
| $A_{IS}$ | 0.94 | 0.73 | 0.67 | 0.34 |
| $A_{FS}$ | | 0.79 | 0.65 | 0.27 |
| $A_{PT}$ | | | 0.71 | 0.33 |
| $A_{E\,max}$ | | | | 0.61 |

The substituent constants $\pi$, $\sigma_m$, $\sigma_p$, $\mathcal{F}$, $\mathcal{R}$, MR, and $\Sigma\pi$ used to derive Hansch-type equations for the benzodiazepines (I) and for the 8-quinolinol derivatives (II) were taken from a compilation given by Hansch et al.[18] and Tables II and VII. Regression equations obtained by using these constants were developed by applying the stepwise multiple linear regression program BMDO2R.[19]

In this work, one- and two-parametral equations were considered only. In most cases, inclusion of a third activity parameter—both primary and transformed—did not improve the multiple correlation coefficient significantly ($p \leq 0.01$). No molecule was excluded from the regression analysis; in this way all results obtained may be compared with one another.

The overall $F$ statistics calculated for eq 6-96 was not listed in Tables III, VIII, XII, and XVIII. It may be obtained using the formula $F_{m,n-m-1} = [R^2/(1 - R^2)][(n - m - 1)/m]$, where $n$ denotes the number of molecules considered, $m$ is the number of the parameters, and $R$ denotes the multiple correlation coefficient.

## Results and Discussion

Tables III, VIII, and XII show the derived regression equations. For each pharmacological index, six equations were listed (except for system *M. aureus*). The first and second equation expresses pharmacological potency as a linear function of physical-chemical indices. The next two ones represent the best results obtained with nontransformed pharmacological activity indices. The last two (fifth and sixth) equations demonstrate the relationships between the dependent activities and the mutually independent components obtained from data subsets *not* containing the actual dependent variable. Some of the components $PR_p^X$ are listed in Tables IV, IX, and XIII. Figures in parentheses denote the standard deviations of the regression coefficients; $s$ is the standard error of the estimate.

**Benzodiazepines (I).** Except for eq 30 and eq 34, the correlations calculated were significant[23] at level $p \leq 0.01$. Table V lists the correlation coefficients between the experimental pharmacological activity indices. In Table XV are listed the portions of the total SV of the given subset "explained" by the components and the correlation coefficients derived between the values $PR_p^X$ and the dependent variable. The transformation coefficients $\|c_{ij}\|$ (eq 1) are not listed but may be obtained on request. Coefficients $c_{i1}$ ($i = 1, \ldots, k$) used to calculate indices $PR_1^X$ were always *positive*. The actual magnitudes of the figures did not differ very much from each other, although coefficients of the activities less related to the others of the subset were generally lower than those of the more closely related activities. The other coefficients will be discussed briefly for each example.

**Incl Screen.** Replacement of variable $\sigma_{m(y)}$ in eq 6 by index $A_{FS}$ (eq 8) improved the correlation coefficient $R$ significantly. The partial $F$ test gives $F_{1,20} = 55.88$ vs. the theoretical value $F_{1,20;p=0.01} = 8.10$. Replacement of index $A_{FS}$ by the component $PR_1^{IS}$ in eq 10 yielded poorer results, the partial $F$ test being $F_{1,20} = 39.49$. Equations 9 and 11 are practically of equal quality. Index $PR_1^{IS}$ accounts for 81% of the total SV of the subset (Table XV). The correlation coefficient $r = 0.479$ demonstrated between $A_{IS}$ and $PR_3^{IS}$ is still significant at level $p \leq 0.05$. $A_{IS}$ seems not to depend on $PR_2^{IS}$, although this component explains a larger part (11%) of the total SV of the subset than $PR_3^{IS}$. $PR_3^{IS}$ is proportional to $2A_{FS} - A_{PT}$, neglecting normalization.

**Foot Shock.** The results obtained for these data are quite similar to those derived for the incl screen data. Equation 14 is significantly more adequate than eq 12, the result of the partial $F$ test being $F_{1,20} = 65.11$. Although eq 16, derived by considering the first independent component $PR_1^{FS}$, is significantly poorer than eq 14 ($F_{1,20} = 26.08$), it can be improved considerably by including component $PR_3^{FS}$ (eq 17). The improvement is significant ($F_{1,19} = 37.98$ vs. $F_{1,19;p=0.01} = 8.18$). Equations 15 and 17 are practically equivalent. Again, components $PR_1^{FS}$ and

(18) C. Hansch, A. Leo, S. H. Unger, Ki Hwan Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973).
(19) BMDO2R, Stepwise Regression Program, UCLA, 1969.
(20) S. S. Wilks, "Mathematical Statistics", Wiley, New York, 1962, p 95.
(21) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, 71, 525 (1971).
(22) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, 1956, p 559.
(23) G. W. Snedecor and W. G. Cochran, "Statistical Methods", The Iowa State University Press, Ames, Iowa, 1972, p 560.

Table VI. Experimental[a] and Predicted Activities [in −Log $C$ (mmol/L) Units] of the 8-Quinolinol Derivatives (II)

| | | | *A. niger* | | *A. oryzae* | | *Trichoderma viride* | | *Trichophyton mentagrophytes* | | *M. verrucaria* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | X | Y | obsd | pred (eq 41) | obsd | pred (eq 47) | obsd | pred (eq 52) | obsd | pred (eq 59) | obsd | pred (eq 65) |
| 1 | H | F | 1.32 | 1.40 | 1.08 | 1.16 | 1.75 | 1.59 | 1.92 | 2.17 | 1.75 | 1.85 |
| 2 | H | Cl | 1.77 | 1.82 | 1.55 | 1.45 | 1.96 | 2.05 | 2.25 | 2.22 | 2.25 | 2.04 |
| 3 | H | Br | 1.89 | 2.10 | 1.89 | 1.76 | 2.35 | 2.22 | 2.35 | 2.40 | 2.35 | 2.15 |
| 4 | H | I | 2.13 | 2.01 | 1.48 | 1.93 | 2.43 | 2.21 | 2.43 | 2.40 | 2.43 | 2.73 |
| 5 | H | $NO_2$ | 0.48 | 0.70 | 0.28 | 0.64 | 1.28 | 0.92 | 1.80 | 2.05 | 1.13 | 1.36 |
| 6 | F | F | 1.36 | 1.56 | 1.08 | 1.02 | 1.77 | 1.64 | 1.66 | 2.19 | 1.96 | 1.91 |
| 7 | F | Cl | 1.82 | 2.00 | 1.70 | 1.69 | 2.29 | 2.12 | 2.30 | 2.38 | 2.29 | 2.20 |
| 8 | F | Br | 1.92 | 2.05 | 1.67 | 1.80 | 2.39 | 2.18 | 2.39 | 2.41 | 2.39 | 2.36 |
| 9 | F | I | 2.00 | 1.82 | 2.62 | 2.30 | 2.46 | 2.12 | 2.46 | 2.37 | 1.16 | 1.78 |
| 10 | Cl | F | 2.00 | 2.00 | 1.70 | 1.77 | 2.29 | 2.18 | 2.30 | 2.35 | 2.29 | 2.36 |
| 11 | Cl | Br | 1.92 | 2.00 | 1.82 | 1.39 | 1.92 | 2.20 | 2.11 | 2.18 | 2.41 | 1.96 |
| 12 | Cl | I | 2.01 | 1.89 | 1.80 | 1.44 | 1.89 | 2.15 | 2.01 | 2.14 | 2.19 | 2.04 |
| 13 | Br | F | 1.92 | 1.87 | 1.62 | 1.50 | 1.92 | 2.17 | 2.39 | 2.18 | 2.39 | 2.09 |
| 14 | Br | Cl | 2.11 | 2.11 | 1.82 | 1.90 | 2.41 | 2.29 | 2.41 | 2.39 | 2.41 | 2.45 |
| 15 | Br | I | 2.07 | 1.71 | 1.24 | 1.58 | 1.96 | 2.06 | 2.24 | 2.17 | 2.24 | 2.54 |
| 16 | Br | $NO_2$ | 0.62 | 0.67 | 0.66 | 0.85 | 1.13 | 1.13 | 2.43 | 1.96 | 1.13 | 1.07 |
| 17 | I | F | 2.00 | 1.86 | 1.46 | 1.59 | 2.00 | 2.18 | 2.46 | 2.21 | 2.46 | 2.33 |
| 18 | I | Br | 2.07 | 2.02 | 1.85 | 1.77 | 2.24 | 2.22 | 2.24 | 2.31 | 2.24 | 2.28 |
| 19 | I | $NO_2$ | 0.70 | 0.40 | 0.57 | 0.69 | 0.89 | 0.92 | 1.89 | 1.80 | 0.60 | 1.08 |
| 20 | $NO_2$ | F | 0.44 | 0.80 | 0.68 | 0.82 | 1.32 | 1.09 | 2.32 | 2.09 | 1.21 | 1.03 |
| 21 | F | $NO_2$ | 1.06 | 0.91 | 0.85 | 0.50 | 1.06 | 1.15 | 1.72 | 1.84 | 1.02 | 1.37 |
| 22 | Cl | $NO_2$ | 1.15 | 0.89 | 1.05 | 0.90 | 1.15 | 1.34 | 1.89 | 1.87 | 1.10 | 1.31 |
| 23 | Br | $NH_2$ | 0.57 | 0.67 | 0.68 | 0.44 | 0.92 | 0.98 | 1.60 | 1.86 | 0.96 | 0.92 |
| 24 | I | $NH_2$ | 1.15 | 1.04 | 1.03 | 0.92 | 1.21 | 1.49 | 2.21 | 1.92 | 1.51 | 1.35 |
| 25 | $NO_2$ | Cl | 0.89 | 1.05 | 0.66 | 0.72 | 1.17 | 1.43 | 2.35 | 1.97 | 1.89 | 1.35 |
| 26 | $NO_2$ | Br | 1.01 | 1.01 | 0.66 | 0.95 | 1.32 | 1.43 | 2.43 | 2.01 | 1.72 | 1.56 |

[a] Experimental values were taken for compounds 1-20 from ref 14, for compounds 21-24 from ref 16, and for compounds 25 and 26 from ref 15, respectively.

Table VII. 8-Quinolinol Derivatives (II). Physicochemical Parameters[a]

| no. | $\pi_x$ | $\sigma_{p(x)}$ | $R_x$ | $MR_x$ | $\pi_y$ | $R_y$ |
|---|---|---|---|---|---|---|
| 1 | 0.00 | 0.00 | 0.00 | 1.03 | 0.14 | −0.34 |
| 2 | 0.00 | 0.00 | 0.00 | 1.03 | 0.71 | −0.15 |
| 3 | 0.00 | 0.00 | 0.00 | 1.03 | 0.86 | −0.17 |
| 4 | 0.00 | 0.00 | 0.00 | 1.03 | 1.12 | −0.19 |
| 5 | 0.00 | 0.00 | 0.00 | 1.03 | −0.28 | 0.16 |
| 6 | 0.14 | 0.06 | −0.34 | 0.92 | 0.14 | −0.34 |
| 7 | 0.14 | 0.06 | −0.34 | 0.92 | 0.71 | −0.15 |
| 8 | 0.14 | 0.06 | −0.34 | 0.92 | 0.86 | −0.17 |
| 9 | 0.14 | 0.06 | −0.34 | 0.92 | 1.12 | −0.19 |
| 10 | 0.71 | 0.23 | −0.15 | 6.03 | 0.14 | −0.34 |
| 11 | 0.71 | 0.23 | −0.15 | 6.03 | 0.86 | −0.17 |
| 12 | 0.71 | 0.23 | −0.15 | 6.03 | 1.12 | −0.19 |
| 13 | 0.86 | 0.23 | −0.17 | 8.88 | 0.14 | −0.34 |
| 14 | 0.86 | 0.23 | −0.17 | 8.88 | 0.71 | −0.15 |
| 15 | 0.86 | 0.23 | −0.17 | 8.88 | 1.12 | −0.19 |
| 16 | 0.86 | 0.23 | −0.17 | 8.88 | −0.28 | 0.16 |
| 17 | 1.12 | 0.18 | −0.19 | 13.94 | 0.14 | −0.34 |
| 18 | 1.12 | 0.18 | −0.19 | 13.94 | 0.86 | −0.17 |
| 19 | 1.12 | 0.18 | −0.19 | 13.94 | −0.28 | 0.16 |
| 20 | −0.28 | 0.78 | 0.16 | 7.36 | 0.14 | −0.34 |
| 21 | 0.14 | 0.06 | −0.34 | 0.92 | −0.28 | 0.16 |
| 22 | 0.71 | 0.23 | −0.15 | 6.03 | −0.28 | 0.16 |
| 23 | 0.86 | 0.23 | −0.27 | 8.88 | −1.23 | −0.68 |
| 24 | 1.12 | 0.18 | −0.19 | 13.94 | −1.23 | −0.68 |
| 25 | −0.28 | 0.78 | 0.16 | 7.36 | 0.71 | −0.15 |
| 26 | −0.28 | 0.78 | 0.16 | 7.36 | 0.86 | −0.17 |

[a] See ref 18.

$PR_3^{FS}$ seem to affect variable $A_{FS}$. The respective ratios of the total SV explained by these two components are similar to the figures obtained for the incl screen data (Table XV). $PR_3^{FS}$ is proportional to $3A_{IS} - A_{PT} - A_{E_{max}} - A_{E_{min}}$; normalization is neglected.

**Pentylenetetrazol.** There is no significant difference between eq 20 and 22. The corresponding two-parametral equations 21 and 23 also do not differ from each other considerably. The quality of the equations does not allow quantitative predictions. Only $PR_1^{PT}$, explaining 77% of the total SV of the subset, seems to affect activity $A_{PT}$. The correlation coefficient was not significant between the dependent variable $A_{PT}$ and $PR_2^{PT}$, $PR_3^{PT}$, and $PR_4^{PT}$ at level $p \leq 0.05$.

**Electroshock Maximum.** Similarly to the pentylenetetrazol data, the first independent component $PR_1^{E_{max}}$ was superior to all other parameters considered (Table III). Replacement of $\sigma_{m(y)}$ in eq 24 by $A_{PT}$ (eq 26) did not improve the equation at level $p \leq 0.01$. Replacement of $\sigma_{m(y)}$ by $PR_1^{E_{max}}$ (eq 28) improves the correlation coefficient significantly; the partial $F$ test yields $F_{1,20} = 9.28$. There is no significant difference between eq 27 and 29, although the latter is slightly better. The derived equations are of no use for quantitative predictions. $PR_1^{E_{max}}$ explains 83% of the total SV of the subset, whereas $PR_2^{E_{max}}$ explains 10% and $PR_3^{E_{max}}$ 7%. Consideration of the corresponding correlation coefficients shows that only $PR_1^{E_{max}}$ is significant at $p \leq 0.01$ ($r = 0.747$). $PR_3^{E_{max}}$ is practically proportional to $A_{E_{min}}$.

**Electroshock Minimum.** The derived equations explain a rather low portion of the variance of the dependent variable $A_{E_{min}}$. Comparisons of the various equations by means of the partial $F$ test revealed no significant differences between them at $p \leq 0.01$. It should be noted that $PR_1^{E_{min}}$, accounting for 84% of the total SV of the subset, explains only $(0.393)^2 \times 100 = 15.4\%$ of the variance in $A_{E_{min}}$ (Table XV), whereas $PR_3^{E_{min}}$, accounting for only 6% of the total SV of the subset, explains 25%. Inspection of Table V shows that this index is but slightly affected by other pharmacological activity indices. $PR_3^{E_{min}}$ is practically proportional to $A_{E_{max}}$.

**8-Quinolinol Derivatives (II).** The derived regression equations are listed in Table VIII. The notations are the same as in Table III. All equations listed were significant at the $p \leq 0.01$ level. Table X lists the correlation coefficients between the pharmacological activity indices.

Table VIII. Regression Equations Derived for the 8-Quinolinol (II) Derivatives

| system | equation | $n$ | $R$ | $s$ | eq no. |
|---|---|---|---|---|---|
| *A. niger* | $A_{A.n.} = 0.70(\pm0.10)\Sigma\pi + 0.94$ | 26 | 0.807 | 0.36 | 36 |
| | $A_{A.n.} = 0.67(\pm0.09)\Sigma\pi - 0.79(\pm0.28)\sigma_{p(x)} + 1.13$ | 26 | 0.862 | 0.31 | 37 |
| | $A_{A.n.} = 1.01(\pm0.10)A_{T.v.} - 0.28$ | 26 | 0.903 | 0.26 | 38 |
| | $A_{A.n.} = 0.45(\pm0.17)A_{A.o.} + 0.59(\pm0.18)A_{T.v.} - 0.14$ | 26 | 0.927 | 0.23 | 39 |
| | $A_{A.n.} = 0.61(\pm0.04)PR_1^{A.n.} - 0.50$ | 26 | 0.943 | 0.20 | 40 |
| | $A_{A.n.} = 0.61(\pm0.04)PR_1^{A.n.} - 0.33(\pm0.13)PR_3^{A.n.} - 0.05$ | 26 | 0.956 | 0.18 | 41 |
| *A. oryzae* | $A_{A.o.} = 0.57(\pm0.12)\Sigma\pi + 0.85$ | 26 | 0.698 | 0.41 | 42 |
| | $A_{A.o.} = 0.63(\pm0.11)\Sigma\pi - 0.04(\pm0.02)MR_x + 1.05$ | 26 | 0.779 | 0.37 | 43 |
| | $A_{A.o.} = 0.84(\pm0.09)A_{A.n.} + 0.04$ | 26 | 0.890 | 0.26 | 44 |
| | $A_{A.o.} = 1.15(\pm0.14)A_{A.n.} - 0.37(\pm0.14)A_{M.v.} + 0.27$ | 26 | 0.916 | 0.23 | 45 |
| | $A_{A.o.} = 0.49(\pm0.07)PR_1^{A.o.} - 0.31$ | 26 | 0.832 | 0.32 | 46 |
| | $A_{A.o.} = 0.49(\pm0.05)PR_1^{A.o.} - 0.78(\pm0.18)PR_3^{A.o.} - 0.70$ | 26 | 0.911 | 0.24 | 47 |
| *T. viride* | $A_{T.v.} = 0.57(\pm0.11)\pi_y + 1.56$ | 26 | 0.720 | 0.38 | 48 |
| | $A_{T.v.} = 0.58(\pm0.09)\pi_y - 0.97(\pm0.27)\sigma_{p(x)} + 1.76$ | 26 | 0.831 | 0.31 | 49 |
| | $A_{T.v.} = 0.81(\pm0.08)A_{A.n.} + 0.55$ | 26 | 0.903 | 0.23 | 50 |
| | $A_{T.v.} = 0.74(\pm0.08)A_{A.n.} + 0.29(\pm0.14)A_{T.m.} + 0.04$ | 26 | 0.918 | 0.22 | 51 |
| | $A_{T.v.} = 0.52(\pm0.04)PR_1^{T.v.} + 0.17$ | 26 | 0.930 | 0.20 | 52 |
| | $A_{T.v.} = 0.52(\pm0.04)PR_1^{T.v.} + 0.13(\pm0.14)PR_3^{T.v.} - 0.01$ | 26 | 0.933 | 0.20 | 53 |
| *T. mentagrophytes* | $A_{T.m.} = 0.25(\pm0.09)\pi_y + 2.06$ | 26 | 0.500 | 0.30 | 54 |
| | $A_{T.m.} = 0.32(\pm0.09)\pi_y + 0.03(\pm0.01)MR_x + 1.86$ | 26 | 0.632 | 0.28 | 55 |
| | $A_{T.m.} = 0.35(\pm0.11)A_{T.v.} + 1.54$ | 26 | 0.535 | 0.30 | 56 |
| | $A_{T.m.} = 0.22(\pm0.18)A_{T.v.} + 0.14(\pm0.17)A_{M.v.} + 1.50$ | 26 | 0.556 | 0.30 | 57 |
| | $A_{T.m.} = 0.16(\pm0.06)PR_1^{T.m.} + 1.63$ | 26 | 0.508 | 0.30 | 58 |
| | $A_{T.m.} = 0.16(\pm0.06)PR_1^{T.m.} + 0.51(\pm0.33)PR_3^{T.m.} + 1.45$ | 26 | 0.570 | 0.30 | 59 |
| *M. verrucaria* | $A_{M.v.} = 0.56(\pm0.14)\pi_y + 1.64$ | 26 | 0.636 | 0.47 | 60 |
| | $A_{M.v.} = 0.63(\pm0.12)\pi_y - 1.13(\pm0.37)R_y + 1.41$ | 26 | 0.760 | 0.40 | 61 |
| | $A_{M.v.} = 0.83(\pm0.11)A_{A.n.} + 0.60$ | 26 | 0.828 | 0.34 | 62 |
| | $A_{M.v.} = 1.35(\pm0.23)A_{A.n.} + 0.62(\pm0.24)A_{A.o.} + 0.63$ | 26 | 0.870 | 0.31 | 63 |
| | $A_{M.v.} = 0.49(\pm0.08)PR_1^{M.v.} + 0.38$ | 26 | 0.785 | 0.38 | 64 |
| | $A_{M.v.} = 0.49(\pm0.06)PR_1^{M.v.} - 1.27(\pm0.29)PR_3^{M.v.} + 0.37$ | 26 | 0.890 | 0.28 | 65 |

Table IX. 8-Quinolinol Derivatives (II). Mutually Independent Components of Antibacterial Activities (Table V)

| no. | $PR_1^{A.n.}$ | $PR_3^{A.n.}$ | $PR_1^{A.o.}$ | $PR_3^{A.o.}$ | $PR_1^{T.v.}$ | $PR_3^{T.v.}$ | $PR_1^{T.m.}$ | $PR_3^{T.m.}$ | $PR_1^{M.v.}$ | $PR_3^{M.v.}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.01 | 1.18 | 3.09 | −0.44 | 2.72 | 1.20 | 2.93 | 0.46 | 2.70 | −0.13 |
| 2 | 3.76 | 1.31 | 3.83 | −0.36 | 3.60 | 1.36 | 3.76 | 0.29 | 3.41 | 0.00 |
| 3 | 4.23 | 1.36 | 4.18 | −0.53 | 3.92 | 1.47 | 4.21 | 0.50 | 3.90 | 0.09 |
| 4 | 4.13 | 1.42 | 4.44 | −0.59 | 3.91 | 1.38 | 4.24 | 0.49 | 3.88 | −0.37 |
| 5 | 1.92 | 1.29 | 1.97 | −0.48 | 1.42 | 1.28 | 1.56 | 0.69 | 1.47 | −0.21 |
| 6 | 3.09 | 0.86 | 3.20 | −0.20 | 2.81 | 0.89 | 3.07 | 0.45 | 2.69 | −0.18 |
| 7 | 4.06 | 1.33 | 4.07 | −0.52 | 3.74 | 1.41 | 4.04 | 0.52 | 3.71 | −0.01 |
| 8 | 4.18 | 1.39 | 4.25 | −0.54 | 3.86 | 1.44 | 4.17 | 0.54 | 3.83 | −0.10 |
| 9 | 4.04 | 1.84 | 3.64 | −1.56 | 3.73 | 2.02 | 4.10 | 0.48 | 4.46 | 0.60 |
| 10 | 4.06 | 1.33 | 4.18 | −0.55 | 3.84 | 1.37 | 4.13 | 0.42 | 3.82 | −0.10 |
| 11 | 3.94 | 1.12 | 3.97 | −0.20 | 3.89 | 1.21 | 4.03 | 0.13 | 3.61 | 0.14 |
| 12 | 3.76 | 1.10 | 3.85 | −0.33 | 3.79 | 1.16 | 3.94 | 0.07 | 3.61 | 0.07 |
| 13 | 3.88 | 1.39 | 4.01 | −0.31 | 3.83 | 1.43 | 3.92 | 0.16 | 3.55 | 0.01 |
| 14 | 4.29 | 1.39 | 4.40 | −0.58 | 4.07 | 1.44 | 4.37 | 0.43 | 4.04 | −0.08 |
| 15 | 3.58 | 1.31 | 4.00 | −0.42 | 3.61 | 1.23 | 3.77 | 0.18 | 3.42 | −0.39 |
| 16 | 2.19 | 1.88 | 2.11 | −0.66 | 1.83 | 1.91 | 1.75 | 0.43 | 1.81 | 0.14 |
| 17 | 3.89 | 1.43 | 4.15 | −0.34 | 3.84 | 1.42 | 3.96 | 0.21 | 3.56 | −0.18 |
| 18 | 4.08 | 1.30 | 4.15 | −0.60 | 3.93 | 1.35 | 4.20 | 0.33 | 3.91 | 0.00 |
| 19 | 1.58 | 1.55 | 1.61 | −0.77 | 1.43 | 1.52 | 1.38 | 0.23 | 1.57 | 0.05 |
| 20 | 2.33 | 1.75 | 2.12 | −0.62 | 1.76 | 1.82 | 1.79 | 0.68 | 1.79 | 0.17 |
| 21 | 1.88 | 0.58 | 1.98 | −0.30 | 1.86 | 0.59 | 2.00 | 0.11 | 1.88 | −0.06 |
| 22 | 2.28 | 1.37 | 2.30 | −0.60 | 2.24 | 1.38 | 2.22 | 0.10 | 2.25 | 0.12 |
| 23 | 1.80 | 1.16 | 1.70 | −0.39 | 1.55 | 1.21 | 1.55 | 0.29 | 1.52 | 0.15 |
| 24 | 2.61 | 1.54 | 2.63 | −0.43 | 2.52 | 1.56 | 2.44 | 0.13 | 2.34 | 0.13 |
| 25 | 2.64 | 1.55 | 2.71 | −0.12 | 2.40 | 1.56 | 2.29 | 0.28 | 1.98 | −0.01 |
| 26 | 2.64 | 1.68 | 2.78 | −0.37 | 2.40 | 1.66 | 2.35 | 0.34 | 2.15 | −0.11 |

Table X. 8-Quinolinol Derivatives (II). Correlations between Experimental Activities

| | $A_{A.o.}$ | $A_{T.v.}$ | $A_{T.m.}$ | $A_{M.v.}$ |
|---|---|---|---|---|
| $A_{A.n.}$ | 0.89 | 0.90 | 0.42 | 0.83 |
| $A_{A.o.}$ | | 0.87 | 0.42 | 0.62 |
| $A_{T.v.}$ | | | 0.54 | 0.79 |
| $A_{T.m.}$ | | | | 0.52 |

Table XVI shows the principal components of the SV of the various data subsets and also the correlation coefficients derived between the dependent variables and the mutually independent components. All the transformation coefficients (eq 1) used to calculate $PR_1^X$ were *positive*. Their behavior was very similar to those calculated for the benzodiazepines (I). Only coefficients $c_{i3}$ belonging to $PR_3^X$

Table XI. Experimental[a] and Predicted Activities [in −Log $C$ (μmol/L) Units] of Rifamycin B Amides (III)

| | | | *M. aureus* | | *S. faecalis* | | *S. hemolyticus* | | *B. subtilis* | |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | $R_1$ | $R_2$ | obsd | pred (eq 70) | obsd | pred (eq 76) | obsd | pred (eq 82) | obsd | pred (eq 88) |
| 1 | H | H | 5.70 | 5.86 | 4.91 | 5.20 | 6.62 | 6.26 | 4.78 | 4.75 |
| 2 | H | Me | 6.68 | 6.52 | 5.89 | 5.73 | 5.09 | 6.21 | 7.11 | 6.05 |
| 3 | H | Et | 6.99 | 7.05 | 6.20 | 6.25 | 7.50 | 7.35 | 5.40 | 5.69 |
| 4 | H | *n*-Pr | 6.50 | 6.43 | 5.82 | 5.77 | 6.42 | 6.89 | 5.41 | 5.59 |
| 5 | H | *i*-Pr | 6.70 | 6.76 | 5.90 | 5.99 | 7.12 | 7.03 | 5.41 | 5.52 |
| 6 | H | *t*-Bu | 6.73 | 6.44 | 5.83 | 5.95 | 6.43 | 7.00 | 5.42 | 5.68 |
| 7 | H | Ph | 6.92 | 6.71 | 6.04 | 6.14 | 6.84 | 7.22 | 5.43 | 5.75 |
| 8 | H | *p*-Cl-Ph | 6.54 | 6.96 | 6.39 | 5.83 | 6.86 | 7.12 | 5.64 | 5.78 |
| 9 | H | *p*-Br-Ph | 6.48 | 7.00 | 6.56 | 5.77 | 6.66 | 7.12 | 5.78 | 5.90 |
| 10 | H | *p*-I-Ph | 6.90 | 7.25 | 6.78 | 6.12 | 6.98 | 7.45 | 5.80 | 6.09 |
| 11 | H | CH(OH)Me | 7.03 | 6.81 | 6.12 | 6.27 | 7.25 | 7.47 | 5.11 | 5.73 |
| 12 | Me | Me | 7.12 | 7.25 | 6.02 | 6.38 | 7.89 | 7.17 | 5.72 | 5.54 |
| 13 | Et | Et | 7.91 | 7.87 | 7.01 | 6.99 | 8.01 | 7.99 | 6.03 | 6.33 |
| 14 | *n*-Pr | *n*-Pr | 8.15 | 8.18 | 7.15 | 7.17 | 8.15 | 7.96 | 6.53 | 6.45 |
| 15 | *n*-Bu | *n*-Bu | 8.46 | 8.43 | 7.46 | 7.37 | 7.86 | 7.99 | 7.16 | 6.81 |
| 16 | *i*-Bu | *i*-Bu | 8.86 | 8.78 | 7.86 | 7.70 | 8.16 | 8.37 | 7.28 | 7.09 |
| 17 | *n*-Ph | *n*-Ph | 8.65 | 8.35 | 7.65 | 7.49 | 7.55 | 8.25 | 7.05 | 7.07 |
| 18 | allyl | allyl | 8.22 | 8.38 | 7.22 | 7.25 | 8.44 | 7.97 | 6.67 | 6.44 |
| 19 | Bzl | Bzl | 8.49 | 8.36 | 7.49 | 7.40 | 7.89 | 8.15 | 6.89 | 6.83 |
| 20 | Me | Et | 7.95 | 8.87 | 7.06 | 7.02 | 7.95 | 8.04 | 6.03 | 6.38 |
| 21 | Me | Pr | 7.91 | 8.29 | 7.31 | 6.98 | 8.13 | 7.87 | 6.65 | 6.45 |
| 22 | Me | *i*-Pr | 8.61 | 8.54 | 7.61 | 7.51 | 8.13 | 8.25 | 6.96 | 6.88 |
| 23 | Me | *n*-Bu | 8.44 | 8.34 | 7.22 | 7.44 | 8.62 | 8.23 | 6.35 | 6.48 |
| 24 | Me | *t*-Bu | 8.62 | 8.51 | 7.62 | 7.55 | 8.31 | 8.40 | 6.66 | 6.84 |
| 25 | Et | *n*-Pr | 8.01 | 8.17 | 7.22 | 7.08 | 8.22 | 8.01 | 6.35 | 6.42 |
| 26 | Et | *n*-Bu | 8.62 | 8.66 | 7.62 | 7.51 | 8.15 | 8.11 | 6.27 | 6.88 |
| 27 | *n*-Pr | propynyl | 8.44 | 8.53 | 7.14 | 7.43 | 8.62 | 7.89 | 6.97 | 6.44 |
| 28 | Me | cyclopentyl | 8.14 | 8.18 | 7.22 | 7.18 | 8.22 | 8.07 | 6.36 | 6.47 |
| 29 | Me | cyclohexyl | 8.15 | 8.34 | 7.53 | 7.15 | 7.98 | 8.10 | 6.68 | 6.70 |
| 30 | Et | Ph | 8.46 | 8.21 | 7.33 | 7.42 | 8.16 | 8.29 | 6.37 | 6.66 |
| 31 | Me | Bzl | 8.24 | 8.10 | 7.09 | 7.25 | 8.16 | 8.04 | 6.37 | 6.46 |
| 32 | Me | $-CH_2CH_2OH$ | 6.93 | 6.68 | 5.85 | 6.18 | 7.15 | 7.21 | 5.23 | 5.58 |
| 33 | Et | $-CH_2CH_2OH$ | 7.52 | 6.94 | 6.18 | 6.60 | 6.96 | 7.46 | 5.73 | 6.03 |
| 34 | Me | $-CH_2CH_2CN$ | 6.97 | 6.89 | 6.05 | 6.18 | 6.97 | 7.10 | 5.74 | 5.74 |
| 35 | $-CH_2CH_2Cl$ | $-CH_2CH_2Cl$ | 7.24 | 7.20 | 5.77 | 6.41 | 7.47 | 6.77 | 6.38 | 5.57 |
| 36 | $-(CH_2)_4-$ | | 7.26 | 7.54 | 6.34 | 6.52 | 8.21 | 7.42 | 5.73 | 5.67 |
| 37 | $-CH(CH_3)(CH_2)_2CH(CH_3)-$ | | 8.22 | 8.40 | 7.45 | 7.23 | 8.22 | 8.10 | 6.67 | 6.62 |
| 38 | $-(CH_2)_5-$ | | 8.01 | 7.92 | 6.92 | 7.09 | 8.22 | 7.99 | 6.04 | 6.26 |
| 39 | $-(CH_2)_2CH(CH_3)(CH_2)_2-$ | | 8.22 | 8.08 | 7.27 | 7.21 | 7.92 | 8.14 | 6.36 | 6.61 |
| 40 | $-(CH_2)_4CH(CH_3)-$ | | 8.22 | 8.27 | 7.45 | 7.20 | 7.92 | 8.10 | 6.67 | 6.70 |
| 41 | $-(CH_2)_6-$ | | 8.32 | 8.19 | 7.45 | 7.29 | 7.92 | 8.25 | 6.45 | 6.74 |
| 42 | $-(CH_2)_2O(CH_2)_2-$ | | 6.44 | 6.91 | 5.84 | 5.80 | 7.26 | 6.71 | 5.74 | 5.35 |
| 43 | $-(CH_2)_2OCH_2CH(CH_3)-$ | | 7.92 | 7.88 | 6.22 | 7.01 | 8.36 | 7.24 | 6.67 | 5.83 |
| 44 | $-CH(CH_3)CH_2OCH_2CH(CH_3)-$ | | 7.93 | 7.80 | 6.98 | 6.98 | 7.76 | 7.93 | 6.15 | 6.39 |

[a] The experimental data have been taken from ref 17.

will be given for each subset.

***Aspergillus niger.*** The correlation demonstrated between $A_{A.n.}$ and index $\Sigma\pi$ in eq 36 was improved significantly by replacing $\Sigma\pi$ with index $A_{T.v.}$ (eq 38). The partial $F$ test yields $F_{1,24} = 21.37$ vs. $F_{1,24;p=0.01} = 7.82$. The replacement of index $A_{T.v.}$ by $PR_1^{A.n.}$ (eq 40) improved the correlation coefficient again significantly; the partial $F$ test yields now $F_{1,24} = 16.00$. Comparing the corresponding eq 39 and 41, the latter turns out to be better ($F_{2,23} = 14.59$ vs. $F_{2,23;p=0.01} = 5.66$). $PR_1^{A.n.}$ explains 78% of the total SV of the subset, $PR_2^{A.n.}$ accounts for 12%, and $PR_3^{A.n.}$ for 8% only. Although the correlation coefficient between $PR_3^{A.n.}$ and $A_{A.n.}$ is $r = -0.157$ only (Table XVI), its consideration still improves eq 40 significantly ($F_{1,23} = 6.60$ vs. $F_{1,23;p=0.05} = 4.28$). Again, consideration of $PR_2^{A.n.}$ would not improve the multiple correlation coefficient significantly. $PR_3^{A.n.}$ is essentially proportional to $3A_{T.m.} - A_{M.v.}$.

***Aspergillus oryzae.*** The correlation coefficient demonstrated between $A_{A.o.}$ and $A_{A.n.}$ (eq 44) is significantly higher than the correlation coefficient found between $A_{A.o.}$ and index $PR_1^{A.o.}$ (eq 46), the result of the partial $F$ test if $F_{1,24} = 11.53$. Equations 45 and 47 are of practically the same quality. The first principal component accounts for 84% of the total SV of the subset, the second for 8%, and the third for 6%. Again, consideration of $PR_3^{A.o.}$ improves the quality of eq 46 significantly (eq 47); the partial $F$ test yields $F_{1,23} = 18.62$ vs. $F_{1,23;p=0.01} = 7.88$. $PR_3^{A.o.}$ is proportional to $4A_{M.v.} - 2.5A_{T.v.} - 2A_{T.m.} - A_{A.n.}$.

***Trichoderma viride.*** For this system, the replacement of the index $A_{A.n.}$ in eq 50 by $PR_1^{T.v.}$ (eq 52) leads to a significant improvement of the correlation coefficient ($F_{1,24} = 8.79$). Although eq 53 is slightly better than eq 51, the difference is not significant. The various ratios of the total SV of the subset explained by the mutually independent components do not differ remarkably from the values obtained in the previous examples. The index $A_{T.v.}$ seems not to depend on $PR_2^{T.v.}$, $PR_3^{T.v.}$, and $PR_4^{T.v.}$. $PR_3^{T.v.}$ is practically proportional to $4A_{T.m.} - A_{A.n.} - A_{A.o.} - A_{M.v.}$.

***Trichophyton mentagrophytes.*** Comparison of the derived regression equations shows no significant differences (eq 54–59) between them at level $p \leq 0.01$. The equations are not appropriate for quantitative predictions. The ratios of the total SV explained by the components $PR_p^{T.m.}$ are similar to those figures obtained for systems *A. niger* and *A. oryzae*. $PR_3^{T.m.}$ is practically proportional to $1.6A_{A.o.} - A_{A.n.} + A_{T.v.}$.

Table XII. Regression Equations Derived for the Rifamycin B Amides (III)

| system | equation | $n$ | $R$ | $s$ | eq no. |
|---|---|---|---|---|---|
| *M. aureus* | $A_{M.a} = 1.46(\pm0.33)D + 6.63$ | 42 | 0.820 | 0.43 | 66 |
| $A_{M.a.} = -\log C$ | $A_{M.a.} = 0.51(\pm0.23)\log P - 0.06(\pm0.06)(\log P)^2 + 1.30(\pm0.24)D + 6.20$ | 42 | 0.920 | 0.32 | 67 |
| | $A_{M.a.} = 1.02(\pm0.07)A_{S.f.} + 0.77$ | 44 | 0.919 | 0.32 | 68 |
| | $A_{M.a.} = 0.79(\pm0.08)A_{S.f.} + 0.32(\pm0.08)A_{S.n.} + 0.17$ | 44 | 0.943 | 0.27 | 69 |
| | $A_{M.a.} = 0.72(\pm0.03)PR_1^{M.a.} - 0.93$ | 44 | 0.961 | 0.22 | 70 |
| *S. faecalis* | $A_{S.f.} = 1.00(\pm0.43)D + 6.05$ | 42 | 0.599 | 0.57 | 71 |
| $A_{S.f.} = -\log C$ | $A_{S.f.} = 0.74(\pm0.19)\log P - 0.10(\pm0.05)(\log P)^2 + 0.79(\pm0.23)D + 5.43$ | 42 | 0.915 | 0.29 | 72 |
| | $A_{S.f.} = 0.83(\pm0.05)A_{M.a.} + 0.42$ | 44 | 0.919 | 0.29 | 73 |
| | $A_{S.f.} = 0.75(\pm0.09)A_{M.a.} + 0.13(\pm0.12)A_{B.s.} + 0.27$ | 44 | 0.921 | 0.29 | 74 |
| | $A_{S.f.} = 0.57(\pm0.04)PR_1^{S.f.} - 0.32$ | 44 | 0.899 | 0.32 | 75 |
| | $A_{S.f.} = 0.57(\pm0.04)PR_1^{S.f.} - 0.53(\pm0.22)PR_3^{S.f.} + 0.32$ | 44 | 0.912 | 0.30 | 76 |
| *S. hemolyticus* | $A_{S.h.} = 1.23(\pm0.31)D + 0.74$ | 41 | 0.786 | 0.39 | 77 |
| $A_{S.h.} = -\log C$ | $A_{S.h.} = 0.48(\pm0.22)\log P - 0.10(\pm0.05)(\log P)^2 + 1.18(\pm0.26)D + 6.40$ | 41 | 0.866 | 0.33 | 78 |
| | $A_{S.h.} = 0.72(\pm0.09)A_{M.a.} + 2.11$ | 44 | 0.792 | 0.45 | 79 |
| | $A_{S.h.} = 1.10(\pm0.13)A_{M.a.} - 0.58(\pm0.17)A_{B.s.} + 2.82$ | 44 | 0.844 | 0.40 | 80 |
| | $A_{S.h.} = 0.44(\pm0.07)PR_1^{S.h.} + 2.39$ | 44 | 0.718 | 0.51 | 81 |
| | $A_{S.h.} = 0.44(\pm0.06)PR_1^{S.h.} - 0.79(\pm0.21)PR_2^{S.h.} + 2.81$ | 44 | 0.800 | 0.45 | 82 |
| *B. subtilis* | $A_{B.s.} = 0.96(\pm0.32)D + 5.42$ | 41 | 0.690 | 0.46 | 83 |
| $A_{B.s.} = -\log C$ | $A_{B.s.} = 0.27(\pm0.08)\log P - 0.15(\pm0.10)E_s - 0.62(\pm0.17)\sigma^* + 5.74$ | 39 | 0.924 | 0.24 | 84 |
| | $A_{B.s.} = 0.65(\pm0.07)A_{M.a.} + 1.22$ | 44 | 0.816 | 0.37 | 85 |
| | $A_{B.s.} = 0.94(\pm0.10)A_{M.a.} - 0.40(\pm0.11)A_{S.h.} + 2.05$ | 44 | 0.861 | 0.33 | 86 |
| | $A_{B.s.} = 0.40(\pm0.05)PR_1^{B.s.} + 1.16$ | 44 | 0.755 | 0.42 | 87 |
| | $A_{B.s.} = 0.40(\pm0.04)PR_1^{B.s.} - 0.58(\pm0.13)PR_2^{B.s.} + 1.77$ | 44 | 0.844 | 0.35 | 88 |

Table XIII. Rifamycin B Amides (III). Mutually Independent Components of Antibacterial Activities (Table IX)

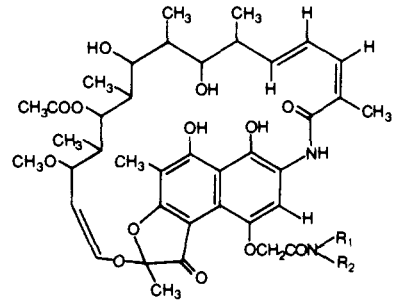
| no. | $PR_1^{M.a.}$ | $PR_1^{S.f.}$ | $PR_3^{S.f.}$ | $PR_1^{S.h.}$ | $PR_2^{S.h.}$ | $PR_1^{B.s.}$ | $PR_2^{B.s.}$ |
|---|---|---|---|---|---|---|---|
| 1 | 9.39 | 9.83 | 1.39 | 8.89 | 0.59 | 9.88 | 1.61 |
| 2 | 10.30 | 10.74 | 2.00 | 11.23 | 1.96 | 10.25 | −0.38 |
| 3 | 11.04 | 11.49 | 1.18 | 10.79 | 0.25 | 11.89 | 1.38 |
| 4 | 10.17 | 10.56 | 1.09 | 10.25 | 0.55 | 10.80 | 0.79 |
| 5 | 10.63 | 11.09 | 1.24 | 10.43 | 0.46 | 11.34 | 1.28 |
| 6 | 10.19 | 10.73 | 0.93 | 10.41 | 0.49 | 10.96 | 0.74 |
| 7 | 10.57 | 11.09 | 0.97 | 10.66 | 0.36 | 11.41 | 0.93 |
| 8 | 10.91 | 10.94 | 1.37 | 10.72 | 0.51 | 11.37 | 0.86 |
| 9 | 10.97 | 10.85 | 1.41 | 10.85 | 0.59 | 11.32 | 0.62 |
| 10 | 11.31 | 11.33 | 1.25 | 11.26 | 0.40 | 11.88 | 0.67 |
| 11 | 10.69 | 11.25 | 0.89 | 10.63 | 0.02 | 11.74 | 1.20 |
| 12 | 11.31 | 11.95 | 1.43 | 10.92 | 0.57 | 12.08 | 1.76 |
| 13 | 12.17 | 12.70 | 1.09 | 12.17 | 0.22 | 13.20 | 1.17 |
| 14 | 12.59 | 13.18 | 1.26 | 12.65 | 0.53 | 13.51 | 1.15 |
| 15 | 12.94 | 13.53 | 1.27 | 13.33 | 0.87 | 13.73 | 0.68 |
| 16 | 13.43 | 14.02 | 1.18 | 13.88 | 0.70 | 14.37 | 0.63 |
| 17 | 12.82 | 13.43 | 0.94 | 13.51 | 0.64 | 13.79 | 0.28 |
| 18 | 12.87 | 13.45 | 1.41 | 12.80 | 0.60 | 13.75 | 1.34 |
| 19 | 12.84 | 13.44 | 1.11 | 13.24 | 0.61 | 13.78 | 0.68 |
| 20 | 12.16 | 12.70 | 1.04 | 12.22 | 0.19 | 13.23 | 1.08 |
| 21 | 12.74 | 13.06 | 1.49 | 12.64 | 0.64 | 13.43 | 1.11 |
| 22 | 13.09 | 13.69 | 1.16 | 13.42 | 0.59 | 14.05 | 0.79 |
| 23 | 12.82 | 13.56 | 1.15 | 12.79 | 0.26 | 13.98 | 1.44 |
| 24 | 13.05 | 13.65 | 1.07 | 13.29 | 0.32 | 14.16 | 0.93 |
| 25 | 12.58 | 13.04 | 1.29 | 12.51 | 0.38 | 13.50 | 1.21 |
| 26 | 13.26 | 13.85 | 1.34 | 13.58 | 0.85 | 14.07 | 0.80 |
| 27 | 13.07 | 13.85 | 1.50 | 13.04 | 0.84 | 13.94 | 1.48 |
| 28 | 12.59 | 13.13 | 1.20 | 12.60 | 0.36 | 13.58 | 1.18 |
| 29 | 12.81 | 13.16 | 1.27 | 12.94 | 0.51 | 13.63 | 0.82 |
| 30 | 12.63 | 13.33 | 0.95 | 12.88 | 0.23 | 13.81 | 1.00 |
| 31 | 12.48 | 13.17 | 1.11 | 12.59 | 0.39 | 13.54 | 1.17 |
| 32 | 10.52 | 11.18 | 0.98 | 10.46 | 0.26 | 11.48 | 1.28 |
| 33 | 10.88 | 11.71 | 0.76 | 11.28 | 0.40 | 11.94 | 0.82 |
| 34 | 10.80 | 11.34 | 1.17 | 10.85 | 0.61 | 11.52 | 1.02 |
| 35 | 11.23 | 12.10 | 1.54 | 11.17 | 1.21 | 11.80 | 1.51 |
| 36 | 11.70 | 12.23 | 1.47 | 11.21 | 0.41 | 12.52 | 1.83 |
| 37 | 12.89 | 13.33 | 1.32 | 12.93 | 0.51 | 13.76 | 1.04 |
| 38 | 12.24 | 12.89 | 1.12 | 12.18 | 0.23 | 13.33 | 1.36 |
| 39 | 12.48 | 13.02 | 1.02 | 12.68 | 0.31 | 13.50 | 0.89 |
| 40 | 12.72 | 13.17 | 1.19 | 12.93 | 0.51 | 13.60 | 0.79 |
| 41 | 12.61 | 13.13 | 1.00 | 12.89 | 0.29 | 13.66 | 0.77 |
| 42 | 10.83 | 11.14 | 1.67 | 10.38 | 0.85 | 11.21 | 1.49 |
| 43 | 12.18 | 13.20 | 1.59 | 12.02 | 1.09 | 12.96 | 1.86 |
| 44 | 12.06 | 12.64 | 1.04 | 12.22 | 0.33 | 13.07 | 0.97 |

Table XIV. Rifamycin B Amides (III). Correlations between Experimental Activities

| | $A_{S.f.}$ | $A_{S.h.}$ | $A_{B.s.}$ |
|---|---|---|---|
| $A_{M.a.}$ | 0.92 | 0.79 | 0.82 |
| $A_{S.f.}$ | | 0.70 | 0.79 |
| $A_{S.h.}$ | | | 0.48 |

***Myrothecium verrucaria.*** For this system too, rather low correlation coefficients were derived. There is no significant difference between eq 62 and 64 and also between eq 63 and 65. Consideration of $PR_3^{M.v.}$ improved significantly the correlation coefficient calculated with eq 64; the partial $F$ test yields $F_{1,23} = 19.46$. The ratios of the total SV of the subset explained by the components $PR_p^{M.v.}$ do not differ from the figures of the examples discussed above. $PR_3^{M.v.}$ is practically proportional to $1.6A_{A.o.} - A_{A.n.}$.

**Rifamycin B Amides (III).** The derived regression equations are given in Table XII. Equations 66, 67, 71, 72, 77, 78, 83, and 84 were calculated by Quinn et al.[17] Here, $P$ denotes the partition coefficient of the molecules,[21] $E_s$ is the Taft constant,[22] $\sigma^*$ denotes the aliphatic substituent constant,[19] and $D$ is a dummy variable, being 1



III.

if N,N-disubstituted molecules are treated and is 0 if otherwise. Since these equations were obtained by dropping at least two observations, they are not comparable directly with the equations derived in this work. All equations listed are significant at $p \leq 0.01$. Table XIV shows the intercorrelations of the pharmacological activity indices. Table XVII lists the ratios of the total SV of the subsets explained by the components $PR_p^X$ ($p$ = 1–3) and also the correlation coefficients calculated between these

Table XV. Benzodiazepine Derivatives (I). Correlations between the Dependent Variables and Mutually Independent Components.[a] Principal Components of Variances

| dependent variable $A$ | $\frac{l_1}{n-1}$ | $r_{A,PR_1}$ | $\frac{l_2}{n-1}$ | $r_{A,PR_2}$ | $\frac{l_3}{n-1}$ | $r_{A,PR_3}$ | $\frac{l_4}{n-1}$ | $r_{A,PR_4}$ | total SV |
|---|---|---|---|---|---|---|---|---|---|
| | $PR_1^{IS}$ | | $PR_2^{IS}$ | | $PR_3^{IS}$ | | $PR_4^{IS}$ | | |
| $A_{IS}$ | 2.07 | 0.812 | 0.27 | 0.023 | 0.14 | 0.479 | 0.08 | 0.089 | 2.56 |
| | $PR_1^{FS}$ | | $PR_2^{FS}$ | | $PR_3^{FS}$ | | $PR_4^{FS}$ | | |
| $A_{FS}$ | 2.09 | 0.858 | 0.27 | 0.018 | 0.18 | 0.420 | 0.08 | 0.022 | 2.62 |
| | $PR_1^{PT}$ | | $PR_2^{PT}$ | | $PR_3^{PT}$ | | $PR_4^{PT}$ | | |
| $A_{PT}$ | 1.22 | 0.804 | 0.26 | −0.012 | 0.08 | −0.134 | 0.03 | 0.188 | 1.59 |
| | $PR_1^{E_{max}}$ | | $PR_2^{E_{max}}$ | | $PR_3^{E_{max}}$ | | $PR_4^{E_{max}}$ | | |
| $A_{E_{max}}$ | 2.16 | 0.747 | 0.26 | 0.027 | 0.17 | 0.366 | 0.02 | −0.039 | 2.61 |
| | $PR_1^{E_{min}}$ | | $PR_2^{E_{min}}$ | | $PR_3^{E_{min}}$ | | $PR_4^{E_{min}}$ | | |
| $A_{E_{min}}$ | 2.40 | 0.393 | 0.26 | 0.044 | 0.18 | 0.501 | 0.02 | −0.106 | 2.86 |

[a] The dependent variable was not used to derive the mutually independent components.

Table XVI. 8-Quinolinol Derivatives (II). Correlations between the Dependent Variables and Mutually Independent Components.[a] Principal Components of Variances

| dependent variable $A$ | $\frac{l_1}{n-1}$ | $r_{A,PR_1}$ | $\frac{l_2}{n-1}$ | $r_{A,PR_2}$ | $\frac{l_3}{n-1}$ | $r_{A,PR_3}$ | $\frac{l_4}{n-1}$ | $r_{A,PR_4}$ | total SV |
|---|---|---|---|---|---|---|---|---|---|
| | $PR_1^{A.n.}$ | | $PR_2^{A.n.}$ | | $PR_3^{A.n.}$ | | $PR_4^{A.n.}$ | | |
| $A_{A.n.}$ | 0.83 | 0.943 | 0.13 | −0.089 | 0.08 | −0.157 | 0.02 | −0.075 | 1.06 |
| | $PR_1^{A.o.}$ | | $PR_2^{A.o.}$ | | $PR_3^{A.o.}$ | | $PR_4^{A.o.}$ | | |
| $A_{A.o.}$ | 0.92 | 0.832 | 0.09 | −0.217 | 0.07 | −0.372 | 0.02 | −0.092 | 1.10 |
| | $PR_1^{T.v.}$ | | $PR_2^{T.v.}$ | | $PR_3^{T.v.}$ | | $PR_4^{T.v.}$ | | |
| $A_{T.v.}$ | 0.90 | 0.930 | 0.14 | −0.068 | 0.08 | 0.071 | 0.02 | 0.036 | 1.14 |
| | $PR_1^{T.m.}$ | | $PR_2^{T.m.}$ | | $PR_3^{T.m.}$ | | $PR_4^{T.m.}$ | | |
| $A_{T.m.}$ | 1.13 | 0.507 | 0.13 | 0.129 | 0.03 | 0.259 | 0.02 | 0.188 | 1.31 |
| | $PR_1^{M.v.}$ | | $PR_2^{M.v.}$ | | $PR_3^{M.v.}$ | | $PR_4^{M.v.}$ | | |
| $A_{M.v.}$ | 0.91 | 0.785 | 0.09 | 0.143 | 0.04 | −0.420 | 0.03 | −0.099 | 1.07 |

[a] See Table XV, footnote *a*.

Table XVII. Rifamycin B Amides (III). Correlations between the Dependent Variables and Mutually Independent Components.[a] Principal Components of Variances

| dependent variable $A$ | $\frac{l_1}{n-1}$ | $r_{A,PR_1}$ | $\frac{l_2}{n-1}$ | $r_{A,PR_2}$ | $\frac{l_3}{n-1}$ | $r_{A,PR_3}$ | total SV |
|---|---|---|---|---|---|---|---|
| | $PR_1^{M.a.}$ | | $PR_2^{M.a.}$ | | $PR_3^{M.a.}$ | | |
| $A_{M.a.}$ | 1.12 | 0.961 | 0.25 | 0.035 | 0.07 | 0.007 | 1.44 |
| | $PR_1^{S.f.}$ | | $PR_2^{S.f.}$ | | $PR_3^{S.f.}$ | | |
| $A_{S.f.}$ | 1.28 | 0.899 | 0.24 | 0.132 | 0.04 | −0.150 | 1.56 |
| | $PR_1^{S.h.}$ | | $PR_2^{S.h.}$ | | $PR_3^{S.h.}$ | | |
| $A_{S.h.}$ | 1.41 | 0.718 | 0.11 | −0.352 | 0.05 | −0.271 | 1.57 |
| | $PR_1^{B.s.}$ | | $PR_2^{B.s.}$ | | $PR_3^{B.s.}$ | | |
| $A_{B.s.}$ | 1.47 | 0.755 | 0.17 | −0.376 | 0.04 | −0.182 | 1.68 |

[a] See Table XV, footnote *a*.

Table XVIII. 8-Quinolinol Derivatives (II). Regression Equations Derived between Index $A_{A.o.}$[a] and Mutually Independent Components of Reduced Data Subsets ($k = 3$)

| act. deleted from data set ($X$) | equation | $n$ | $R$ | $s$ | eq no. |
|---|---|---|---|---|---|
| $A_{A.o.}$ and $A_{A.n.}$ | $A_{A.o.} = 0.55(\pm0.09)PR_1^X - 0.37$ | 26 | 0.764 | 0.37 | 89 |
| | $A_{A.o.} = 0.55(\pm0.07)PR_1^X + 0.98(\pm0.22)PR_3^X - 0.05$ | 26 | 0.882 | 0.28 | 90 |
| $A_{A.o.}$ and $A_{T.v.}$ | $A_{A.o.} = 0.54(\pm0.09)PR_1^X - 0.20$ | 26 | 0.787 | 0.35 | 91 |
| | $A_{A.o.} = 0.54(\pm0.06)PR_1^X - 1.08(\pm0.21)PR_3^X - 0.63$ | 26 | 0.907 | 0.25 | 92 |
| $A_{A.o.}$ and $A_{T.m.}$ | $A_{A.o.} = 0.50(\pm0.07)PR_1^X - 0.16$ | 26 | 0.834 | 0.32 | 93 |
| | $A_{A.o.} = 0.50(\pm0.04)PR_1^X - 0.88(\pm0.15)PR_2^X - 0.04$ | 26 | 0.937 | 0.21 | 94 |
| $A_{A.o.}$ and $A_{M.v.}$ | $A_{A.o.} = 0.63(\pm0.06)PR_1^X - 0.43$ | 26 | 0.899 | 0.25 | 95 |
| | $A_{A.o.} = 0.63(\pm0.06)PR_1^X - 0.19(\pm0.16)PR_2^X - 0.13$ | 26 | 0.905 | 0.25 | 96 |

[a] See Table VI.

components and the respective dependent variable $A_X$. All the transformation coefficients $c_{i1}$ (eq 1) belonging to $PR_1^X$ were positive in this series too.

***Micrococcus aureus.*** Variable $PR_1^{M.a.}$ is clearly more appropriate than index $A_{S.f.}$ (eq 68 and 70). The partial $F$ test indicates that the improvement is significant ($F_{1,42} = 43.46$ vs. $F_{1,42,p=0.01} = 7.27$). Equation 70 is significantly better than eq 69. For the calculation of the partial $F$ test, eq 69 was used as an equation with one parameter. The result of the partial $F$ test performed in this way is $F_{1,42} = 18.82$. This indicates a difference significant at $p \leq 0.01$. The first component $PR_1^{M.a.}$ accounts for 78%, $PR_2^{M.a.}$ for 17%, and $PR_3^{M.a.}$ for 5% of the total SV of the subset (Table XVII).

***Streptococcus faecalis.*** For this strain, the original pharmacological index $A_{M.a.}$ yielded a higher correlation coefficient than variable $PR_1^{S.f.}$ (eq 73 and 75). The partial $F$ test indicates that the difference is significant ($F_{1,42} = 9.82$). There is no significant difference between eq 74 and 76. The relative ratios of the total SV of the subset explained by the components $PR_p^{S.f.}$ ($p = 1$–3) are similar to the figures given for system *M. aureus*. $PR_3^{S.f.}$ is practically proportional to $A_{B.s.} - A_{S.h.}$.

***Streptococcus hemolyticus* and *Bacillus subtilis.*** For both strains, the derived regression equations are inadequate for quantitative predictions. Formally, as indicated by the partial $F$ test, the correlation between indices $A_{S.h.}$ and $A_{M.a.}$ (eq 79) is significantly better than the correlation coefficient calculated between indices $A_{S.h.}$ and $PR_1^{S.h.}$ (eq 81). The partial $F$ test yields $F_{1,42} = 12.59$. Similarly, eq 85 should be preferred to eq 87 ($F_{1,42} = 12.85$). Indices $PR_1^{S.h.}$ and $PR_1^{B.s.}$ explain 90 and 88% of the total SV of the corresponding subsets, respectively. Consideration of $PR_2^{S.h.}$ and of $PR_2^{B.s.}$ (eq 82 and 88) improves significantly the multiple correlation coefficients obtained for eq 81 and 87. The partial $F$ test yields $F_{1,41} = 14.18$ and $F_{1,41} = 20.28$ vs. the theoretical value $F_{1,41,p=0.01} = 7.29$.

Positive correlation coefficients were always obtained between the dependent activity $A_X$ and the corresponding values of $PR_1^X$ (Tables XV, XVI, and XVII), where $X$ denotes the activity index *not* considered in the decomposition procedure. In all cases but one (eq 34), these coefficients were superior to those calculated between the dependent variable and the other components, $PR_p^X$ ($p \neq 1$). The first (main) component is also the one which accounts for the highest portion (75–90%) of the total SV of the subset. The importance of the main component may be explained by the similarity of the processes following the administration of the drug molecules.

Pharmacological activities of the benzodiazepine derivatives (I) and of the 8-quinolinols (II) seem not to depend on component $PR_2^X$. The correlation coefficients between values $A_X$ and $PR_2^X$ are definitely lower than those derived for $A_X$ and $PR_3^X$.

The correlation coefficients calculated between the activity indices of the benzodiazepines (I) and of the 8-quinolinol derivatives (II) and the corresponding indices $PR_3^X$ (Tables XV and XVI) may be either positive or negative. $PR_3^X$ accounts for 2–8% of the total SV of the subsets. Factors collected in this component may account for the *secondary* effects, favoring some types of activities and hindering others.

There are no relationships between indices $PR_4^X$ and the corresponding dependent variables $A_X$. $PR_4^X$ accounts for 1–2% of the total SV of the subsets (Tables XV and XVI) and may be considered as random noises.

As indicated by the results for the rifamycin B amides (III), $PR_1^X$ may be followed by either $PR_2^X$ or by $PR_3^X$ (eq 76, 82, and 88). The relative importance of component $PR_2^X$ in this series may be explained by the smaller number of variables ($k = 3$). Factors causing secondary effects may appear now either in $PR_2^X$ or in $PR_3^X$. The implication that at $k = 4$ $PR_3^X$ would be the second variable to follow $PR_1^X$ in the stepwise development of the regression equations is supported by *additional* calculations performed within the series of 8-quinolinol (II) derivatives.

The dependent activity was the pharmacological potency of the molecules determined on the strain *A. oryzae* (Table VI). Out of the remaining *four* indices, *three* ($k = 3$) were used to extract the independent components. The decomposition procedure was applied for $\binom{4}{3} = 4$ different subsets. Four sets of mutually independent components were calculated. Each set was used to derive multiple linear regression equations. Here again, it was component $PR_1^X$ to be considered first by the stepwise regression program.[19] $PR_1^X$ is followed by $PR_3^X$ in two cases (eq 90 and 92). The partial $F$ test indicates that the improvements are significant at $p \leq 0.01$, the respective values being $F_{1,23} = 19.94$ and $R_{1,23} = 26.31$ (Table XVIII). $PR_1^X$ may also be followed by $PR_2^X$ (eq 94); the improvement is again significant ($F_{1,23} = 33.97$). There is no significant difference between eq 95 and 96. Reduction of the dimension of data subset produced an effect, similar to that obtained for the rifamycin B amides (III).

## Conclusions

It seems that biological activities, both primary and transformed (eq 1), are more effective in quantitative predictions than standard substituent constants.

Decomposition of pharmacological activity indices into mutually independent components yields a "main" component, comprising the common factors of the physiological action of the molecules, and a secondary one, accounting for *dissimilarities* between the various types of the pharmacological activity indices. The main component $PR_1^X$ explains the highest ratio of the total SV of the given subset. It was shown that the correlation coefficient, demonstrated between the dependent pharmacological

index and the main component, is positive and may be larger than any of the correlation coefficients calculated between pairs of nontransformed pharmacological activity indices. The dependent variable was not included into the data subset subjected to the decomposition procedure.

There is virtually no correlation between the dependent variable and component $PR_2^X$, extracted from four variate data subsets, although $PR_2^X$ explains after $PR_1^X$ the next highest part of the total SV of the subsets. The factors accounting for the secondary effects appear in $PR_3^X$, if four variate subsets are investigated. The factors accounting for the secondary effects may also appear in $PR_2^X$, if three variate subsets are considered.

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# *Notes*

## Mutagenicity of Substituted (*o*-Phenylenediamine)platinum Dichloride in the Ames Test. A Quantitative Structure–Activity Analysis

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A set of 13 substituted (*o*-phenylenediamine)platinum dichlorides has been studied in the Ames test using *Salmonella typhimurium* (TA-92). These *cis*-platinum compounds are mutagenic without activation by microsomes. The following correlation equation shows that the most important determinant of mutagenicity by substituents (X) is electron withdrawal via through resonance: $\log 1/C = 2.23\sum\sigma^- + 5.78$. $C$ in this expression is the molar concentration of compound producing 30 mutations/$10^8$ bacteria initially delivered above background mutation, and $\sigma^-$ is the Hammett constant obtained from substituted anilines.

Despite the huge amount of work being undertaken studying the mutagenicity of organic compounds with the Ames test, very little has been reported on quantitative structure–activity relationships (QSAR). Sugiura et al.[1] have shown a linear relationship between the mutagenicity of *Salmonella typhimurium* (TA-100) acting on four styrene oxides (I) and the Hammett $\sigma$ constant. We have formulated eq 1 from their data, where $C$ is the molar

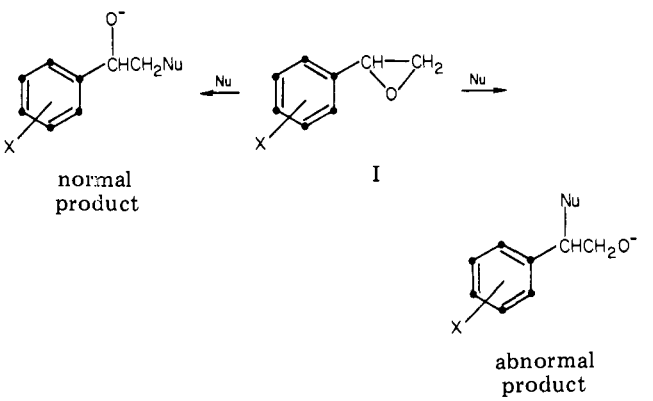
$$\log 1/C = -1.56(\pm 1.2)\sigma + 6.18(\pm 0.27) \quad (1)$$

$$n = 4;\ r = 0.971;\ s = 0.113$$

concentration of styrene oxide producing 200 mutants/$10^9$ survivors, the figures in parentheses are the 95% confidence limits, $n$ represents the number of data points, $r$ is the correlation coefficient, and $s$ is the standard deviation from regression. Equation 1 is statistically significant ($F_{1,2}$ = 32.1; $F_{1,2;\alpha=0.05}$ = 18.5). The negative slope of eq 1 shows that electron release by substituents increases mutagenicity. Sugiura et al. concluded that there was little, if any, dependence of activity on the hydrophobic parameter $\pi$.[2] Using $\pi$ in place of $\sigma$, we find a poor correlation ($r$ = 0.492; $s$ = 0.411). However, there are not enough data points to test the linear combination of $\pi$ and $\sigma$ so that hydrophobic effects cannot be completely ruled out.

Sugiura et al. noted that there are two ways styrene oxides might react with nucleophiles (Scheme I). They show that $\rho$ (slope of Hammett equation) is 0.87 for the "normal" reaction of styrene oxide with a typical nucleophilic reagent, benzylamine, while $\rho$ for the "abnormal" reaction has been shown to be negative (−1.15 for reaction with benzylamine and −1.6 for reduction with lithium borohydride). Thus, the negative slope of eq 1 suggests that the abnormal (possibly $S_N1$) type of reaction in the bacterial cell is apparently causing the mutation. While the results of Sugiura et al. are most interesting and highly suggestive, one cannot place much weight on a biological QSAR based on only four data points which, moreover, are not widely separated in data space. It would be interesting to test substituents such as OH, $NH_2$, and $OCH_3$ to see if $\sigma^+$ might give a better correlation than $\sigma$. If so, this would establish a role for through resonance and an $S_N1$-type mechanism. It should be noted that the styrene oxides are mutagenic as such and do not require microsomal activation.

Scheme I




In a recent study of the mutagenic potency of nitroimidazoles, nitrobenzenes, and nitrofurans, Chin et al.[3]

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