clearance from plasma. Since renal clearances of sulpiride and creatinine were simultaneously evaluated in all subjects in this study (Table I), we attempted to correlate these two values. With the large intraindividual variability (Table II, Fig. 5) in sulpiride renal clearance, it was not possible to find a positive correlation with creatinine clearance, but subjects 3 and 9 who had the highest sulpiride clearances also had the highest creatinine clearances.

REFERENCES

(1) A. Benakis and Ch. Rey, *J. Pharmacol. (Paris)*, **77**, 367 (1976).

(2) Y. Stefan and A. Benakis, *J. Pharmacol. (Paris)*, **77**, 379 (1976).

(3) F. A. Wiesel, G. Alfredsson, M. Ehrnebo, and G. Sedvall, *Eur. J. Clin. Pharmacol.*, **17**, 385 (1980).

(4) G. Alfredsson, G. Sedvall, and F. A. Wiesel, *J. Chromatogr.*, **164**, 187 (1979).

(5) J. Bres, F. Bressolle, M. D. Blanchin, and E. Rechencq, Congrès hispano-français de Biopharmacie et de Pharmacocinétique, Barcelona, Spain, April 1979, vol. III, pp. 23–38.

(6) J. Bres, F. Bressolle, D. Monsoncles, and M. D. Blanchin, Premier Congrès Européen de Biopharmacie et de Pharmacocinétique, Clermont-Ferrand, France, April 1981, vol. II, pp. 335–345.

(7) M. D. Blanchin, Thèse de 3ème Cycle, Montpellier, France, July 1981.

(8) J. Bres, F. Bressolle, M. D. Blanchin, and E. Rechencq, Congrès hispano-français de Biopharmacie et de Pharmacocinétique, Barcelona, Spain, April 1979, vol. III, pp. 11–23.

(9) N. Verbiese Genard, M. Hanocq, and L. Molle, *Chromatogr. Symp. Sci.*, **1**, 79 (1979).

(10) N. Verbiese Genard, M. Hanocq, M. Van Damme, and L. Molle, *Int. J. Pharm.*, **2**, 155 (1979).

(11) N. Verbiese Genard, M. Hanocq, and L. Molle, *J. Pharm. Belg.*, **1**, 24 (1980).

(12) T. Kleimola, O. Leppanen, J. Kanto, R. Mantyla, and E. Syvalahti, *Ann. Clin. Res.*, **8**, 104 (1976).

(13) J. K. Salminen, V. Lehtonen, H. Allonen, and J. Kanto, *Curr. Ther. Res.*, **27**, 109 (1980).

(14) L. Bjerkenstedt, C. Harnryd, and G. Sedvall, *Psychopharmacology*, **64**, 135 (1979).

(15) F. Bressolle, J. Bres, S. Brun, and E. Rechencq, *J. Chromatogr.*, **174**, 421 (1979)

(16) J. Bres, A. F. Gaillot, D. Monsoncles, J. C. Penochet, and G. Vidal, "Progress in Clinical Pharmacy," vol. III, H. Turraka and E. Van Der Kleijn, Eds., Elsevier North Holland, 1981, pp. 61–70.

(17) F. Bressolle, J. Bres, E. Fuseau, and A. M. Siouffi, *J. Pharm. Clin.*, **2**, 127 (1982).

(18) M. Rowland and T. N. Tozer, "Clinical Pharmacokinetics," Lea and Febiger, Philadelphia, Pa., 1980.

(19) M. Gibaldi and D. Perrier, in "Drugs and the Pharmaceutical Sciences," Vol. I, J. Swarbrick, Ed., Dekker, New York, N.Y., 1975.

(20) L. B. Sheiner, "ELSFIT Users Manual," Division of Clinical Pharmacology, University of California, San Francisco, 1981.

(21) R. Gomeni, "The Impact of Computer Technology on Drug Information," P. Manell and S. G. Johansson, Eds., Elsevier North Holland, 1982, p. 32.

(22) L. B. Sheiner, B. Rosenberg, and K. L. Melmon, *Comput. Biomed. Res.*, **5**, 441 (1972).

(23) H. D. Vinod and A. Ullah, "Recent Advances in Regression Methods," Dekker, New York, N.Y., 1981, pp. 1–9.

(24) C. Gomeni and R. Gomeni, *Comput. Biomed. Res.*, **11**, 345 (1978).

(25) A. R. Imondi, A. S. Alam, J. J. Brennan, and L. M. Hagerman, *Arch. Int. Pharmacodyn.*, **232**, 79 (1978).

(26) A. S. Alam, A. R. Imondi, J. Udinsky, and L. M. Hagerman, *Arch. Int. Pharmacodyn.*, **242**, 4 (1979).

ACKNOWLEDGMENTS

The authors gratefully acknowledge support of this work by Delagrange (Paris, France).

Pulmonary Absorption and Excretion of Compounds in the Gas Phase: Theoretical Pharmacokinetic and Toxicokinetic Analysis

PETER VENG-PEDERSEN

Received September 1, 1982, from *Division of Pharmacokinetics, School of Pharmacy, Purdue University, West Lafayette, IN 47907.* Accepted for publication July 29, 1983. Present address: College of Pharmacy, University of Iowa, Iowa City, IA 52242.

Abstract □ Kinetic equations were derived that describe the plasma concentration of an inhaled compound during and following single or repeated regular and irregular pulmonary exposures. The equations are based on a diffusional type of input function and assume a linear disposition with a biexponential unit-impulse response. The use of linear system analysis avoids the complexity of modeling the disposition processes; yet, the effect of these processes is still accounted for mathematically. The approach, therefore, appears to be more general and rational than approaches based on linear compartmental modeling. The ways in which the kinetic equations can be readily applied in pharmacokinetic or toxicokinetic analyses to obtain valuable parameters that enable kinetic predictions of the cumulation during prolonged exposure are discussed. The toxicokinetic problem of comparing the effect of different work schedules in occupational environments with air contaminants is discussed. Formulas derived from considerations of the blood plasma kinetics are presented for the calculation of an adjustment factor for the adjustment of the contaminant threshold limit value for abnormal work weeks. The use of these formulas appears to be more rational than that of similar formulas that have been proposed.

Keyphrases □ Absorption—pulmonary, excretion, theoretical pharmacokinetic and toxicokinetic analyses □ Pharmacokinetics—pulmonary absorption and excretion, toxicokinetics □ Toxicokinetics—pulmonary absorption and excretion, pharmacokinetics

Little attention has been given to the pharmacokinetic-toxicokinetic characterization of the pulmonary absorption and excretion of compounds in the gas phase. The kinetic investigations of the volatile drugs used in general anesthetics has been limited mainly to empirical quantitative analysis of uptake, metabolism, and pulmonary excretion (1–3), without a formal mathematical, pharmacokinetic analysis of the plasma level-time profile (4, 5).

The study of pulmonary absorption kinetics is also of particular interest in environmental toxicology (6–9). Special attention has been given to the risk assessment of work place exposures to vaporous air contaminants. Of particular concern

0022-3549/84/0800-1136$01.00/0

has been the effect of the work schedule on the toxicokinetic effect (10–15). It is recognized that an assessment of the toxic effect cannot simply be determined on the basis of exposure level and total exposure time. Two different work schedules with the same exposure level and the same total hours of exposure may give substantially different plasma and tissue levels resulting in different toxic effects. Therefore, attempts have been made to predict and compare the biological effect of different work schedules by using the exposure limits established by the U.S. government, since these limits are based on exposures of a normal work week schedule (16, 17). However, the formulas that have been proposed are based on a one-compartment kinetic model, despite the fact that most gases show definite biphasic kinetics (10–14). The shortcomings of conceiving the body as exhibiting properties of a single compartment are well recognized (18). The formulas that have been proposed inappropriately deal with "the body burden" (the total amount of substance in the body) instead of plasma concentration (10, 11). Not only is it virtually impossible to experimentally determine "the body burden," but it is also misleading and inaccurate to conceive the body as a "homogeneous box," ignoring the pronounced tissue distribution of volatile lipophilic substances. The formulas presented are essentially "one-point comparisons" that only consider the peak "body burdens" (10, 11). No attempts have been made to describe the complete kinetics (10, 11).

The work presented here should overcome the shortcomings of previous analyses through a rigorous pharmacokinetic analysis that is based on more realistic and rational kinetic assumptions. A linear system-analysis approach is used to account for the disposition kinetics. This model-independent system approach requires fewer assumptions and is more general than conventional classical compartmental approaches and, therefore, should provide a more rational toxicokinetic basis for the development of exposure guidelines. By giving a complete pharmacokinetic description of the plasma level–time profile during and following multiple daily or weekly exposures, the analysis allows criteria other than peak plasma levels to be considered in a toxicokinetic assessment. By using this analysis, the daily and weekly accumulation effects are isolated and considered, thereby facilitating the assessment of prolonged exposures.

THEORETICAL SECTION

Single-Exposure Kinetics—The mass transfer rate $f(t)$ of a gas into the blood plasma from inhaled air containing a gas at a concentration C_g can be described by:

$$f(t) = K_1[C_g - K_2 \cdot c(t)] \qquad (0 \le t > T) \qquad \text{(Eq. 1)}$$

during the exposure period and:

$$f(t) = 0 \qquad (t \ge T) \qquad \text{(Eq. 2)}$$

in the postexposure period.

K_1 is a positive constant, and K_2 is the air/plasma partition coefficient of the gas. The plasma concentration of the gas [$c(t)$] depends on the input rate $f(t)$, as well as the disposition (distribution, metabolism, and excretion) of the gas in the body. It is assumed that the disposition processes result in a linear kinetic system in the sense that the superposition principle holds, so that the plasma response $c(t)$ is related to the systemic input rate, $f(t)$, by[1]:

$$c(t) = \int_0^t f(u)c_\delta(t-u)du \qquad \text{(Eq. 3)}$$

where $c_\delta(t)$ is the unit impulse response.

[1] See references 19–22 for a discussion of linear system analysis in pharmacokinetics.

The pulmonary excretion of gases appears to be well characterized by a biexponential decay, indicating that the unit-impulse response can be described by a biexponential expression:

$$c_\delta(t) = Ae^{-\alpha t} + Be^{-\beta t} \qquad (A, B, \alpha, \beta > 0) \qquad \text{(Eq. 4)}$$

The choice of Eq. 4 is also supported by the fact that most volatile drugs show a biexponential response to a bolus input.

Insertion of Eqs. 1 and 4 into Eq. 3 yields:

$$c(t) = \int_0^t K_1[C_g - K_2c(u)][Ae^{-\alpha(t-u)} + Be^{-\beta(t-u)}]du \qquad (t < T)$$

$$\text{(Eq. 5)}$$

Equation 5 is recognized as a Volterra integral equation of the second kind with a convolution-type kernel and can therefore be solved by Laplace transforms giving:

$$c(t) = K_1C_g[A'(1 - e^{-\alpha' t}) + B'(a - e^{-\beta' t})] \qquad (t < T) \qquad \text{(Eq. 6)}$$

where $-\alpha'$ and $-\beta'$ are the roots of the polynomial:

$$P(s) = (s + \alpha)(s + \beta) + K_1K_2[A(s + \beta) + B(S + \alpha)] \qquad \text{(Eq. 7)}$$

[$P(-\alpha') = P(-\beta') = 0$], and A' and B' are given by:

$$A' = \frac{A(\beta - \alpha') + B(\alpha - \alpha')}{\alpha'(\beta' - \alpha')} \qquad \text{(Eq. 8)}$$

$$B' = \frac{A(\beta - \beta') + B(\alpha - \beta')}{\beta'(\alpha' - \beta')} \qquad \text{(Eq. 9)}$$

Equation 6 describes the plasma level of the gas during the exposure period only. The plasma level in the postexposure period is subsequently obtained from the following:

$$c(t) = \int_0^T K_1[C_g - K_2c(u)][Ae^{-\alpha(t-u)} + Be^{-\beta(t-u)}]du \qquad (t \ge T)$$

$$\text{(Eq. 10)}$$

where the $c(u)$ term is given by Eq. 6 by substituting t with the dummy integration variable u.

Equation 10 then gives:

$$c(t) = K_1C_gAe^{-\alpha t}\left[\frac{K_1K_2A'}{\alpha - \alpha'} \cdot e^{(\alpha-\alpha')T} + \frac{K_1K_2B'}{\alpha - \beta'} \cdot e^{(\alpha-\beta')T} + \frac{\beta}{\alpha'\beta'} \cdot e^{\alpha T}\right] + K_1C_gBe^{-\beta t}\left[\frac{K_1K_2A'}{\beta - \alpha'} \cdot e^{(\beta-\alpha')T} + \frac{K_1K_2B'}{\beta - \beta'} \cdot e^{(\beta-\beta')T} + \frac{\alpha}{\alpha'\beta'} \cdot e^{\beta T}\right] \qquad \text{(Eq. 11)}$$

where $t \ge T$. The exposure solution (Eq. 6, $t < T$) and the postexposure solution (Eq. 11, $t \ge T$) can be combined to yield the following final equation, which describes the plasma concentration of the gas at any time during or after a single pulmonary exposure:

$$c(t) = A_T(t) \cdot e^{-\alpha(t-T)_+} + B_T(t) \cdot e^{-\beta(t-T)_+} \qquad \text{(Eq. 12)}$$

where:

$$A_T(t) = K_1C_gA\left(\frac{K_1K_2A'}{\alpha - \alpha'} \cdot e^{-\alpha' t'} + \frac{K_1K_2B'}{\alpha - \beta'} \cdot e^{-\beta' t'} + \frac{\beta}{\alpha'\beta'}\right) \qquad \text{(Eq. 13)}$$

$$B_T(t) = K_1C_gB\left(\frac{K_1K_2A'}{\beta - \alpha'} \cdot e^{-\alpha' t'} + \frac{K_1K_2B'}{\beta - \beta'} \cdot e^{-\beta' t'} + \frac{\alpha}{\alpha'\beta'}\right) \qquad \text{(Eq. 14)}$$

and

$$t' = t \text{ (for } t < T) \qquad \text{(Eq. 15)}$$

$$t' = T \text{ (for } t \ge T) \qquad \text{(Eq. 16)}$$

$$(t - T)_+ = 0 \text{ (for } t < T) \qquad \text{(Eq. 17)}$$

$$(t - T)_+ = t - T \text{ (for } t \ge T) \qquad \text{(Eq. 18)}$$

$A_T(t)$ and $B_T(t)$ are constants [$A_T(T)$, $B_T(T)$] in the postexposure phase ($t \ge T$); thus, Eq. 12 predicts a simple biexponential decay in this phase. The time coefficients in the decay are equal to those of the unit-impulse-response function (Eq. 4).

If the unit-impulse-response function is described by a single-exponential expression, $Ae^{-\alpha t}$, then Eq. 12 simplifies to:

$$c(t) = A_T'(t) \cdot e^{-\alpha(t-T)_+} \qquad \text{(Eq. 19)}$$

where:

$$A_T'(t) = \frac{K_1 C_g A}{\alpha + K_1 K_2 A} \cdot (1 - e^{-(\alpha + K_1 K_2 A)t'}) \quad \text{(Eq. 20)}$$

Multiple-Exposure Kinetics—*Regular Dosing Cycle*—Consider a repeated exposure cycle consisting of an exposure period of length T followed by a postexposure period of length H. The plasma kinetics during the first cycle are described by Eq. 12. At the start of the second cycle, there is a residual concentration of gas in the plasma equal to:

$$c_2(0) = A_T(T) \cdot e^{-\alpha H} + B_T(T) \cdot e^{-\beta H} \qquad (t_r = 0) \quad \text{(Eq. 21)}$$

The notation $c_n(t_r)$ is introduced here to denote the plasma concentration of the gas in the nth exposure cycle at a time t_r, measured relative to the start of the cycle (*i.e.*, relative to the start of the most recent exposure period).

Due to the superposition principle of linear systems, the plasma concentration of the gas in the second cycle is given by:

$$c_2(t_r) = A_T(T) \cdot e^{-\alpha(H+t_r)} + B_T(T) \cdot e^{-\beta(H+t_r)} + A_T(t_r) \cdot e^{-\alpha(t_r-T)+} + B_T(t_r) \cdot e^{-\beta(t_r-T)+} \quad \text{(Eq. 22)}$$

Thus, the residual plasma concentration at the start of the third exposure cycle is:

$$c_3(0) = A_T(T) \cdot e^{-\alpha(H+L)} + B_T(T) \cdot e^{-\beta(H+L)} + A_T(T) \cdot e^{-\alpha H} + B_T(T) \cdot e^{-\beta H} \quad \text{(Eq. 23)}$$

where L is the length of the exposure cycle:

$$L = T + H \quad \text{(Eq. 24)}$$

By deduction from Eqs. 21–23, it is concluded that:

$$c_n(t_r) = A_T(T) \cdot e^{-\alpha(H+t_r)} \sum_{j=0}^{n-2} e^{-jL\alpha} + B_T(t) \cdot e^{-\beta(H+t_r)} \sum_{j=0}^{n-2} e^{-jL\beta} + A_T(t_r) \cdot e^{-\alpha(t_r-T)+} + B_T(t_r) \cdot e^{-\beta(t_r-T)+} \quad \text{(Eq. 25)}$$

Equation 25 simplifies to the following final equation that describes the plasma concentration of the gas at any time (t_r) in any exposure cycle (n) during (or any time after) a regular repeated pulmonary exposure:

$$c_n(t_r) = \frac{1 - e^{-(n-1)L\alpha}}{1 - e^{-L\alpha}} A_T(T) \cdot e^{-\alpha(H+t_r)} + \frac{1 - e^{-(n-1)L\beta}}{1 - e^{-L\beta}} B_T(T) \cdot e^{-\beta(H+t_r)} + A_T(t_r) \cdot e^{-\alpha(t_r-T)+} + B_T(t_r) \cdot e^{-\beta(t_r-T)+} \quad \text{(Eq. 26)}$$

To simplify the notation and better conceptualize the cumulative effect of multiple exposures, it is convenient to introduce and define the function:

$$\phi_i(x) = \frac{1 - e^{-ix}}{1 - e^{-x}} = \sum_{j=0}^{i-1} e^{-jx} \quad \text{(Eq. 27)}$$

It can be seen in Eq. 26 that the first two terms of this equation represent the cumulation from the previous $(n-1)$ exposure cycles. Therefore, it appears to be more descriptive to present Eq. 26 in the following simplified form:

$$c_n(t_r) = A_T(t_r) \cdot e^{-\alpha(t_r-T)+} + B_T(t_r) \cdot e^{-\beta(t_r-T)+} + P_{n-1}(t_r) \quad \text{(Eq. 28)}$$

$P_{n-1}(t_r)$, the cumulation from the previous exposure cycles can, according to Eqs. 26 and 27, be simplified as:

$$P_{n-1}(t_r) = \phi_{n-1}(L\alpha) \cdot A_T(T) \cdot e^{-\alpha(H+t_r)} + \phi_{n-1}(L\beta) \cdot B_T(T) \cdot e^{-\beta(H+t_r)} \quad \text{(Eq. 29)}$$

Irregular Dosing Cycle Case.—In the context of occupational exposure to toxic substances, Eq. 28 is limited to a description of the kinetics during and following exposure to a gas for a single work week (or any fraction thereof). If there is a significant residual concentration left after the exposure-free weekend, then Eq. 28 should not be used for the second or subsequent work weeks. The following derivation includes cumulations from previous work weeks.

Consider a work schedule consisting of N working days (*i.e.*, N exposure cycles) and M nonworking days ($N + M = 7$). On each working day, the subject is exposed for T hours to a constant concentration (C_g) of a gas in the air. There are H hours between the exposure periods ($T + H = L = 24$), except for the period of nonworking days where there are ($H + M \cdot L$) hours without exposure. According to the superposition principle of linear systems, the plasma gas concentration at time t_r in the nth exposure cycle[2] in the mth work week is:

$$c_{n,m}(t_r) = c_n(t_r) + Q_{m-1}(t_r) \quad \text{(Eq. 30)}$$

where $c_n(t_r)$ is given by Eq. 28, and $Q_{m-1}(t_r)$ is given by Eq. 38. The function $Q_{m-1}(t_r)$ in Eq. 30, which is given by:

$$Q_{m-1}(t_r) = \sum_{i=1}^{m-1} c_N[(M+1)L + (m-i-1)7L + (n-1)L + t_r] \quad \text{(Eq. 31)}$$

represents the cumulations from the $(m-1)$ previous weeks. The residue from the exposure in week i ($i = 1, \ldots, m-1$) is derived as follows. The concentration left from this exposure is $c_N(t_i)$, where t_i is the time elapsed since the start of the last exposure cycle of the ith work week, and $c_N(\ )$ is given by Eq. 28 substituting n with N where N is the total number of exposure cycles in the work week. The time span t_i can be considered to consist of the following three components:

1. $(M+1)L$ is the time from the start of the last exposure cycle of week i to the start of the first exposure cycle of week $(i+1)$.
2. $(m-i-1)7L$ is the time from the start of the first exposure cycle of week $(i+1)$ to the start of the first exposure cycle of week m.
3. $(n-1)L + t_r$ is the time from the start of the first exposure cycle of week m to the current time t_r, where t_r as previously defined is measured relative to the start of the current exposure cycle, *i.e.*, cycle n. Thus:

$$t_i = (M+1)L + (m-i-1)7L + (n-1)L + t_r \quad \text{(Eq. 32)}$$

which is in agreement with Eq. 31.

The time span t_i stretches beyond the last exposure period of week i. Thus, according to Eqs. 28, 29, and 16, $c_N(t_i)$ becomes:

$$c_N(t_i) = A_T(T) \cdot e^{-\alpha(t_i-T)} + B_T(T) \cdot e^{-\beta(t_i-T)} + \phi_{N-1}(L\alpha) \cdot A_T(T) \cdot e^{-\alpha(H+t_i)} + \phi_{N-1}(L\beta) \cdot B_T(T) \cdot e^{-\beta(H+t_i)} \quad \text{(Eq. 33)}$$

According to $L = T + H$, Eq. 33 can be written:

$$c_N(t_i) = [1 + e^{-L\alpha} \cdot \phi_{N-1}(L\alpha)] A_T(T) \cdot e^{\alpha T} \cdot e^{-\alpha t_i} + [1 + e^{-L\beta} \cdot \phi_{N-1}(L\beta)] B_T(T) \cdot e^{\beta T} \cdot e^{-\beta t_i} \quad \text{(Eq. 34)}$$

This equation can be further simplified[3]:

$$c_N(t_i) = \phi_N(L\alpha) \cdot A_T(T) \cdot e^{-\alpha(t_i-T)} + \phi_N(L\beta) \cdot B_T(T) \cdot e^{-\beta(t_i-T)} \quad \text{(Eq. 35)}$$

To simplify the expression for the cumulation function $Q_{m-1}(t_r)$, it is convenient to rewrite the summation in Eq. 31 so that the formula in Eq. 27 can be employed:

$$Q_{m-1}(t_r) = \sum_{i=0}^{m-2} c_N(x_i) \quad \text{(Eq. 36)}$$

where:

$$x_i = (M-n)L + (m-2)7L - i7L + t_r \quad \text{(Eq. 37)}$$

When t_i is substituted by x_i in Eq. 35 and this equation is subsequently inserted in Eq. 36, the following final expression for the cumulation term in Eq. 30 is obtained:

$$Q_{m-1}(t_r) = \phi_N(L\alpha) \cdot \phi_{m-1}(7L\alpha) \cdot e^{-(M+n)L\alpha} \cdot A_T(T) \cdot e^{-\alpha(t_r-T)} + \phi_N(L\beta) \cdot \phi_{m-1}(7L\beta) \cdot e^{-(M+n)L\beta} \cdot B_T(T) \cdot e^{-\beta(t_r-T)} \quad \text{(Eq. 38)}$$

In deriving Eq. 37, the following property of the ϕ function was used:

$$e^{-(i-1)x} \cdot \phi_i(-x) = \phi_i(x) \quad \text{(Eq. 39)}$$

RESULTS AND DISCUSSION

The analysis described above is based on certain kinetic assumptions. It is assumed that the compound is present in the inhaled air at a constant concentration during the exposure. It is also assumed that the transport of the agent into the pulmonary blood plasma is proportional to the difference between the partial pressures of the agent in the inhaled air and in the blood plasma. It is assumed that the compound shows a linear disposition in the body in the sense that the linear superposition principle holds, so that input and plasma level response are functionally related through a convolution. Furthermore, it is assumed that the system is time invariant with a unit-impulse response that is well approximated by a biexponential expression. These assumptions that form the basis for the fundamental Eqs. 1–4 appear fairly well justified. The kinetics of gas diffusion is well understood, and many drugs and compounds have been shown to exhibit a linear disposition. In fact, a linear disposition is expected most often for compounds that are only slightly me-

[2] Note that the nth working day usually contains part of exposure cycle $(n-1)$ and cycle n, so it would be misleading in general to define n as the nth working day.

[3] Note that the ϕ function has the simple progression formula $e^{-x}\phi_{i-1}(x) = \phi_i(x) - 1$.

tabolized, such as the volatile, lipophilic compounds used in general anesthetics. The choice of a biexponential expression to represent the unit-impulse response appears to be appropriate, since this leads to kinetic equations that agree with the typical biexponential pulmonary excretion decay that is often observed. A biexponential expression also agrees with the elimination behavior most frequently seen in pharmacokinetic studies. The very distinct advantages of using a linear system approach instead of a classical compartmental approach have been discussed previously (19–22).

Three main equations have been derived that describe the plasma concentration of a gas at any time during or after (*a*) a single pulmonary exposure (Eq. 12), (*b*) a series of regular, constant exposures (Eq. 28), and (*c*) 1 or more weeks of exposures to a gas during the working days of the week (Eq. 30).

Single-Exposure Kinetics—The kinetic equation for a single pulmonary exposure (Eq. 12) is of particular pharmacokinetic interest, as it deals with the type of drug exposure found in general anesthetics. The equation also forms the basis for the multiexposure equations (Eqs. 28 and 30) that are of special toxicokinetic interest. An important use of the equation is in nonlinear regression analysis of single exposure data to obtain useful pharmacokinetic parameters. The data can be obtained either from a blood gas analysis or from excretion data obtained from the postexposure phase by analyzing the expired air for the gas.

Kinetic Analysis Based on Sampling of Expired Air—Pulmonary excretion data are typically in the form of the cumulative amount of gas excreted at various times, $M(t)$. According to Eq. 1, the rate of pulmonary excretion in the postexposure phase is $K_1K_2 \cdot c(t)$. Integration of Eq. 12 gives:

$$M(t) = \int_T^t K_1K_2 \cdot c(t)dt = K_1K_2 \frac{A_T(t)}{\alpha}[1 - e^{-\alpha(t-T)}] + K_1K_2 \frac{B_T(T)}{\beta}[1 - e^{-\beta(t-T)}] \qquad (t \geq T) \quad \text{(Eq. 40)}$$

In its simplest form, this equation is uniquely defined by only four quantities [$\alpha, \beta, K_1K_2 \cdot A_T(T)$, and $K_1K_2 \cdot B_T(T)$]. Therefore, it is not possible to determine all of the six basic parameters (*Appendix*) from pulmonary excretion data alone. However, Eq. 40 allows the two important parameters, α and β, to be accurately determined.

Although general kinetic predictions require that all six basic parameters (see *Appendix*) be determined, a closer analysis of Eq. 40 reveals that some important predictions can still be made from pulmonary excretion data alone. For example, it can be predicted how much the plasma concentration in the postexposure phase increases in multiple exposures relative to that resulting from a single exposure, *i.e.*, the ratio $c_n(t_r)/c(t_r)$, where $t_r > T$, can be predicted. To prove this, it is convenient to rewrite Eq. 28 in the following form[3]:

$$c_n(t_r) = \phi_n(L\alpha) \cdot A_T(T) \cdot e^{-\alpha(t_r-T)} + \phi_n(L\beta) \cdot B_T(T) \cdot e^{-\beta(t_r-T)} \qquad (t_r \geq T) \quad \text{(Eq. 41)}$$

By multiplying this equation and Eq. 12 ($t \geq T$) by K_1K_2, the following ratio is obtained:

$$\frac{c_n(t_r)}{c(t_r)} = \frac{\phi_n(L\alpha) \cdot [K_1K_2A_T(T)] \cdot e^{-\alpha(t_r-T)} + \phi_n(L\beta) \cdot [K_1K_2B_T(T)] \cdot e^{-\beta(t_r-T)}}{[K_1K_2A_T(t)] \cdot e^{-\alpha(t_r-T)} + [K_1K_2B_T(T)] \cdot e^{-\beta(t_r-T)}} \qquad (t_r \geq T) \quad \text{(Eq. 42)}$$

Fitting Eq. 40 to pulmonary excretion data yields values for $\alpha, \beta, K_1K_2 \cdot A_T(T)$, and $K_1K_2 \cdot B_T(T)$, so that Eq. 42 can be calculated at any time $t_r > T$ for any values of n and L. Thus, excretion data from a single exposure provide quite extensive and valuable information about the plasma accumulation of the compound. In particular, such data allow a comparison of the maximum plasma concentration by letting $t_r = T$ in Eq. 42:

$$\frac{\max c_n(t_r)}{\max c(t_r)} = \frac{c_n(T)}{c(T)} = \frac{\phi_n(L\alpha) \cdot [K_1K_2 \cdot A_T(T)] + \phi_n(L\beta) \cdot [K_1K_2 \cdot B_T(T)]}{[K_1K_2 \cdot A_T(T)] + [K_1K_2 \cdot B_T(T)]} \quad \text{(Eq. 43)}$$

A comparison of the minimum values is achieved by letting $t_r = L = (T + H)$ in Eq. 42, noting that $\min c_{n+1}(t_r) = c_{n+1}(0) = c_n(L)$:

$$\frac{\min c_{n+1}(t_r)}{c(L)} = \frac{\phi_n(L\alpha) \cdot [K_1K_2 \cdot A_T(T)] \cdot e^{-\alpha H} + \phi_n(L\beta) \cdot [K_1K_2 \cdot B_T(T)] \cdot e^{-\beta H}}{[K_1K_2 \cdot A_T(T)] \cdot e^{-\alpha H} + [K_1K_2 \cdot B_T(T)] \cdot e^{-\beta H}} \quad \text{(Eq. 44)}$$

Although the above analyses (Eqs. 42 and 43) are limited to the postexposure phase ($t \geq T$), the characterization is complete enough to get an adequate assessment of the accumulation tendency of the compound. It is particularly valuable to be able to determine the relative change in the maximum (Eq. 43) and minimum (Eq. 44) plasma level concentrations.

Kinetic Analysis Based on Blood Sampling—Plasma level data in the exposure phase provide a more comprehensive kinetic characterization than pulmonary excretion data. All six basic kinetic parameters are determined by fitting Eq. 6 to the plasma level data[4]. Thus, once these parameters are determined by a suitable nonlinear regression technique, then predictions can be made as to which plasma-time profiles or accumulations can be reasonably expected from other single or multiple exposures (Eqs. 12, 28, and 30).

If the plasma level data are obtained only in the postexposure phase ($t \geq T$), then it is not possible to determine more than two (α and β) of the six basic parameters. However, despite this, some useful predictions can still be made.

The postexposure phase, according to Eq. 12, is described by:

$$c(t) = A_T(T) \cdot e^{-\alpha(t-T)} + B_T(T) \cdot e^{-\beta(t-T)} \qquad (t \geq T) \quad \text{(Eq. 45)}$$

By fitting this equation to the data, values for $\alpha, \beta, A_T(T)$, and $B_T(T)$ are obtained which, according to Eqs. 42 and 43, permit the following predictions to be made from the single exposure response, $c(t)$:

$$c_n(t_r) = \left[\frac{\phi_n(L\alpha) \cdot A_T(T) \cdot e^{-\alpha(t_r-T)} + \phi_n(L\beta) \cdot B_T(T) \cdot e^{-\beta(t_r-t)}}{A_T(T) \cdot e^{-\alpha(t_r-T)} + B_T(T) \cdot e^{-\beta(t_r-T)}}\right] c(t) \qquad (t \geq T) \quad \text{(Eq. 46)}$$

$$\max c_n(t_r) = c_n(T) = \left[\frac{\phi_n(L\alpha) \cdot A_T(T) + \phi_n(L\beta) \cdot B_T(T)}{A_T(T) + B_T(T)}\right] c(t) \quad \text{(Eq. 47)}$$

$$\min c_{n+1}(t_r) = \left[\frac{\phi_n(L\alpha) \cdot A_T(T) \cdot e^{-\alpha H} + \phi_n(L\beta) \cdot B_T(T) \cdot e^{-\beta H}}{A_T(T) \cdot e^{-\alpha H} + B_T(T) \cdot e^{-\beta H}}\right] c(L) \quad \text{(Eq. 48)}$$

Thus, although pulmonary excretion data in the postexposure phase allow only relative comparisons (Eqs. 42–44), plasma data obtained in the same phase permit absolute predictions (Eqs. 46–48). In both cases, the predictions can only be made for exposure duration(s) of the same length, T, as in the single-exposure experiment. This limitation is not found when data are obtained during the exposure. Equations analogous to Eqs. 42–48 are readily obtained from Eq. 30 to extend the analysis to irregular exposures.

The single-exposure equation (Eq. 12) shows an interesting, unusual kinetic behavior. The exponential time coefficients in the exposure phase (α' and β') are different from those in the postexposure phase (α and β). This is in contrast to the equations of classical linear compartmental modeling, which have constant time coefficients (the eigenvalues). The different kinetic behavior is due to the use in pharmacokinetics of input functions that do not depend on the concentration or the amount of drug in the blood. Such input functions are likely to be encountered during oral absorption, because the GI concentration is much greater than the plasma concentration. However, in pulmonary absorption, the plasma concentration cannot be ignored in defining the input function. The concentration (partial pressure) gradient in the absorption path is considerably smaller because of an often very low concentration of the gas, a slow nonpulmonary elimination, and a rapid tissue equilibration.

The simple diffusional pulmonary absorption and excretion of a gas is intrinsically very regular and much less erratic and complex than the GI absorption and metabolism and renal excretion of regular drugs. A much smaller intra- and intersubject variability is expected. Kinetic predictions and estimations such as those described above should, therefore, be considerably more accurate than those made in general pharmacokinetic practice.

Multiple-Exposure Kinetics with Regular Dosing Cycle—Similar to the above (Eq. 40), the cumulative amount of gas excreted in the postexposure phase can be determined by integration of Eq. 41:

$$M_n(t_r) = \int_T^{t_r} K_1K_2 \cdot c_n(t)dt = \phi_n(L\alpha) \cdot \left[K_1K_2 \frac{A_T(T)}{\alpha}\right]\left[1 - e^{-\alpha(t_r-T)}\right] + \phi_n(L\beta) \cdot \left[K_1K_2 \frac{B_T(T)}{\beta}\right]\left[1 - e^{-\beta(t_r-T)}\right] \qquad (t_r \geq T) \quad \text{(Eq. 49)}$$

[4] Equation 6 is the explicit $c(t)$ function obtained directly from the implicit relationship in Eq. 5 which contains all six basic parameters. Equation 6, therefore, contains the exact same basic parameters as Eq. 5. The basic parameters are related to the macroparameters A', α', B', β' (introduced for simplification) through Eqs. 7–9. Determination of the macroparameters and their basic parameters by least-squares regression of Eq. 6 poses no real problem. The procedure is completely analogous to the determination of macroparameters and micro-rate constants in classical linear compartmental modeling, which is routinely done with well-established computer programs.

By fitting this expression to pulmonary excretion data, the same quantities [α, β, $K_1K_2 \cdot A_T(T)$, and $K_1K_2 \cdot B_T(T)$] as in the single-exposure case (Eq. 40) can be determined. Thus, the same predictions (Eqs. 42-44) can be made as before. Similarly, if plasma level data are obtained in the postexposure phase ($t_r \geq T$), then by fitting Eq. 41, the quantitites α, β, $A_T(T)$, and $B_T(T)$ are obtained and predictions can be made as before (Eqs. 46-48).

Irregular Dosing Cycle—By combining Eqs. 30, 41, and 38, the following expression for the plasma level in the postexposure phase is obtained:

$$c_{n,m}(t_r) = [\phi_n(L\alpha) + \phi_N(L\alpha) \cdot \phi_{m-1}(7L\alpha) \cdot e^{-(M+n)L\alpha}]A_T(T) \cdot e^{-\alpha(t_r-T)} + [\phi_n(L\beta) + \phi_N(L\beta) \cdot \phi_{m-1}(7L\beta) \cdot e^{-(M+n)L\beta}]B_T(T) \cdot e^{-\beta(t_r-T)} \quad (t_r \geq T) \quad \text{(Eq. 50)}$$

By integrating this equation, the cumulative amount of gas excreted in the postexposure phase can be described as:

$$M_{n,m}(t_r) = [\phi_n(L\alpha) + \phi_N(L\alpha) \cdot \phi_{m-1}(7L\alpha) \cdot e^{-(M+n)L\alpha}] \left[K_1K_2 \frac{A_T(T)}{\alpha}\right] [1 - e^{-\alpha(t_r-T)}] + [\phi_n(L\beta) + \phi_N(L\beta) \cdot \phi_{m-1}(7L\beta) \cdot e^{-(M+n)L\beta}] \left[K_1K_2 \frac{B_T(T)}{\beta}\right] [1 - e^{-\beta(t_r-T)}] \quad (t_r \geq T) \quad \text{(Eq. 51)}$$

In analogy to the regular dosing cycle case, the quantities α, β, $K_1K_2 \cdot A_T(T)$, and $K_1K_2 \cdot B_T(T)$ can be determined by fitting Eq. 51 to pulmonary excretion data. Similarly α, β, $A_T(T)$, and $B_T(T)$ are obtained from plasma level data by Eq. 50.

Thus, a kinetic analysis of data in the postexposure phase(s) of multiple exposures provides the same basic kinetic information as an analysis of postexposure data from a single exposure.

Occupational Exposure Limit Adjustment in Unusual Work Schedules—The regulatory threshold limit values (TLV) for exposure in air contaminants administered by the Occupational Safety and Health Administration are based on exposure during a normal work week of five 8-h days (16). If a person with a non-normal work week is not going to be exposed to a greater toxic burden than allowed, if may be appropriate to consider a different TLV. There is no general consensus of how to best compare the toxic burden from different exposure schemes. One approach that seems to have received particular interest is based on a comparison of the predicted maximum amount of the contaminant in the body (10). Such an approach appears to be unsatisfactory because of the experimental difficulties of estimating such a quantity and because of the kinetic misconception of treating the body as a homogeneous "box."

A more appropriate approach would be based on a comparison of peak plasma levels predicted from kinetic equations based on rational assumptions. In the comparison of two exposure schemes (denoted with superscripts I and II), it is of interest to determine a TLV adjustment factor, F, defined as follows. The maximum plasma level of the contaminant predicted for exposure scheme II with contamination level C_g^{II} is the same as that predicted for scheme I with contamination level C_g^{I} when:

$$C_g^{II}F \cdot C_g^{I} \quad \text{(Eq. 52)}$$

An analysis of Eq. 30 reveals that $c_{n,m}$ is directly proportional to the contamination level C_g. The adjustment factor F can therefore be calculated from the relationship:

$$F = \frac{\max c_{n,m}{}^{I}}{\max c_{n,m}{}^{II}} \quad \text{(Eq. 53)}$$

where

$$\max c_{n,m} = c_{N,m}(T) \quad \text{(Eq. 54)}$$

The predicted maximum plasma level, max $c_{n,m}$, can be calculated by Eq. 50:

$$\max c_{n,m} = \phi_N(L\alpha) \cdot [1 + \phi_{m-1}(7L\alpha) \cdot e^{-(M+n)L\alpha}] \cdot A_T(T) + \alpha_N(L\beta) \cdot [1 + \alpha_{m-1}(7L\beta) \cdot e^{-(M+n)L\beta}] \cdot B_T(T) \quad \text{(Eq. 55)}$$

If there is no more than one work week exposure ($m = 1$), Eq. 55 reduces to the regular dosing cycle case:

$$\max c_{n,1} = \phi_N(L\alpha) \cdot A_T(T) + \phi_N(L\beta) \cdot B_T(T) \quad \text{(Eq. 56)}$$

Although the above equations used to calculate the adjustment factor may appear complex and demanding in kinetic terms, F can be determined most simply from two sets of pulmonary excretion data; one set can be determined from a single or multiple exposure with an exposure period T^{I}, and another set can be determined with an exposure period T^{II}. By fitting a simple biexponential expression to the two sets of data, values for α, β, $K_1K_2 \cdot A_T(T)^{I}$, $K_1K_2 \cdot A_T(T)^{II}$, $K_1K_2 \cdot B_T(T)^{I}$, and $K_1K_2 \cdot B_T(T)^{II}$ can then be determined as previously discussed. In calculating F, it is important to realize that it is not necessary to know $A_T(T)$ and $B_T(T)$. It is sufficient to know the products $K_1K_2 \cdot A_T(T)$ and $K_1K_2 \cdot B_T(T)$, since in forming the ratio in Eq. 53, it makes no difference if $A_T(T)$ and $B_T(T)$ are replaced with the products.

The above analysis of the pulmonary kinetics is for the non-steady-state case. The steady-state cases are easily considered by letting n or $m = \infty$ and by noting that:

$$\phi_\infty(x) = \frac{1}{1 - e^{-x}} \quad \text{(Eq. 57)}$$

For most practical purposes, it is adequate to approximate the unit-impulse response by a biexponential equation (Eq. 4). However, the analysis can be readily extended to consider any number of exponential terms in the approximation.

APPENDIX: GLOSSARY

Basic Kinetic Parameters:

K_1	Mass transfer constant for transport of the inhaled gas into the blood plasma (Eq. 1)
K_2	Partition coefficient between air and blood plasma for the inhaled gas; $K_2c(t)$ is the partial pressure of the gas in plasma (Eq. 1)
A,B,α, β	Parameters defining the unit-impulse response of the gas in the subject, *i.e.*, the parameters describing the plasma concentration-time profile if a unit amount of the gas was introduced momentarily into the plasma (Eq. 4)

Parameters Defining the Exposure:

C_g	Concentration of gas in the inhaled air (Eq. 1)
T	Duration of single or multiple exposures (Eq. 1)
H	Duration between regular exposures (T) (Eq. 22)
t_r	Time elapsed since the start of the most recent exposure for multiple exposures (Eq. 21)
n	Number of the current exposure cycle (n runs from 1 to N each week for exposure for multiple weeks) (Eq. 25)
m	Number of the current week ($m = 1$ for exposure for the first week) (Eq. 30)
N	Total number of exposure periods in each week for exposure for multiple weeks (Eq. 31)
M	Number of exposure-free periods in each week for exposure for multiple weeks (Eq. 32)
L	$T + H$

Auxilliary Functions and Parameters:

α', β'	Parameters calculated from the fundamental parameters K_1, K_2, A, B, α, and β according to Eq. 7
A',B'	Parameters calculated from the fundamental parameters K_1, K_2, A, B, α, and β; A' and B' are calculated according to Eqs. 8 and 9 after α' and β' are calculated
$(x)_+$	Truncation function equal to x for $x \geq 0$ and 0 for $x < 0$ (Eqs. 17 and 18)
$A_T(t)/B_T(t)$	Functions introduced to simplify the mathematical notation [note that these functions are constant ($A_T(T)$,$B_T(T)$) for $t_r \geq T$ (Eqs. 13-16)]
t'	min (t,T) (Eqs. 15 and 16)
$\phi_i(x)$	Function introduced to simplify the mathematical notation (Eq. 27)
$P_{n-1}(t_r)$	Function describing the plasma accumulation of gas at time t_r resulting from the previous ($n - 1$) exposure periods (Eq. 29)
$Q_{m-1}(t_r)$	Function describing the plasma accumulation of the gas at time t_r resulting from the previous ($m - 1$) weeks of exposure (Eq. 38)

REFERENCES

(1) R. A. VanDyke, M. D. Chenoweth, and A. Van Poznak, *Biochem. Pharmacol.*, **13**, 1239 (1964).

(2) E. N. Cohen, *Anesthesiology*, **35**, 193 (1971).

(3) V. Fiserova-Bergerova and D. A. Holaday, *Drug Metab. Rev.*, **9**(1), 43 (1979).

(4) E. M. Paper and R. J. Kitz (Eds.), "Uptake and Distribution of Anesthetic Agents," McGraw-Hill, New York, N.Y., 1963.
(5) S. S. Kety, *Pharmacol. Rev.*, **3**, 1 (1951).
(6) K. Nomiyama and H. Nomiyama, *Int. Arch. Arbeitsmed.*, **32**, 75 (1974).
(7) M. E. Andersen, M. L. Gargas, R. A. Jones, and L. J. Jenkins, *Toxicol. Appl. Pharmacol.*, **54**, 100 (1980).
(8) I. Astrand, *Scand. J. Work Environ. Health*, **1**, 199 (1975).
(9) I. Astrand and F. Gamberale, *Environ. Res.*, **15**, 1 (1978).
(10) J. L. S. Hickey and C. Reist, *Am. Ind. Hyg. Assoc. J.*, **38**, 613 (1977).
(11) J. L. S. Hickey and C. Reist, *Am. Ind. Hyg. Assoc. J.*, **40**, 727 (1979).
(12) J. W. Mason and H. Dershin, *J. Occup. Med.*, **18**, 603 (1976).
(13) S. A. Roach, *Am. Ind. Hyg. Assoc. J.*, **27**, 1 (1966).
(14) S. A. Roach, *Am. Ind. Hyg. Assoc. J.*, **39**, 345 (1978).
(15) R. D. Stewart, H. H. Gay, D. S. Erley, C. L. Hake, and J. E. Peterson, *J. Occup. Med.*, **3**, 586 (1961).
(16) "Occupational Safety and Health Standards: Title 9 Code of Federal Regulations, Part 1910," Occupational Safety and Health Administration, Washington, D.C., 1976.
(17) "Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1976," American Conference Industrial Hygiene, Cincinnati, Ohio, 1976.
(18) S. Riegelman, J. C. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117 (1968).
(19) P. Veng-Pedersen, *J. Pharm. Sci.*, **69**, 298 (1980).
(20) P. Veng-Pedersen, *J. Pharm. Sci.*, **69**, 305 (1980).
(21) P. Veng-Pedersen, *J. Pharmacokinet. Biopharm.*, **8**, 463 (1980).
(22) D. J. Cutter, *J. Pharmacokinet. Biopharm.*, **6**, 243 (1973).

Synthesis of 4-Substituted Aminoquinoline-3-carboxylates as Potential Antimicrobial Agents

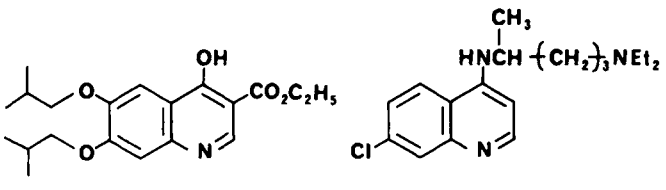
PAUL E. MARECKI *x and RONALD E. BAMBURY

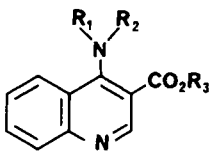
Received March 7, 1983, from *SDS Biotech Corporation, World Headquarters, Concord Township, Painesville, OH 44077.* Accepted for publication July 19, 1983. *Present address: Ohio Medical Anesthetics, AIRCO Central Research Laboratories, Murray Hill, NJ 07974.

Abstract □ A series of 4-substituted aminoquinoline-3-carboxylates was prepared and evaluated for antimicrobial activity. Four of the compounds (VIII, XIII, XV, and XXIII) exhibited low activity against *Staphylococcus aureus*.

Keyphrases □ 4-Substituted aminoquinoline-3-carboxylates—synthesis, antimicrobial activity □ Antimicrobial agents—potential, 4-substituted aminoquinoline-3-carboxylates

The structural similarity between the coccidiostat buquinolate (I) (1) and the antimalarial 4-aminoquinolines (*e.g.*, chloroquin; II) (2) raised the question as to whether combination of the major functional groups of each class might lead to useful agents. This work sought to determine if the quinoline-3-carboxylate moiety of the coccidiostats could be successfully combined with 4-amino substituents, some of which have shown promise in antimalarial quinolines. A series of 4-aminoquinoline-3-carboxylates (III) was necessary, and a search of the literature revealed that these compounds had not previously been synthesized. To determine if antibacterial properties were associated with this new substituent pattern, the synthesis of several examples was undertaken.





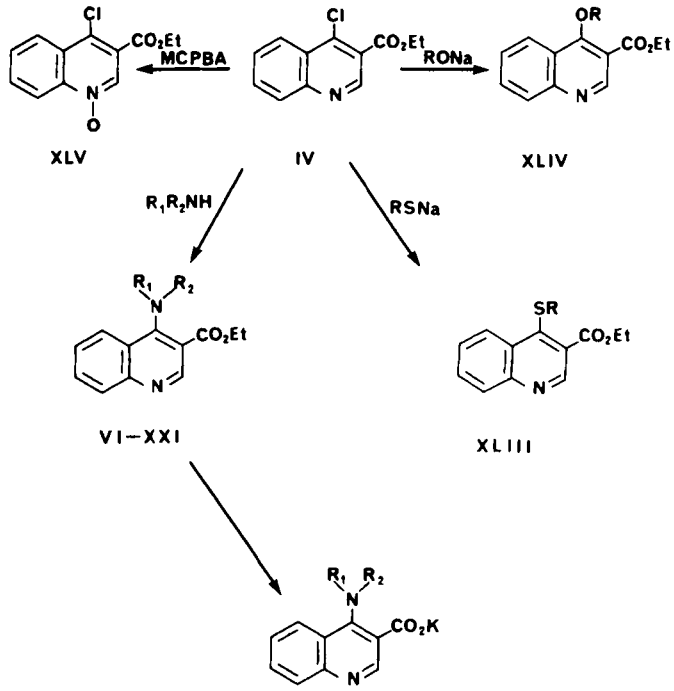
III

R_1, R_2 = H, alkyl, aralkyl
R_3 = K, C_2H_5

RESULTS AND DISCUSSION

Ethyl 4-chloroquinoline-3-carboxylate, IV (3), was the key intermediate from which the target compounds were prepared (Scheme I). The immediate precursor to IV, ethyl 4-hydroxyquinoline-3-carboxylate V, was prepared in satisfactory yield by the method of Gould and Jacobs (4) as modified by Price and Roberts (5) and by Riegel *et al.* (6). The importance of short reaction times in the preparation of V was noted (7); yields of V decrease for reaction times exceeding 30 min. Reaction of V with phosphorus oxychloride smoothly led to IV (3).

Nucleophilic displacement of the 4-chloro substituent occurred in high yield after a few hours in refluxing toluene; several cases were noted where the reaction started while still at room temperature. The relative ease of displace-



Scheme I

0022-3549/84/0800-1141$01.00/0