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# Pharmacokinetic Model for Chlordiazepoxide·HCl in the Dog

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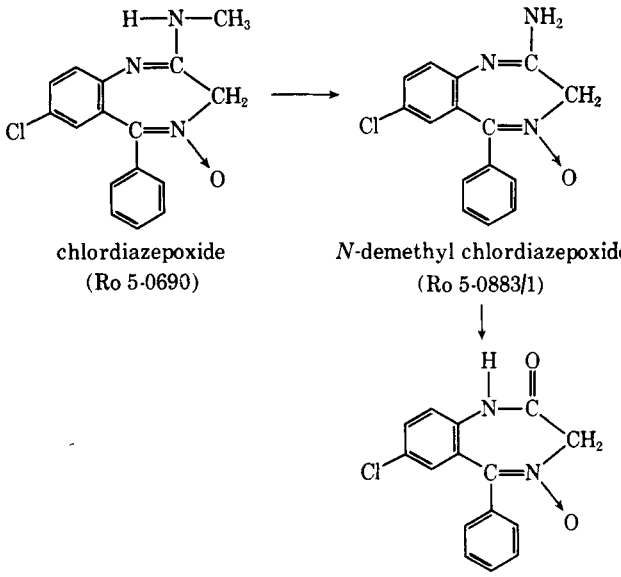
**Abstract** □ A six-compartment open-system model is presented to elucidate the physiological disposition of chlordiazepoxide and its two pharmacologically active biotransformation products, Ro 5-0883/1 and Ro 5-2092, in the dog following the intravenous administration of 10 mg./kg. chlordiazepoxide·HCl. The pharmacokinetic parameters used in the model were obtained by administering each of the three compounds separately. Excellent agreement was obtained between the plasma levels of intact drug, Ro 5-0883/1, and Ro 5-2092 found after administration of chlordiazepoxide·HCl and the calculated levels of each generated from the model. The main features of chlordiazepoxide disposition were: (*a*) its complete biotransformation to Ro 5-0883/1; (*b*) elimination of Ro 5-0883/1 almost entirely by biotransformation with up to 50% proceeding to Ro 5-2092 by oxidative deamination; and (*c*) elimination of Ro 5-2092 by urinary excretion and further biotransformation.

**Keyphrases** □ Chlordiazepoxide·HCl and metabolites, disposition—pharmacokinetic model □ Biotransformation, dogs—chlordiazepoxide·HCl □ Plasma levels—chlordiazepoxide and metabolites □ Urinary excretion—chlordiazepoxide and metabolites □ TLC—separation □ Fluorometry—analysis

Chlordiazepoxide[1] (7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide) is extensively used in the treatment of anxiety states and other psychic disorders (1, 2). Chlordiazepoxide has been shown (3–5) to be biotransformed in dog and man to the *N*-demethyl chlordiazepoxide (Ro 5-0883/1), which undergoes further deamination to form the "lactam" (Ro 5-2092). The structure of chlordiazepoxide together with those of the two biotransformation products, both of which are pharmacologically active (2, 6, 7), is presented in Scheme I.

This study reports the development of a pharmacokinetic model to describe the physiological disposition of chlordiazepoxide, Ro 5-0883/1, and Ro 5-2092 following the intravenous administration of chlordiazepoxide·HCl to dogs. To elucidate an appropriate pharmacokinetic model, each of the three compounds was separately administered intravenously to two dogs. The pharmacokinetic parameters thus obtained for each compound were used to establish the model for the disposition of chlordiazepoxide·HCl.




*Scheme I*

## EXPERIMENTAL

**Protocol**—Two male dogs, weighing 10.5 and 13.0 kg., each received single 10-mg./kg. i.v. doses of chlordiazepoxide·HCl, Ro

[1] Chlordiazepoxide·HCl is the active ingredient in Librium marketed by Hoffmann-La Roche Inc., Nutley, N. J.

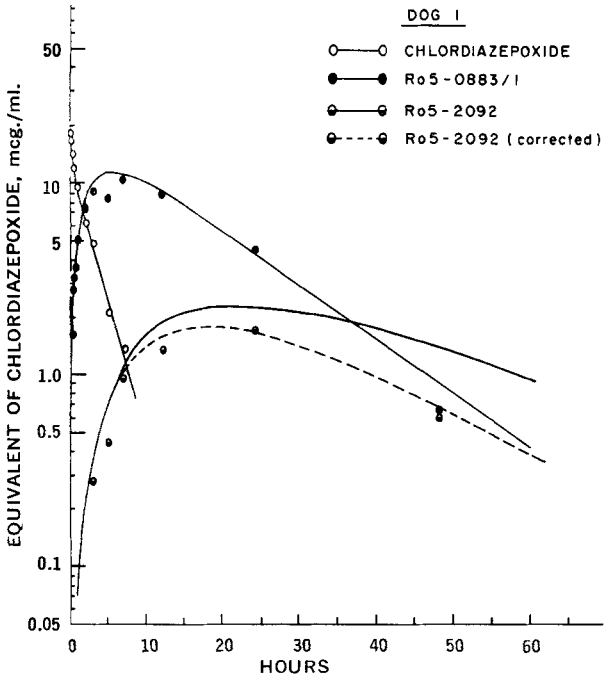



**Figure 1**—*Computer-simulated curves and experimental data points following the intravenous administration of 10 mg./kg. chlordiazepoxide·HCl to Dog 1.*

5-0883/1, and Ro 5-2092, with approximately 2 weeks between doses. The chlordiazepoxide and Ro 5-0883/1 were administered in aqueous solution as the hydrochloride, whereas the Ro 5-2092 was administered in propylene glycol solution. Five-milliliter blood specimens (heparinized) were obtained at various times after drug administration, and the plasma was separated. Total urine output for 3 days was collected following the administration of each drug.

**Analytical Method**—A differential fluorometric assay procedure (5) allowed for the specific determination of chlordiazepoxide, Ro 5-0883/1, and Ro 5-2092 when all three were present in a single plasma specimen. The sensitivity of the procedure was 0.2–0.3 mcg. of each compound per milliliter of plasma using a 1-ml. specimen.

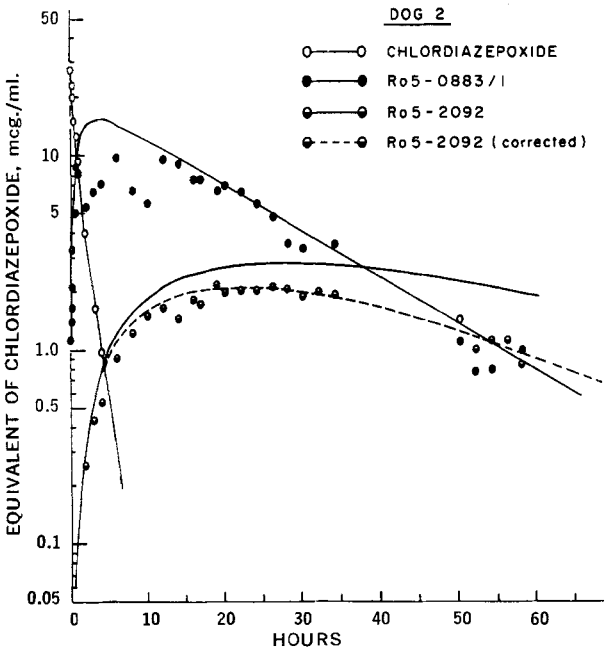



**Figure 2**—*Computer-simulated curves and experimental data points following the intravenous administration of 10 mg./kg. chlordiazepoxide·HCl to Dog 2.*

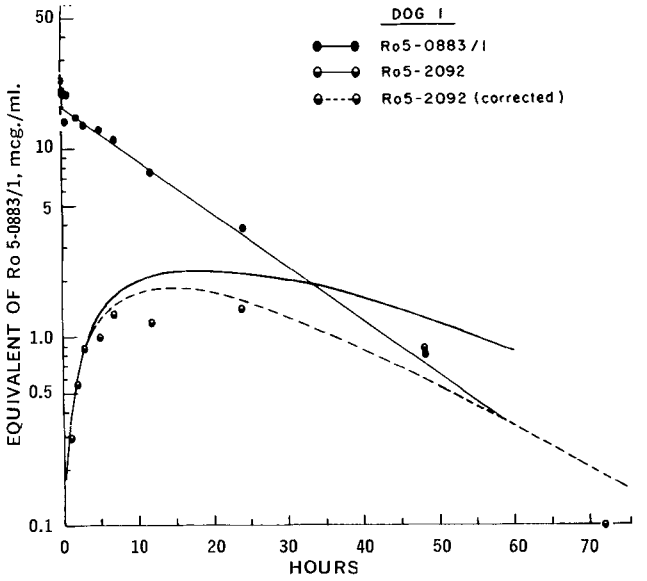



**Figure 3**—*Computer-simulated curves and experimental data points following the intravenous administration of 10 mg./kg. Ro 5-0883/1 to Dog 1.*

For the analyses of urine, a TLC step was added to the assay procedure to eliminate interfering urinary fluorescence. The ether extract of urine was evaporated to dryness; the residue was reconstituted in 100 μl. ethanol and spotted on Brinkmann neutral TLC plates, F-254, with appropriate standards. Following development in ethyl acetate–ethanol (90:10), the areas corresponding to chlordiazepoxide ($R_f$ 0.25), Ro 5-0883/1 ($R_f$ 0.16), and Ro 5-2092 ($R_f$ 0.43) were scraped from the plate. Chlordiazepoxide was eluted from the silica gel with 0.1 *N* sulfuric acid, Ro 5-0883/1 with 7.0 *N* sulfuric acid, and Ro 5-2092 with 0.1 *N* sodium hydroxide. The analytical procedure for each compound then followed that described for plasma specimens (5). This procedure was carried out with 10-ml. urine specimens.

## RESULTS AND DISCUSSION

The plasma level curves following the administration of 10-mg./kg. i.v. doses of chlordiazepoxide·HCl, Ro 5-0883/1, and Ro 5-2092 to Dogs 1 and 2 are presented in Figs. 1–6.

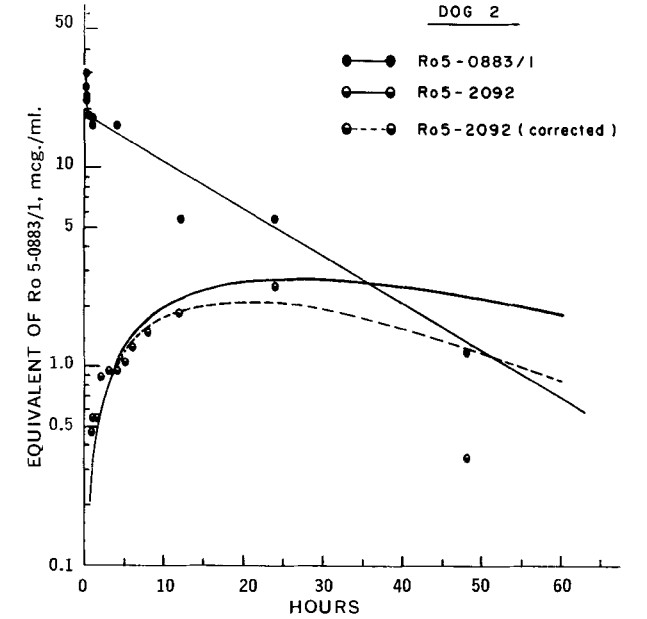



**Figure 4**—*Computer-simulated curves and experimental data points following the intravenous administration of 10 mg./kg. Ro 5-0883/1 to Dog 2.*

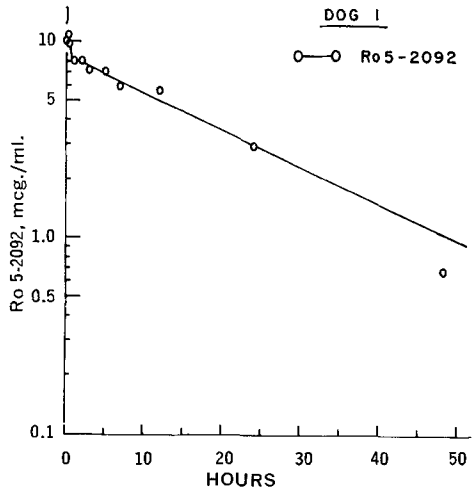



**Figure 5**—*Computer-simulated curve and experimental data points following the intravenous administration of 10 mg./kg. Ro 5-2092 to Dog 1.*

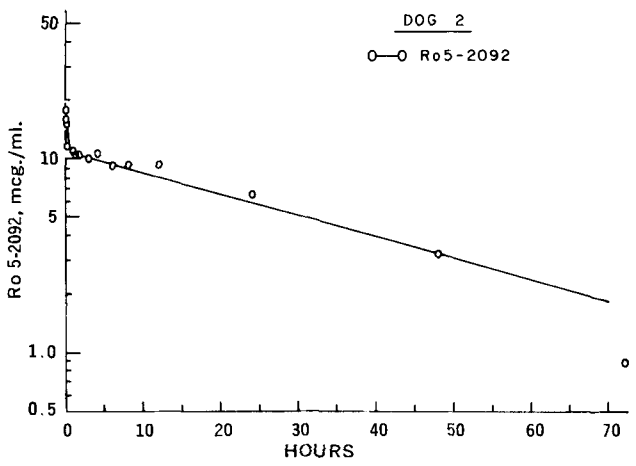



**Figure 6**—*Computer-simulated curve and experimental data points following the intravenous administration of 10 mg./kg. Ro 5-2092 to Dog 2.*

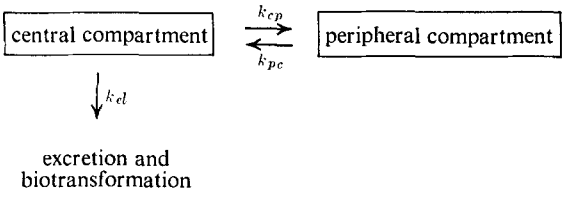
The plasma level curves of each of the three intravenously administered compounds were apparently biexponential. This suggested that the pharmacokinetic evaluation of each compound would require a minimum of a two-compartment open-system model (8). The calculated volume of the central compartment, $V_p$, for each of the three compounds was never less than 30% of body weight. This further suggested that the central compartment of the two-compartment open-system model consisted of plasma plus readily accessible body spaces, *e.g.*, liver and kidneys. Therefore, elimination was assumed to occur from the central compartment, as indicated in the model presented in Scheme II.

In this model, $k_{cp}$ and $k_{pc}$ are the first-order rate constants into and out of the peripheral compartment, and $k_{el}$ is the sum of the simultaneous processes of biotransformation and elimination, all assumed to be first-order processes.

The experimental plasma level data of chlordiazepoxide, Ro 5-0883/1, and Ro 5-2092 obtained following the intravenous administration of each of the three compounds were fit to the biexponential equation, $C_p = Ae^{-\alpha t} + Be^{-\beta t}$, by means of a "least-squares estimation of nonlinear parameters" evaluation programmed in FORTRAN IV for use on a GE-605 digital time-sharing system (9). The parameters thus obtained ($A$, $\alpha$, $B$, and $\beta$) are presented in Table I. $A$ and $B$ are the ordinate axis intercepts of the biexponential curve, and $\alpha$ and $\beta$ are the hybrid rate constants reflecting the overall rate processes. The individual rate constants ($k_{cp}$, $k_{pc}$, and $k_{el}$) associated with the two-compartment open-system model were calculated according to Riegelman *et al.* (8) and are presented in Table I.

The 0–74-hr. urinary excretion levels in Dog 2 following the administration of chlordiazepoxide·HCl indicated no excretion of intact chlordiazepoxide, whereas 1.6% of the administered dose was recovered as Ro 5-0883/1 and 5.0% was recovered as Ro 5-2092.

Previous studies (10) indicated that following an oral 10-mg./kg. dose of chlordiazepoxide·HCl to a dog and examination of the 0–48-hr. urine, there was no recovery of intact chlordiazepoxide and that 1.1% of the dose was recovered as Ro 5-0883/1 and 7.2% was recovered as Ro 5-2092. These findings are similar to those of Dog 2. Schwartz (11) found that following the single oral administration of 4 mg./kg. $^{14}$C-chlordiazepoxide·HCl to two dogs and examination of the 0–72-hr. urinary excretion levels, there was no recovery of intact chlordiazepoxide, whereas 0.2 and 0.5% of the dose were excreted as Ro 5-0883/1 and 1.3 and 3.0% were excreted as Ro 5-2092 in the two dogs, respectively.




*Scheme II—Two-compartment open-system pharmacokinetic model*

Further information on the biotransformation of chlordiazepoxide and of Ro 5-0883/1 was obtained by examining the areas under the Ro 5-0883/1 plasma level curves following the intravenous administration of chlordiazepoxide·HCl, *i.e.*, formed Ro 5-0883/1, and of administered Ro 5-0883/1, respectively. The (formation curve/administered curve) area ratios for Ro 5-0883/1 were 0.88 and 0.99 in Dogs 1 and 2, respectively. This would suggest virtually complete conversion of chlordiazepoxide to Ro 5-0883/1.

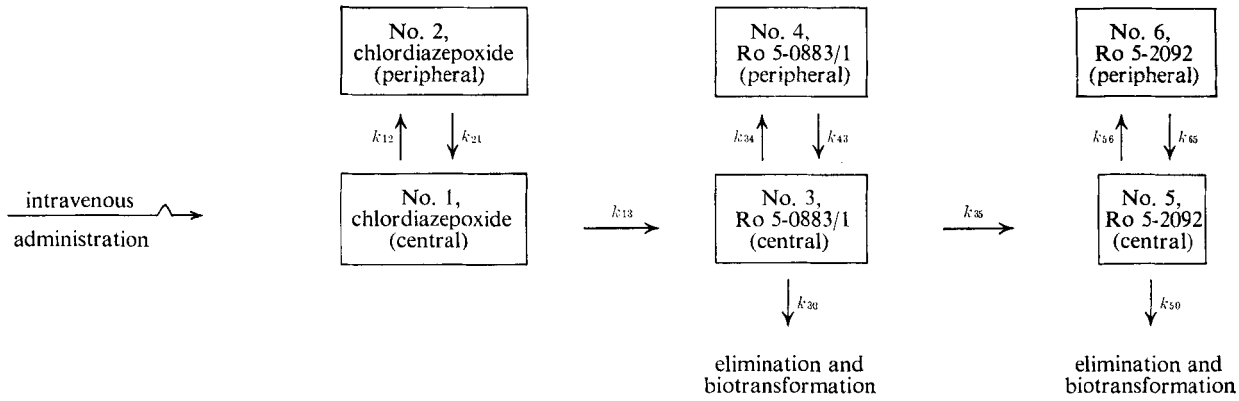
The areas under the formation curves of Ro 5-2092 were determined following the administrations of both chlordiazepoxide·HCl and Ro 5-0883/1 and compared with those following the administration of Ro 5-2092. The (formation curve/administered curve) area ratios were 0.28 and 0.28 in Dog 1 following chlordiazepoxide·HCl and Ro 5-0883/1 administration, respectively, and 0.24 and 0.22 in Dog 2. This would further indicate that chlordiazepoxide is completely biotransformed to Ro 5-0883/1 since Ro 5-0883/1 is the precursor of Ro 5-2092, and both chlordiazepoxide and Ro 5-0883/1 produce equivalent amounts of Ro 5-2092.

Therefore, inasmuch as all the chlordiazepoxide·HCl administered was biotransformed to Ro 5-0883/1, the formation constant of Ro

**Table I**—Pharmacokinetic Evaluation of Intravenously Administered Chlordiazepoxide·HCl, Ro 5-0883/1, and Ro 5-2092 According to a Two-Compartment Open-System Model

| Parameter | Compound Administered: Chlordiazepoxide | Ro 5-0883/1 | Ro 5-2092 |
|---|---|---|---|
| | **Dog 1** | | |
| Dose, mg./kg. | 10 | 10 | 10 |
| Dog weight, kg. | 10.5 | 10.2 | 9.5 |
| $A$, mcg./ml. | 7.86 | 13.26 | 3.14 |
| $\alpha$ hr.$^{-1}$ | 2.80 | 13.18 | 3.38 |
| $B$, mcg./ml. | 12.26 | 17.10 | 8.41 |
| $\beta$, hr.$^{-1}$ | 0.33 | 0.066 | 0.04 |
| $k_{cp}$, hr.$^{-1}$ | 0.79 | 5.75 | 0.89 |
| $k_{pc}$, hr.$^{-1}$ | 1.84 | 7.45 | 2.47 |
| $k_{el}$, hr.$^{-1}$ | 0.50 | 0.12 | 0.059 |
| $V_p$, l. | 5.22 | 3.36 | 8.21 |
| % $V_p$[a] | 49.7 | 32.9 | 86.6 |
| | **Dog 2** | | |
| Dose, mg./kg. | 10 | 10 | 10 |
| Dog weight, kg. | 13.0 | 13.0 | 13.6 |
| $A$, mcg./ml. | 19.18 | 13.06 | 7.72 |
| $\alpha$, hr.$^{-1}$ | 1.56 | 11.20 | 11.14 |
| $B$, mcg./ml. | 9.19 | 19.04 | 11.26 |
| $\beta$, hr.$^{-1}$ | 0.53 | 0.054 | 0.025 |
| $k_{cp}$, hr.$^{-1}$ | 0.24 | 4.51 | 4.51 |
| $k_{pc}$, hr.$^{-1}$ | 0.89 | 6.65 | 6.62 |
| $k_{el}$, hr.$^{-1}$ | 1.00 | 0.091 | 0.043 |
| $V_p$, l. | 4.58 | 4.05 | 7.17 |
| % $V_p$[a] | 35.3 | 31.2 | 52.7 |

[a] % $V_P$ = $V_P$ × 100/dog wt.




*Scheme III—Six-compartment open-system pharmacokinetic model for the physiological disposition of chlordiazepoxide·HCl*

5-0883/1, $k_{13}$, was taken to be equal to that of the elimination-rate constant, $k_{el}$, of chlordiazepoxide. The formation constant of Ro 5-2092, $k_{35}$, was determined by adapting the absorption-rate equation of Loo and Riegelman (12). This constant was determined by utilizing the formation data of Ro 5-2092 following the administrations of both chlordiazepoxide·HCl and Ro 5-0883/1, and the rate constants, $k_{cp}$, $k_{pc}$, and $k_{el}$ obtained following the intravenous administration of Ro 5-2092.

Based on these considerations, a six-compartment open-system pharmacokinetic model to describe the physiological disposition of chlordiazepoxide in the dog was developed, as indicated in Scheme III.

In the model, $k_{12}$, $k_{21}$, $k_{34}$, $k_{43}$, $k_{56}$, and $k_{65}$ are the first-order rate constants of distribution of the compounds indicated in the model; $k_{13}$ and $k_{35}$ are the first-order rate constants of formation of Ro 5-0883/1 and Ro 5-2092, respectively; $k_{30}$ is the sum of the simultaneous processes of elimination of Ro 5-0883/1 and biotransformation to compounds other than Ro 5-2092; and $k_{50}$ is the sum of the simultaneous processes of elimination and biotransformation of Ro 5-2092. All the elimination and biotransformation processes are assumed to be first order.

Solution of the differential equations (13) describing the six-compartment open-system model, as presented in *Appendix A*, yields the following expressions to describe the plasma level–time curves for Compartments 1, 3, and 5, respectively, following a single intravenous administration of chlordiazepoxide·HCl:

$$C_1 = A_{13}\,e^{-a_3 t} + A_{14}\,e^{-a_4 t} \qquad \text{(Eq. 1)}$$

$$C_3 = A_{33}\,e^{-a_3 t} + A_{34}\,e^{-a_4 t} + A_{35}\,e^{-a_5 t} + A_{36}\,e^{-a_6 t} \qquad \text{(Eq. 2)}$$

$$C_5 = A_{53}\,e^{-a_3 t} + A_{54}\,e^{-a_4 t} + A_{55}\,e^{-a_5 t} + A_{56}\,e^{-a_6 t} + A_{57}\,e^{-a_7 t} + A_{58}\,e^{-a_8 t} \qquad \text{(Eq. 3)}$$

where $C_1$, $C_3$, and $C_5$ are the concentrations of the three compounds in the central compartment. The coefficients $A_{1j}$, $A_{3j}$, and $A_{5j}$ and the hybrid rate constants $a_3$–$a_8$ are determined as a function of all the rate constants: $k_{12}$, $k_{21}$, $k_{13}$, $k_{34}$, $k_{43}$, $k_{30}$, $k_{35}$, $k_{56}$, $k_{65}$, and $k_{50}$. The six-compartment open-system model describing the physiological disposition of chlordiazepoxide was programmed in FORTRAN IV for use in the GE-605 digital time-sharing system (14). This program allowed for the simulation of drug quantity in the various compartments of the model as a function of time.

**Table II**—Pharmacokinetic Parameters for the Physiological Disposition of Chlordiazepoxide·HCl in Dogs in Terms of a Six-Compartment Open System

| Rate Constant | Dog 1 | Dog 2 |
|---|---|---|
| $k_{12}$, hr.$^{-1}$ | 0.792 | 0.24 |
| $k_{21}$, hr.$^{-1}$ | 1.836 | 0.892 |
| $k_{13}$, hr.$^{-1}$ | 0.503 | 1.001 |
| $k_{34}$, hr.$^{-1}$ | 5.754 | 4.510 |
| $k_{43}$, hr.$^{-1}$ | 7.447 | 6.651 |
| $k_{30}$, hr.$^{-1}$[a] | 0.045 | 0.047 |
| $k_{35}$, hr.$^{-1}$ | 0.072 | 0.045 |
| $k_{56}$, hr.$^{-1}$ | 0.892 | 4.508 |
| $k_{65}$, hr.$^{-1}$ | 2.473 | 6.619 |
| $k_{50}$, hr.$^{-1}$ | 0.059 | 0.043 |
| $k_{50}$, hr.$^{-1}$[b] | 0.099 | 0.080 |

[a] $k_{30} = k_{el}$ (Ro 5-0883/1) − $k_{35}$. [b] $k_{50}$ corrected for formation data.

Confirmation of the proposed model required coincidence of simulated and experimental plasma level curves for Compartments 1, 3, and 5 following a single intravenous administration of chlordiazepoxide·HCl. The pharmacokinetic parameters ($k_{cp}$, $k_{pc}$, and $k_{el}$) obtained for each of the three individually administered compounds (Table I) were utilized as computer input for the six-compartment open-system model. The constants for the six-compartment model are summarized in Table II. In addition, to allow for comparison of the experimental and simulated data of the three compounds following the administration of chlordiazepoxide·HCl, the plasma levels of Ro 5-0883/1 and Ro 5-2092 were converted to chlordiazepoxide equivalents. The three curves drawn in solid lines in Figs. 1 and 2 represent the simulated curves and corresponding experimental data points following the intravenous administration of 10 mg./kg. chlordiazepoxide·HCl to Dogs 1 and 2, respectively.

The simulated plasma curves agreed very well with the experimental data in the chlordiazepoxide and Ro 5-0883/1 compartments utilizing the pharmacokinetic parameters obtained following the intravenous administration of each of the three compounds. The simulated plasma level curves of Ro 5-2092, however, did not correlate as well since they exhibited a slower elimination rate than did the experimentally obtained plasma level curves. This small deviation appears to be reflected in differences noted in the experimentally obtained plasma level data following the intravenous administration of Ro 5-2092 as compared with the Ro 5-2092 plasma levels obtained following the administration of chlordiazepoxide or Ro 5-0883/1. The data indicate that the apparent elimination-rate constant of Ro 5-2092 when produced as a biotransformation product was greater than the apparent elimination-rate constant observed after administered Ro 5-2092. This phenomenon has been previously observed for other drugs (15, 16).

These findings indicated that $k_{50}$ of the six-compartment open-system model would have to be calculated from the formation curve of Ro 5-2092 and not from the data following the intravenous administration of Ro 5-2092. Therefore, the elimination-rate constant of Ro 5-2092 was recalculated utilizing the formation data by rearranging Eq. A13 of *Appendix A* and solving for $k_{50}$;

$$k_{50} = \frac{\beta \cdot k_{56} - \beta^2 + \beta \cdot k_{65}}{(k_{65} - \beta)} \qquad \text{(Eq. 4)}$$

where $\beta$ is $a_8$ of Eq. 3. Since the data of the elimination phase of the Ro 5-2092 formation curve are utilized, the terms $A_{53}\,e^{-a_3 t}$, $A_{55}\,e^{-a_5 t}$, and $A_{57}\,e^{-a_7 t}$ of Eq. 3 rapidly approach zero. Therefore, Eq. 3 reduces to

$$C_5 = A_{54}\,e^{-a_4 t} + A_{56}\,e^{-a_6 t} + A_{58}\,e^{-a_8 t} \qquad \text{(Eq. 5)}$$

This elimination phase was fit to the triexponential equation by means of the "least-squares estimation of nonlinear parameters" (9), keeping $A_{54}$, $A_{56}$, $A_{58}$, $a_4$, and $a_6$ constant.

Substituting the new $k_{50}$ into the computer program for the six-compartment open-system model resulted in an excellent simulation of the Ro 5-2092 levels in both dogs (dashed lines in Figs. 1 and 2).

## CONCLUSION

A pharmacokinetic model for the disposition of chlordiazepoxide·HCl in the dog has been presented in terms of a six-compartment open system. The excellent agreement between the simulated and experimental data reflects the reliability of the assumption of first-order kinetics for all processes. The model (Scheme III) provides a basis for the elucidation and quantitation of chlordiazepoxide and its pharmacologically active biotransformation products, Ro 5-0883/1 and Ro 5-2092. The pathways in man (3–5) have been shown to be similar to those in the dog to the extent to which they are described in Scheme III. It is expected that this model will be useful for the interpretation of future human pharmacokinetic studies.

The main features of the physiological disposition of chlordiazepoxide·HCl in the dog were: (*a*) its biotransformation to Ro 5-0883/1 as the exclusive route of drug elimination; (*b*) the elimination of Ro 5-0883/1 almost entirely by biotransformation, with up to 50% going to Ro 5-2092 and the remainder going to an unidentified biotransformation product; and (*c*) the elimination of Ro 5-2092 by urinary excretion and further biotransformation.

$$\begin{bmatrix} a_3-(k_{12}+k_{13}) & k_{21} & 0 & 0 & 0 & 0 \\ k_{12} & a_4-k_{21} & 0 & 0 & 0 & 0 \\ k_{13} & 0 & a_5-(k_{34}+k_{35}+k_{30}) & k_{43} & 0 & 0 \\ 0 & 0 & k_{34} & a_6-k_{43} & 0 & 0 \\ 0 & 0 & k_{35} & 0 & a_7-(k_{56}+k_{50}) & k_{65} \\ 0 & 0 & 0 & 0 & k_{56} & a_8-k_{65} \end{bmatrix} \cdot \begin{bmatrix} A_{1j} \\ A_{2j} \\ A_{3j} \\ A_{4j} \\ A_{5j} \\ A_{6j} \end{bmatrix} = \begin{bmatrix} D_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{(Eq. A14)}$$

## APPENDIX A

**Determination of Kinetic Constants for Six-Compartment Open-System Model**—The six-compartment open-system model is presented in Scheme III. The transfer and elimination process in the six-compartment open-system model may be described as follows:

$$\frac{dC_1}{dt} = C_2k_{21} - C_1(k_{12}+k_{13}) \quad \text{(Eq. A1)}$$

$$\frac{dC_2}{dt} = C_1k_{12} - C_2k_{21} \quad \text{(Eq. A2)}$$

$$\frac{dC_3}{dt} = C_1k_{13} - C_3(k_{34}+k_{55}+k_{30}) + C_4k_{43} \quad \text{(Eq. A3)}$$

$$\frac{dC_4}{dt} = C_3k_{34} - C_4k_{43} \quad \text{(Eq. A4)}$$

$$\frac{dC_5}{dt} = C_3k_{35} - C_5(k_{56}+k_{50}) + C_6k_{65} \quad \text{(Eq. A5)}$$

$$\frac{dC_6}{dt} = C_5k_{56} - C_6k_{65} \quad \text{(Eq. A6)}$$

where $C_n$ is the amount of drug in the designated compartment, and the numerical subscripts for $C$ define the compartment. These simultaneous differential equations were solved by: (*a*) obtaining the eigen values of the eigen vector matrix, and (*b*) evaluating the corresponding eigen vectors (9).

The eigen values, $a_j$'s, are obtained as solutions of the characteristic equation:

$$\begin{vmatrix} a_3-(k_{12}+k_{13}) & k_{21} & 0 & 0 & 0 & 0 \\ k_{12} & a_4-k_{21} & 0 & 0 & 0 & 0 \\ k_{13} & 0 & a_5-(k_{34}+k_{35}+k_{30}) & k_{43} & 0 & 0 \\ 0 & 0 & k_{34} & a_6-k_{43} & 0 & 0 \\ 0 & 0 & k_{35} & 0 & a_7-(k_{56}+k_{50}) & k_{65} \\ 0 & 0 & 0 & 0 & k_{56} & a_8-k_{65} \end{vmatrix} = 0 \quad \text{(Eq. A7)}$$

which have the roots:

$$a_3 = \frac{(k_{12}+k_{21}+k_{13}) + \sqrt{(k_{12}+k_{21}+k_{13})^2 - 4(k_{21}k_{13})}}{2} \quad \text{(Eq. A8)}$$

$$a_4 = \frac{(k_{12}+k_{21}+k_{13}) - \sqrt{(k_{12}+k_{21}+k_{13})^2 - 4(k_{21}k_{13})}}{2} \quad \text{(Eq. A9)}$$

$$a_5 = \frac{(k_{34}+k_{43}+k_{30}+k_{35}) + \sqrt{(k_{34}+k_{43}+k_{30}+k_{35})^2 - 4(k_{43}k_{30}+k_{43}k_{35})}}{2} \quad \text{(Eq. A10)}$$

$$a_6 = \frac{(k_{34}+k_{43}+k_{30}+k_{35}) - \sqrt{(k_{34}+k_{43}+k_{30}+k_{35})^2 - 4(k_{43}k_{30}+k_{43}k_{35})}}{2} \quad \text{(Eq. A11)}$$

$$a_7 = \frac{(k_{56}+k_{65}+k_{50}) + \sqrt{(k_{56}+k_{65}+k_{50})^2 - 4(k_{65}k_{50})}}{2} \quad \text{(Eq. A12)}$$

$$a_8 = \frac{(k_{50}+k_{65}+k_{50}) - \sqrt{(k_{56}+k_{65}+k_{50})^2 - 4(k_{65}k_{50})}}{2} \quad \text{(Eq. A13)}$$

The eigen vectors, $A_{ij}$, are then obtained as solutions to the $6(j = 3,4, \ldots 8)$ vector equations:

where $D_0$ = initial dose.

The eigen vectors, $A_{ij}$, thus obtained are:

$$A_{13} = \frac{D_0(k_{21}-a_3)}{(a_4-a_3)} \quad \text{(Eq. A15)}$$

$$A_{14} = D_0 - A_{13} \quad \text{(Eq. A16)}$$

$$A_{2j} = \frac{k_{12}A_{1j}}{(k_{21}-a_j)} \qquad j = 3,4 \quad \text{(Eq. A17)}$$

$$A_{3j} = \frac{k_{13}(k_{43}-a_j)A_{1j}}{[(a_j-k_{34}-k_{35}-k_{30})(a_j-k_{43})-k_{43}k_{34}]} \qquad j = 3,4 \quad \text{(Eq. A18)}$$

$$A_{35} = \left[-A_{33}-A_{34}+\frac{(a_6-k_{43})}{k_{34}}(-A_{43}-A_{44})\right]\frac{(k_{43}-a_5)}{(a_6-a_5)} \quad \text{(Eq. A19)}$$

$$A_{36} = -\sum_{j=3}^{5} A_{3j} \quad \text{(Eq. A20)}$$

$$A_{4j} = \frac{A_{3j}k_{34}}{(k_{43}-a_j)} \qquad j = 3,4,5, \text{ and } 6 \quad \text{(Eq. A21)}$$

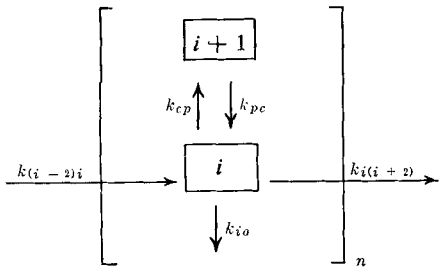
$$A_{5j} = \frac{A_{3j}k_{35}(k_{65}-a_j)}{(a_j-k_{56}-k_{50})(a_j-k_{65})-k_{56}k_{65}} \qquad j = 3,4,5, \text{ and } 6 \quad \text{(Eq. A22)}$$

$$A_{57} = \left[-\sum_{j=3}^{6} A_{5j} + \frac{(a_8-k_{65})}{k_{56}}\left(-\sum_{j=3}^{6} A_{6j}\right)\right]\frac{(k_{65}-a_7)}{(a_8-a_7)} \quad \text{(Eq. A23)}$$

$$A_{58} = -\sum_{j=3}^{7} A_{5j} \quad \text{(Eq. A24)}$$

$$A_{6j} = \frac{A_{5j}k_{56}}{k_{65}-a_j} \qquad j = 3,4,\ldots 8 \quad \text{(Eq. A25)}$$

For a general model composed of $n$ individual two-compartment open-model units, as seen in Scheme IV, the solutions of eigen values




*Scheme IV—General model composed of* n *individual two-compartment open-model units*

and eigen vectors may be generalized as follows. Where:

$i = 1, 3, 5 \ldots$ $\quad i + 1$ = peripheral compartment
$i$ = central compartment $\quad k_{io} + k_{i(i+2)} = k_{el}$

the general solution of the eigen values would therefore be:

$$a_{j-1} = \frac{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)}) + \sqrt{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)})^2 - 4\,(k_{io} + k_{i(i+2)})\,k_{pc}}}{2} \quad \text{(Eq. A26)}$$

$$a_j = \frac{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)}) - \sqrt{(k_{cp} + k_{pc} + k_{io} + k_{i(i+2)})^2 - 4\,(k_{io} + k_{i(i+2)})\,k_{pc}}}{2} \quad \text{(Eq. A27)}$$

Where $j = 3, 4, 5 \ldots i + 3$, the general solution of the eigen vector $A_{ij}$ for the $i$th central compartment is:

$$A_{ij} = \frac{A_{(i-2)j}\,k_{(i-2)i}\,(k_{pc} - a_j)}{(a_j - k_{cp} - k_{el})\,(a_j - k_{pc}) - k_{cp}k_{pc}} \qquad j = 3,4,5 \cdots j - 2 \quad \text{(Eq. 28)}$$

$$A_{i(j-1)} = \left[ -\sum_{j=3}^{j-2} A_{ij} + \frac{(a_{i+3} - k_{pc})}{k_{cp}} \left( -\sum_{j=3}^{j-2} A_{(i+1)j} \right) \right] \times \frac{(k_{pc} - a_{i+2})}{(a_{i+3} - a_{i+2})} \qquad j = i + 2 \quad \text{(Eq. A29)}$$

$$A_{ij} = -\sum_{j=3}^{j-1} A_{ij} \qquad j = i + 3 \quad \text{(Eq. A30)}$$

Therefore, the general solution of the eigen vectors, $A_{ij}$, for the $_{i+1}$th peripheral compartment is:

$$A_{(i+1)j} = \frac{A_{ij}\,K_{cp}}{k_{pc} - a_j} \qquad j = 3, 4, 5 \cdots i + 3 \quad \text{(Eq. A31)}$$

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# Solubility of Alkyl Benzoates I: Effect of Some Alkyl *p*-Hydroxybenzoates (Parabens) on the Solubility of Benzyl *p*-Hydroxybenzoate


**F. SHIHAB, W. SHEFFIELD, J. SPROWLS, and J. NEMATOLLAHI**



**Abstract** □ The solubility features of a homologous series of alkyl *p*-hydroxybenzoates (parabens) with alkyl groups, in an ascending order from methyl to *n*-butyl, were investigated together with benzyl paraben and methyl *p*-methoxybenzoate. A phenomenon of mutual solubilizing potential was observed to exist when the solubility of a mixture of an alkyl paraben and benzyl paraben in 60% polyethylene glycol 400–water was examined. The analysis was carried out by means of UV spectrophotometry and NMR spectroscopy. The scope of application of these esters for their antimicrobial properties, for which they are primarily employed in pharmaceutical sciences, is envisaged to be augmented by considering factors influencing solubility.



**Keyphrases** □ Parabens—mutual solubilizing potential □ Polyethylene glycol–water system—paraben solubility □ UV spectrophotometry—analysis □ NMR spectroscopy—analysis


A gross solubilizing effect of alkyl *p*-hydroxybenzoates (parabens) on benzyl paraben in polyethylene glycol 400–water (designated as PEG–$H_2O$) mixture was first observed by Sprowls (1). Owing to the interest of pharmaceutical scientists in the physicochemical properties of parabens (2–4), which are employed both as medicinal