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CSTRIP, a Fortran IV Computer Program for Obtaining Initial Polyexponential Parameter Estimates

ALLEN J. SEDMAN * and JOHN G. WAGNER [x]

Abstract □ A new exponential stripping program, CSTRIP, has been developed. This program overcomes the problems associated with the use of previously published techniques and enables the rapid economical calculation of initial polyexponential parameter estimates. Values for the coefficients and exponents of the exponential terms are calculated as well as estimates of lag times. An exhaustive search procedure ensures that the results are comparable to, or better than, those obtained by manual residual methods.

Keyphrases □ Pharmacokinetic modeling—calculation of initial polyexponential parameter estimates by a Fortran computer program □ Polyexponential parameter estimates—pharmacokinetic modeling, calculation by a Fortran computer program □ Computer programs, Fortran—calculation of initial polyexponential estimates for use in pharmacokinetic modeling □ Automated computer analysis—initial polyexponential parameter estimates for use in pharmacokinetic modeling, Fortran program

Pharmacokinetic models have proven to be a succinct method of describing the behavior of drugs *in vivo*. Classical linear pharmacokinetic models are represented by systems of homogeneous linear differential equations with constant coefficients. Solutions of such systems are given by the sums of exponential terms. Calculation of the numerical values of the exponents and coefficients of the exponential terms is often laborious and time consuming. Fortunately, the operations involved in exponential stripping are generally systematic and lend themselves to computer programming and solution by machine.

Theoretical approaches to exponential stripping have been discussed (1–7). However, many procedures are difficult to adapt to automated computer analysis.

One technique (1) employed a modification of the standard residual method, where the concentration of drug, C, was plotted against its first derivative, $-\Delta C/\Delta t$. This procedure yielded more erratic results than conventional residual methods because of the extreme sensitivity of the derivative to experimental error. Other techniques (2, 3), based on the theory of difference equations, proved to be impractical due to computational difficulties; unreliable solutions were obtained in the presence of small experimental errors. These methods also required equally spaced time intervals and only resolved the sums of exponentials having *positive* coefficients. Implementation of other approaches (4, 5) was prevented by similar considerations.

A computer algorithm (7), based on the residual method, was reported to be suitable for fully automated data analysis. This procedure had the following desirable characteristics: (*a*) sums of exponentials having positive and/or negative coefficients were accurately analyzed, and numerical values of coefficients and exponents were computed; and (*b*) unequally spaced data were acceptable, and no numerical instability arose during computation. However, this program required a minimum of three points for each exponential, and its use gave results that were not in good agreement with

those obtained by noncomputerized methods.

A computer-oriented technique for obtaining initial estimates of the parameters in exponential fitting was reported (6). This method, based on the "peeling" technique, resolved only the sums of exponentials having positive coefficients and was particularly well adapted to decay-type data. A minimum of three points was required for each exponential to be determined.

The purposes of this paper are to describe a new computer program that overcomes the problems and restrictions associated with previously published exponential stripping methods and to illustrate the use of this program.

COMPUTER PROGRAM

CSTRIP, a Fortran IV computer program for obtaining initial polyexponential parameter estimates, is based on a computer adaptation of the classical residual, peeling-off technique. CSTRIP is composed of 12 separate subroutines, and the most important subroutines are discussed briefly here.

EXP2, EXP4, EXP6, EXP8, and EXP10—These five subroutines strip curves described by one to five exponentials. The number in the name of each subroutine refers to the number of parameters estimated.

A computer adaptation of the manual technique commonly used for exponential stripping was described previously (6). A modification of this technique is employed in these subroutines and the method is summarized below.

It is desired to fit a set of data to the equation:

$$C = \sum_{i=1}^{m} a_i e^{-b_i t} \qquad \text{(Eq. 1)}$$

where C is the concentration of drug at time t, m is the number of exponential terms, t is time, and a_i and b_i are the parameters to be determined.

At large times, a plot of log C against t can generally be approximated by a straight line. The straight-line portion for large t occurs because as t increases the exponentials with large exponents (b_i's) decay to zero, leaving only the exponential with the smallest exponent, $a_m e^{-b_m t}$. Use of the method of least squares enables a straight line to be fitted to the last few data points, so values of a_m and b_m can be obtained. Values for the C residuals can then be calculated by use of:

$$C_{\text{residual}} = C - a_m e^{-b_m t} \qquad \text{(Eq. 2)}$$

By repeating this process utilizing the C residual values at large times, values for a_{m-1} and b_{m-1} can be determined. The process of peeling-off is continued until all coefficients and exponents of the polyexponential equation are determined.

In CSTRIP, the minimum number of points for a computer calculation of a_i and b_i is described by:

$$NPE = L/(3 + M) \qquad \text{(Eq. 3)}$$

where NPE is the minimum number of points per exponential [rounded off to the smallest whole number (≥ 2)], L is the number of distinct time values, and M is the number of exponential terms. These principles are computer implemented as follows. To calculate a first set of initial values, the last NPE data points are used to obtain a_m and b_m, the next NPE points are used to obtain a_{m-1} and b_{m-1}, *etc.* Finally, the remaining $n - NPE(m-1)$ points are used to calculate a_1 and b_1, where n is the total number of data points.

Subroutine LTTEST is called for concentration–time data collected following the oral or intramuscular administration of a drug. An appropriate lag time is calculated, or the sum of the exponential terms is forced through zero.

The value F, the sum of squares of the deviations, is used to evaluate the goodness of fit of the estimates:

$$F = \sum_{i=1}^{n} (C_i - \hat{C}_i)^2 \qquad \text{(Eq. 4)}$$

where $\hat{C}_i$ is the estimated drug concentration.

A second set of initial estimates of the parameters is obtained by utilizing the last $NPE + 1$ to calculate a_m and b_m. The next NPE points are used to determine a_{m-1} and b_{m-1}, and the process is continued until only one exponential is left with $n - NPE(m-1) - 1$ points to calculate a_1 and b_1. The value of F is calculated for this set of parameters. The remaining sets of initial estimates are calculated by combining the data to keep NPE points as a minimum in calculating a_i and b_i.

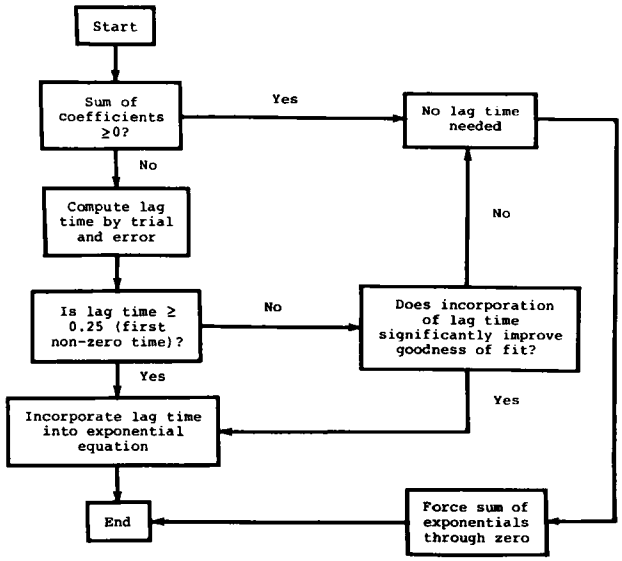

Figure 1—*Flowsheet for LTTEST subroutine.*

Every combination of data that meets these criteria is used to calculate initial estimates of the coefficients and exponents of the polyexponential equation. The set of parameters with the minimum F value is chosen as the best initial estimates. However, the following constraints also were imposed. Exponential terms describing intravenous or postinfusion data could not have negative coefficients. The value of b_{i-1} was required to be $\geq 1.33 b_i$, and exponents, b_i, could not assume values ≤ 0. Sums of exponentials that gave negative estimates at any time greater than zero were excluded.

CALC—Subroutine CALC computes the residual regression lines for the five curve-stripping subroutines discussed previously. Standard least-squares linear regression techniques are used.

FUN and RSQR—These subroutines calculate the goodness of fit for the curve-stripping subroutines. The sum of the squared deviations (Eq. 4) and the value of r^2:

$$r^2 = \left[\sum_{i=1}^{n} C_1^2 - \frac{\left(\sum_{i=1}^{n} C_i\right)^2}{n} - \sum_{i=1}^{n} (C_i - \hat{C}_i)^2 \right] \Bigg/ \left[\sum_{i=1}^{n} C_1^2 - \frac{\left(\sum_{i=1}^{n} C_i\right)^2}{n} \right] \qquad \text{(Eq. 5)}$$

are used as criteria for the goodness of fit.

LTTEST—This subroutine determines the suitability of a lag time for data collected following oral or intramuscular administration of a drug. A flowsheet for the LTTEST algorithm is given in Fig. 1. The lag time, t_1, is determined by trial-and-error solution of:

$$\sum_{i=1}^{m} a_i e^{-b_i t_1} = 0 \qquad \text{(Eq. 6)}$$

USE OF CSTRIP PROGRAM

Input of Data—Input to CSTRIP is specified in Table I. The following restrictions apply to the input of data. Abscissa (time) values must be ascendingly ordered. Although data collected during an intravenous infusion cannot be analyzed by CSTRIP, postinfusion values may be successfully analyzed.

For best results, a (0,0) data point should be used when data collected following oral or intramuscular administration are to be analyzed. The inclusion of the (0,0) point tends to minimize the importance of a lag time. However, if CSTRIP then indicates the presence

Table I—Input to CSTRIP

Format	Columns	Variable	Comments
		Card 1	
I2	1–2	NSET	Number of data sets
		Card 2[a]	
I1	1	MEX	Maximum number of exponential terms of interest
I3	2–4	N	Number of data points
I1	5	NROUTE	Route of administration NROUTE = 0, rapid intravenous injection or intravenous infusion NROUTE = 1, oral or intramuscular administration
		Card 3[a]	
8F10.0		Y(J), J = 1, N	Ordinate values; may take more than one card
		Card 4[a]	
8F10.0		T(J), J = 1, N	Abscissa values; may take more than one card

[a] Cards 2–4 are repeated for each set of data.

of a lag time, the data should be resubmitted without the (0,0) point to obtain a more accurate estimate of the lag time.

Replicate ordinate and/or abscissa values are permitted. Outliers should not be included in data sets.

Data Output—The CSTRIP output format is somewhat variable from one data set to another and is summarized in Fig. 2. The output parameters are defined in Table II.

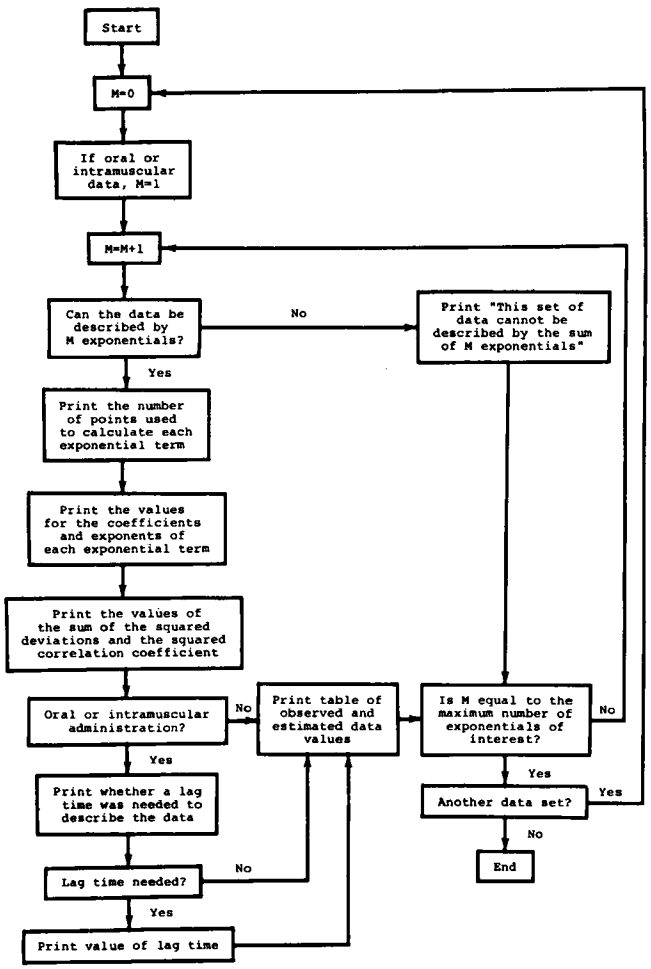

Figure 2—*Schematic diagram of CSTRIP output.*

Table II—CSTRIP Output Parameters

Parameter	Comments
L1, L2, *etc.*	Number of points used to calculate last exponential term (smallest exponent); next to last term; and so on
A1, A2, *etc.*	Coefficients of exponential terms of polyexponential equation
B1, B2, *etc.*	Exponents of polyexponential equation
F	Sum of squared deviations between observed data and values predicted by use of polyexponential equation
R SQUARE	Squared correlation coefficient
NO.	Data point number
TIME	Abscissa values
C(OBS)	Observed ordinate values
C(EST)	Ordinate values predicted by use of polyexponential equation
% DEV	Percent deviation of predicted from observed ordinate values

Table III—Tetracycline Data

Hours	Serum Concentration of Tetracycline Hydrochloride, μg/ml
1	0.7
2	1.2
3	1.4
4	1.4
6	1.1
8	0.8
10	0.6
12	0.5
16	0.3

Table IV—Intramuscular Spectinomycin Data

Hours	Serum Concentration of Spectinomycin, μg/ml
0.	0.
0.1667	15.7
0.3333	23.1
0.5	31.2
1.	31.6
2.	28.2
4.	12.8
6.	5.6
8.	2.4

Examples—Fifty sets of data, some simulated and the rest from the literature, were used to evaluate the capabilities of CSTRIP. Two representative data sets will be used to illustrate the performance of CSTRIP. Table III gives reported tetracycline data (8), and Table IV presents data collected after intramuscular injection of spectinomycin (9). These sets of data were submitted to CSTRIP for exponential analysis. The input format used is given in Table V.

RESULTS AND DISCUSSION

Tetracycline Data—The output resulting from the CSTRIP analysis of tetracycline[1] concentration–time data is given in Fig. 3. The analysis indicated that a biexponential equation:

$$C = -2.13e^{-1.03(t-0.610)} + 2.13e^{-0.129(t-0.610)} \qquad \text{(Eq. 7)}$$

with a lag time best described the concentration–time curve for tetracycline.

A reasonably high value for the goodness of fit parameter, r^2 = 0.979, indicated that the biexponential equation adequately described the data. Moreover, inclusion of an additional exponential term did not improve the goodness of fit.

Wagner (8) analyzed these data graphically and also determined that a biexponential equation was applicable. A comparison of

[1] Panmycin.

Table V—Input Format for Examples

```
02
30091
.7      1.2     1.4     1.4     1.1     .8      .6      .5
.3
1.      2.      3.      4.      6.      8.      10.     12.
16.
30091
0.      15.7    23.1    31.2    31.6    28.2    12.8    5.6
2.4
0.      .1667   .3333   .5      1.      2.      4.      6.
8.
```

graphical with CSTRIP curve stripping is made in Table VI. Although the reported graphical estimates are quite different than those obtained by use of CSTRIP, the goodness of fits, judged by sum of squared deviations, are comparable. Use of each set of parameters as initial parameter estimates for nonlinear least-squares analysis gave slightly different least-squares parameter values. However, each set of least-squares parameters seems to describe the data equally well.

Spectinomycin Data—The output resulting from the CSTRIP analysis of data collected after the administration of spectinomycin by intramuscular injection is given in Fig. 4. These data were described well by both a biexponential and triexponential equation. Wagner *et al.* (9) found that data collected after the intravenous administration

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DATA SET NUMBER  1


THE NUMBER OF EXPONENTIALS = 2
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER OF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST):
    L1=    6
    L2=    3


THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE:
A1= 0.213365E+01      B1= 0.128894E+00
A2=-0.213456E+01      B2= 0.103423E+01
F= 0.265306E-01



A LAG TIME WAS NEEDED TO DESCRIBE THESE DATA

THE LAG TIME =   0.610

R SQUARE(2) =   0.97942

 NO.          TIME          C(OBS)          C(EST)          % DEV
    1        1.0000          0.7000          0.6030          13.86
    2        2.0000          1.2000          1.2767          -6.39
    3        3.0000          1.4000          1.3877           0.88
    4        4.0000          1.4000          1.3143           6.12
    5        6.0000          1.1000          1.0570           3.91
    6        8.0000          0.8000          0.8221          -2.76
    7       10.0000          0.6000          0.6359          -5.99
    8       12.0000          0.5000          0.4915           1.70
    9       16.0000          0.3000          0.2935           2.16


THE NUMBER OF EXPONENTIALS = 3
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER OF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST):
    L1=    3
    L2=    3
    L3=    3


THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE:
A1= 0.184756E+01      B1= 0.117264E+00
A2= 0.969792E+00      B2= 0.462881E+00
A3=-0.282060E+01      B3= 0.896822E+00
F= 0.269580E-01



A LAG TIME WAS NEEDED TO DESCRIBE THESE DATA

THE LAG TIME =   0.587

R SQUARE(3) =   0.97908

 NO.          TIME          C(OBS)          C(EST)          % DEV
    1        1.0000          0.7000          0.6137          12.33
    2        2.0000          1.2000          1.2753          -6.28
    3        3.0000          1.4000          1.3856           1.03
    4        4.0000          1.4000          1.3058           6.73
    5        6.0000          1.1000          1.0365           5.77
    6        8.0000          0.8000          0.8023          -0.29
    7       10.0000          0.6000          0.6245          -4.08
    8       12.0000          0.5000          0.4894           2.12
    9       16.0000          0.3000          0.3039          -1.31
```

Figure 3—*CSTRIP analysis of tetracycline concentration and time data.*

Table VI—Comparison of Automated and Graphical Curve Stripping of Tetracycline Concentration and Time Data[a]

	Value of Parameter Estimate			
Parameter	Graphical[b]	CSTRIP	Nonlinear Least Squares	
A_1	2.30	2.13	2.65[c]	2.42[d]
B_1	0.130	0.129	0.149	0.139
A_2	−2.30	−2.13	−2.65	−2.42
B_2	0.810	1.03	0.716	0.794
t_1	0.328	0.610	0.421	0.436
Sum of squared deviations[e]	0.024	0.026	0.010	0.011

[a] Data fitted to a biexponential equation of the form $C = A_1e^{-B_1(t-t_1)} + A_2e^{-B_2(t-t_1)}$. [b] See Ref. 8 for method. [c] Graphical values used as initial least-squares estimates. [d] CSTRIP values used as initial least-squares estimates. [e] Sum of squared deviations between observed and model-predicted concentrations.

of spectinomycin were described by two exponential terms. They fitted data collected after intramuscular administration to a triexponential equation. Wagner *et al.* (9) did not report the values of their graphical (initial) estimates, but a comparison of final nonlinear

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DATA SET NUMBER  2


THE NUMBER OF EXPONENTIALS = 2
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER OF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST):
    L1=    3
    L2=    6


THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE:
A1= 0.685025E+02      B1= 0.418496E+00
A2=-0.685025E+02      B2= 0.187516E+01
F= 0.186380E+02



NO LAG TIME WAS NEEDED TO DESCRIBE THESE DATA
THEREFORE, THE SUM OF THE EXPONENTIAL TERMS WAS FORCED THROUGH ZERO

R SQUARE(2) =   0.98483

 NO.          TIME          C(OBS)          C(EST)          % DEV
    1        0.0             0.0             0.0             0.0
    2        0.1667         15.7000         13.7734          12.27
    3        0.3333         23.1000         22.9168           0.79
    4        0.5000         31.2000         28.7449           7.87
    5        1.0000         31.6000         34.5735          -9.41
    6        2.0000         28.2000         28.0518           0.53
    7        4.0000         12.8000         12.8062          -0.05
    8        6.0000          5.6000          5.5607           0.70
    9        8.0000          2.4000          2.4082          -0.34


THE NUMBER OF EXPONENTIALS = 3
SUMMARY OF EXPONENTIAL STRIPPING

THE NUMBER OF POINTS IN THE EXPONENTIAL PHASES (LAST TO FIRST):
    L1=    2
    L2=    5
    L3=    2


THE BEST ESTIMATES OF THE COEFFICIENTS AND EXPONENTS ARE:
A1= 0.711825E+02      B1= 0.423653E+00
A2=-0.526339E+02      B2= 0.136295E+01
A3=-0.185087E+02      B3= 0.455966E+01
F= 0.917597E+01



NO LAG TIME WAS NEEDED TO DESCRIBE THESE DATA
THEREFORE, THE SUM OF THE EXPONENTIAL TERMS WAS FORCED THROUGH ZERO

R SQUARE(3) =   0.99253

 NO.          TIME          C(OBS)          C(EST)          % DEV
    1        0.0             0.0             0.0             0.0
    2        0.1667         15.7000         15.7000          -0.00
    3        0.3333         23.1000         24.3070          -5.23
    4        0.5000         31.2000         29.0424           6.92
    5        1.0000         31.6000         32.9106          -4.15
    6        2.0000         28.2000         27.0405           4.11
    7        4.0000         12.8000         12.8411          -0.32
    8        6.0000          5.6000          5.5852           0.26
    9        8.0000          2.4000          2.3990           0.04
```

Figure 4—*CSTRIP analysis of spectinomycin concentration and time data.*

Table VII—Comparison of Automated and Least-Squares Parameter Estimates for Spectinomycin Concentration and Time Data[a]

Parameter	Value of Parameter Estimate	
	CSTRIP	Nonlinear Least Squares
A_1	71.1	70.5
B_1	0.424	0.422
A_2	-52.6	-54.7
B_2	1.36	1.46
A_3	-18.5	-15.8
B_3	4.56	4.61
Sum of squared deviations[b]	9.17	9.11

[a] Data fitted to a triexponential equation of the form $C = A_1e^{-B_1t} + A_2e^{-B_2t} + A_3e^{-B_3t}$. [b] Sum of squared deviations between observed and model-predicted concentrations.

least-squares parameter estimates with CSTRIP estimates is made in Table VII. There was excellent agreement between the CSTRIP and nonlinear least-squares parameter values.

CSTRIP generally gives results comparable to or better than those obtained by laborious graphical or other manual techniques.

CSTRIP not only provides accurate exponential parameter estimates but also is economical, and the input of data does not require excessive time. The total cost for the CSTRIP analyses of the two examples given was $0.51.

SUMMARY

The CSTRIP program provides for fully automated exponential stripping of pharmacokinetic data. This program enables the rapid, accurate, and economical computer analysis of data described by the sums of exponentials and gives results comparable to, or better than, those obtained by laborious manual techniques. Use of the CSTRIP program should greatly reduce the amount of time consumed in obtaining preliminary estimates of exponential parameters by graphical and/or electronic calculator methods and should result in least-squares parameter estimates having less variability and greater accuracy.

The program should prove suitable as an exponential stripping routine in other programs designed for fully automated data analysis.

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‡ To whom inquiries should be directed. (The computer program is not available on tape or cards. A complete microfilm source listing will be supplied upon request. No troubleshooting assistance will be provided.)

Anticonvulsant Activity and Inhibition of Cellular Respiratory Activity by Substituted Imidazolocarbamides

SUNIL K. CHAUDHARY *, SURENDRA S. PARMAR *‡x, MAHIMA CHAUDHARY *, and JAYANTI P. BARTHWAL *

Abstract □ Several 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides were synthesized and characterized by their sharp melting points, elemental analyses, and IR spectra. These substituted imidazolocarbamides possessed anticonvulsant activity, which was reflected by the 20–80% protection observed with these compounds against pentylenetetrazol-induced convulsions in mice. These substituted imidazolocarbamides selectively inhibited the *in vitro* oxidation of nicotinamide adenine dinucleotide (NAD)-dependent oxidations of pyruvate, α-ketoglutarate, β-hydroxybutyrate, and NADH by rat brain homogenates. However, NAD-independent oxidation of succinate was not affected. The anticonvulsant activity possessed by 1-(1-aryl-2-mercaptoacetylimidazole)-3-alkylcarbamides had no relationship to their ability to inhibit cellular respiratory activity.

Keyphrases □ Imidazolocarbamides, substituted—synthesized, screened for anticonvulsant activity, effect on cellular respiratory activity □ Anticonvulsant activity—screened in series of substituted imidazolocarbamides, mice □ Cellular respiration—effect of series of substituted imidazolocarbamides on NAD-dependent and NAD-independent oxidations, rat brain homogenates □ Oxidations, NAD dependent and independent—effect of series of substituted imidazolocarbamides, rat brain homogenates □ Structure–activity relationships—series of imidazolocarbamides, anticonvulsant activity, cellular respiratory activity

Potentiation of pentobarbital-induced hypnosis and protection against pentylenetetrazol-induced convulsions indicated the central nervous system (CNS) depressant property of substituted carbamides (1–4). Certain derivatives of imidazoles also have been reported to possess anticonvulsant activity (5, 6). Earlier studies indicated significant degrees of muscle relaxant and anticonvulsant activities of 1-carbamoylpyrrolidines and 1-carbamoylpiperidines (7). Various aryloxyalkylcarbamides also have been shown to possess the CNS activity (8).

These observations led to the synthesis of 1-(1-aryl-