ion. Ions at 77 and 91 amu represent the phenyl and benzyl groups, respectively.

## REFERENCES


(1) R. E. McMahon, A. S. Ridolfo, H. W. Culp, R. L. Wolen, and F. J. Marshall, *Toxicol. Appl. Pharmacol.*, **19**, 427(1971).

(2) R. E. McMahon, H. R. Sullivan, S. L. Due, and F. J. Marshall, *Life Sci.*, **12**, 463(1973).

(3) R. L. Wolen, C. M. Gruber, Jr., G. F. Kiplinger, and N. E. Scholz, *Toxicol. Appl. Pharmacol.*, **19**, 480(1971).

(4) *Ibid.*, **19**, 493(1971).

(5) R. L. Wolen, C. M. Gruber, Jr., A. Baptisti, Jr., and N. E. Scholz, *Toxicol. Appl. Pharmacol.*, **19**, 498(1971).

(6) R. L. Wolen, C. M. Gruber, Jr., and A. Baptisti, Jr., *ibid.*, **19**, 504(1971).

(7) F. S. Tennant, Jr., Report of Committee on Problems of Drug Dependence, National Academy of Sciences, Chapel Hill, N.C., 1973.

(8) F. S. Tennant, Jr., *J. Amer. Med. Ass.*, **226**, 1012(1973).

(9) R. L. Wolen and C. M. Gruber, Jr., *Anal. Chem.*, **40**, 1243(1968).


## ACKNOWLEDGMENTS AND ADDRESSES


Received June 7, 1974, from *Eli Lilly and Company, Indianapolis, IN 46206*

Accepted for publication September 11, 1974.

Mr. R. N. Booher and Mr. W. W. Turner, Chemical Research, Lilly Laboratories, synthesized the norpropoxyphene citrate and cyclic dinorpropoxyphene perchlorate. Plasma samples for this study were supplied by Dr. Forest S. Tennant, Jr., University of California at Los Angeles. The authors also thank Mr. W. E. Legan for his analysis of the plasma samples.



[x] To whom inquiries should be directed.


# Intersubject Variation in Absorption of Digoxin in Normal Volunteers


**DAVID H. HUFFMAN [*x], CARL V. MANION [‡§], and DANIEL L. AZARNOFF [‡]**



**Abstract** □ The absorption of oral digoxin preparations was evaluated following single-dose administration of 0.5 mg of digoxin to 16 normal volunteers in a randomized crossover design. Absorption was estimated using the cumulative excretion of digoxin in urine for 7 days and the area under the 24-hr serum digoxin concentration curve (*AUC*). Significant intersubject variability was observed with both parameters, but this variability was greater for the *AUC*. After intravenous administration, the 7-day digoxin excretion was 68% of the dose. The elixir and a rapid dissolution tablet were significantly better absorbed (84.5 and 77.8%, respectively) than was a slow dissolution tablet (66.7%), as reflected by the fraction of the amount excreted in the urine following intravenous administration of the same dose. There was a highly significant correlation between the cumulative digoxin excretion in urine during the first 2 days compared to 7 days ($r = +0.972$, $p < 0.001$). Bioavailability of oral digoxin preparations can be reliably determined by comparison of the cumulative 2-day excretion of digoxin following a single dose.



**Keyphrases** □ Digoxin oral preparations—bioavailability in humans, intersubject variations □ Bioavailability of digoxin oral preparations—estimated using cumulative excretion in urine and area under serum concentration curve, intersubject variations □ Absorption of digoxin oral preparations—intersubject variations


The bioavailability of oral digoxin preparations has been studied using various protocols. Clinically important differences in bioavailability have been demonstrated among tablet preparations (1–5). Single-dose studies (1, 4–6) and steady-state studies (7) have used the peak serum concentration, the area under the serum concentration *versus* time curve (*AUC*), and the cumulative excretion of digoxin in the urine to estimate the absorption of oral digoxin preparations. Since there has been no complete agreement on the standard method for estimating digoxin bioavailability, and because a larger study was needed to determine the degree of intersubject variability, the bioavailability of digoxin from three oral preparations relative to an equivalent intravenous dose was determined in 16 normal volunteers in a randomized crossover design.

## EXPERIMENTAL

Sixteen healthy hospital employees, 10 females and six males (ages 21–33), volunteered for the study. Written consent was obtained after discussing with each subject the inconveniences and hazards reasonably to be expected. All subjects had normal history and physical examinations and no evidence of cardiac, hepatic, renal, or GI disease.

After an overnight fast, 0.5 mg of digoxin was administered to each volunteer on four occasions, each 2 weeks apart. This interval allowed for the essentially complete elimination of digoxin given in the previous study. The following dosage forms were administered to each volunteer in a random sequence:

1. Two 0.25-mg digoxin tablets (I)[1,2]
2. Two 0.25-mg digoxin tablets (II)[3]
3. Ten milliliters (0.05 mg/ml) of a digoxin elixir (III)[4]
4. Two milliliters (0.25 mg/ml) of parenteral digoxin (IV)[5]

The dissolution rates of the tablets were determined by the method described by Lindenbaum *et al.* (8).

The digoxin tablets and elixir were given orally with 200 ml of water. The parenteral solution was administered intravenously over 5 min. Regardless of the route of administration, the subjects

[1] Lanoxin, Lot 474-G, Burroughs Wellcome.

[2] The dissolution of the tablets of the two Lanoxin lots resulted in 85% digoxin dissolved in 1 hr for the 474-G tablet and 65% for the 991-F tablet (R. Cresswell, personal communication). These tablets were taken from regular production runs.

[3] Lanoxin, Lot 991-F, Burroughs Wellcome.

[4] Lanoxin, Lot 816-G, Burroughs Wellcome.

[5] Lanoxin, Lot 062-F, Burroughs Wellcome.

**Table I**—Cumulative Excretion of Digoxin in Urine ($\mu$g/7 days)

| Subject | I[a] | II[b] | III[c] | IV[d] |
|---|---|---|---|---|
| 1 | 209.6 | 179.3 | 226.8 | 260.4 |
| 2 | 339.9 | 275.3 | 218.7 | 327.3 |
| 3 | 285.1 | 257.0 | 350.0 | 250.2 |
| 4 | 292.2 | 242.1 | 300.0 | 351.8 |
| 5 | 245.5 | 240.4 | 274.2 | 370.1 |
| 6 | 225.8 | 168.7 | 274.1 | 367.2 |
| 7 | 256.7 | 204.3 | 300.3 | 336.5 |
| 8 | 177.3 | 225.3 | 286.6 | 297.2 |
| 9 | 325.3 | 214.2 | 321.9 | 377.2 |
| 10 | 183.7 | 281.2 | 260.7 | 311.2 |
| 11 | 314.2 | 305.5 | 291.5 | 317.2 |
| 12 | 241.6 | 242.1 | 227.4 | 240.1 |
| 13 | 297.4 | 204.1 | 264.9 | 365.2 |
| 14 | 230.3 | 148.5 | 146.3 | 307.0 |
| 15 | 242.6 | 129.6 | 319.9 | 303.8 |
| 16 | 220.1 | 214.5 | 272.6 | 367.2 |
| Mean | 255.5 | 218.9 | 277.2 | 328.1 |
| *SE* | 12.3 | 11.1 | 12.0 | 10.1 |
| *SD* | 47.5 | 45.9 | 46.7 | 39.0 |
| Percent of IV | 77.8 | 66.7 | 84.5 | 100.0 |

**Analysis of Variance (Cumulative Excretion)**

| Source of Variation | *df* | Sum of Squares | Mean of Squares | *F* Ratio | *p* |
|---|---|---|---|---|---|
| Between individuals | 15 | 65712 | 4381 | 3.90 | $p < 0.01$ |
| Between formulations | 3 | 97012 | 32337 | 28.79 | $p < 0.005$ |
| Between periods | 3 | 17490 | 5830 | 5.19 | $p < 0.01$ |
| Error | 42 | 47177 | 1123 | — | — |
| Total | 63 | 227391 | — | — | — |

**Multiple Range Analysis: Test for Digoxin Excretion**

| Drug | I | II | III | IV |
|---|---|---|---|---|
| Cumulative excretion | 255.5 | 218.9 | 377.2 | 328.1 |

IV *versus* III, $p < 0.005$
IV *versus* I, $p < 0.005$
IV *versus* II, $p < 0.005$
III *versus* I, $p > 0.05$, NS[e]
III *versus* II, $p < 0.005$
I *versus* II, $p < 0.05$

**Multiple Range Analysis: Test for Periods**

| Period | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Cumulative excretion | 272.6 | 252.2 | 296.1 | 260.7 |

1 *versus* 2, $p > 0.05$, NS
1 *versus* 3, $p > 0.05$, NS
1 *versus* 4, $p > 0.05$, NS
2 *versus* 3, $p < 0.05$
2 *versus* 4, $p > 0.05$, NS
3 *versus* 4, $p < 0.05$

[a] Lanoxin tablet, Lot 474-G, Burroughs Wellcome. [b] Lanoxin tablet, Lot 991-F, Burroughs Wellcome. [c] Lanoxin elixir, Lot 816-G, Burroughs Wellcome. [d] Lanoxin parenteral, Lot 062-F, Burroughs Wellcome. [e] NS = not significant.

remained upright and ambulatory and were not allowed to eat for 4 hr following drug administration.

Blood for serum digoxin concentration was obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 7, 10, and 24 hr. Serum was separated and frozen at −18° until assayed. All urine excreted during the study was collected as follows: blank, 0–6, 6–12, and 12–24 hr and daily for the next 6 days.

The serum digoxin concentration was estimated by the radioimmunoassay of Smith *et al.* (9). Digoxin concentration in the urine was assayed by adding 10–50 $\mu$l of urine to blank serum. The radioimmunoassay procedure was the same as for the serum, and the concentration of digoxin in the urine was determined on the basis of the aliquot that produced values in the linear portion of the standard curve prepared in serum (5). Internal standards were used as a means of monitoring the accuracy and reproducibility of the digoxin determinations. The interassay coefficient of variation was 3.2%.

Statistical significance was determined by a two-way analysis of variance (ANOVA). When there were significant differences among the four groups by ANOVA, differences between the individual groups were determined by Duncan's multiple range test (10, 11).

## RESULTS

The 7-day cumulative excretion of digoxin in the urine of the volunteers following each dosage form is given in Table I. The variability for these 16 subjects depended upon the dosage form. The coefficient of variation for the intravenous dose was 11.9%. This value is less than the coefficient of variation for the three oral dosage forms: 16.8, 18.6, and 21% for III, I, and II, respectively. This variation correlated with the percent absorbed, as reflected by the fraction of the amount excreted in urine following intravenous administration of the same dose from the three oral dosage forms, *i.e.*, the smaller the fraction absorbed, the greater the variability.

The elixir (III) was absorbed best with a mean value of 84.5%. Of the two tablets, I was 77.8% absorbed whereas II was only 66.7% absorbed. Although the mean absorption of I was less than the elixir, this difference was not statistically significant. The excretion of digoxin in the urine was significantly less for all three oral dosage forms than for the same dose given intravenously ($p < 0.005$). Sixty-six percent of the intravenous dose of digoxin was excreted during the 7-day collection period. In addition to significant differences among the various dosage forms, there were also interindividual differences (Table I).

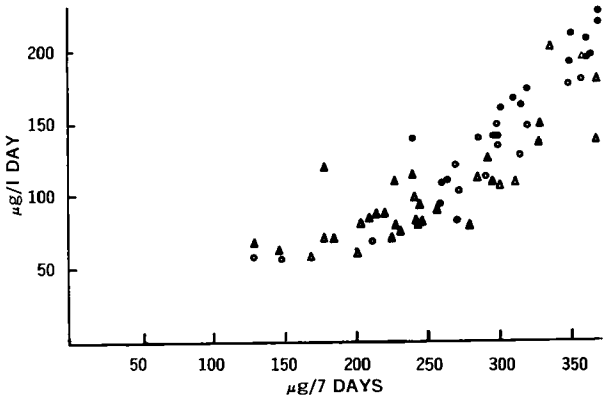


**Figure 1**—*Correlation between the digoxin excretion during the 1st day and the cumulative excretion of digoxin. Each value represents a separate study. Key:* ●, *intravenous;* ○, *elixir;* △, *Tablet I; and* ▲, *Tablet II* ($r = +0.84$, $p < 0.01$).

Greenblatt *et al.* (5) found a highly significant correlation between the excretion of digoxin in the urine during the 1st day following a single 0.75-mg dose and the cumulative 6-day digoxin excretion. They suggested that urine collection for 1 day was sufficient for most digoxin bioavailability studies. A significant correlation ($r = 0.84$, Fig. 1) was also found between the 1- and 7-day cumulative digoxin excretion, but the correlation ($r = 0.972$, Fig. 2) between the 2- and 7-day excretion in the urine was much better.

The mean serum digoxin concentration *versus* time following the administration of 0.5 mg of each dosage form is given in Fig. 3. The better absorbed oral preparations, I and III, had higher peak serum concentrations than II. Thereafter, the serum digoxin concentrations declined in a similar manner for the four studies. The *AUC* for the first 24 hr following drug administration was determined by the trapezoidal rule (Table II). Compared to the *AUC* for the intravenous dose, the elixir was 88% absorbed. Both tablets were significantly less well absorbed than the elixir.

Two differences were apparent between the cumulative urine excretion and the *AUC*. There was no significant difference in bioavailability between the two tablets using the *AUC*, whereas there was a significant difference between these tablets using the cumulative excretion of digoxin in the urine. Based on the *AUC*, Tablet I was significantly less well absorbed than the elixir. This finding was in contrast with the urine data in which a significant difference between Tablet I and the elixir was not demonstrated.

Two volunteers (Nos. 3 and 16) had unusual results for the *AUC* when compared to their cumulative excretion of digoxin in the urine. Unlike all other volunteers, their *AUC* was less for the intravenous dosage form than for the three oral dosage forms. The reason for this finding is unexplained. The *AUC* data were reanalyzed utilizing the mean of the 14 other volunteers for the two spurious values (Table III). Although the absorption of the oral digoxin preparations based on comparison of the *AUC*'s following intravenous administration of the same dose was now in closer agreement with the urine data, the difference in absorption of the two tablets still was not significant.

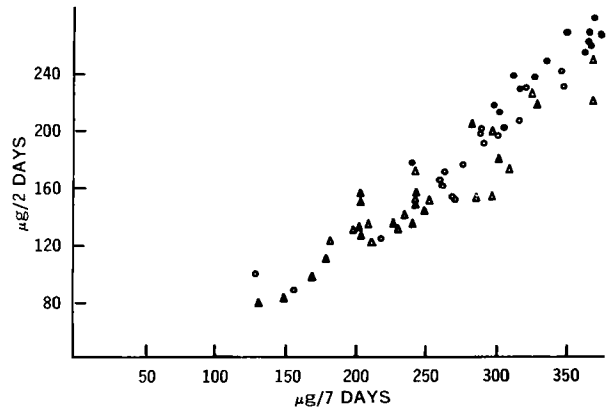


**Figure 2**—*Correlation between the digoxin excretion during the first 2 days and the 7-day cumulative excretion of digoxin. Each value represents a separate study. Key:* ○, *intravenous;* ○, *elixir;* △, *Tablet I; and* ▲, *Tablet II* ($r = +0.972$, $p < 0.001$).

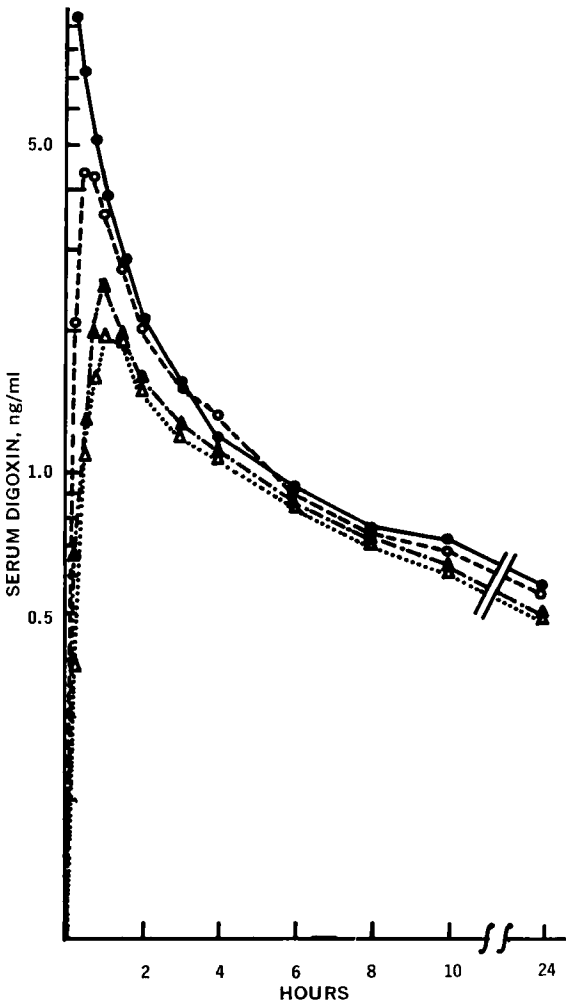


**Figure 3**—*Mean serum digoxin concentration during the first 24 hr following digoxin administration. Key:* ●—●, *intravenous;* ○---○, *elixer;* ▲··▲, *Tablet I; and* △···△, *Tablet II.*

## DISCUSSION

These studies help to define further the variability in the cumulative excretion of digoxin and the *AUC* following a single dose administered to normal volunteers. While the results were similar using the two variables, there were important differences. Based on the cumulative excretion of digoxin in urine, the difference in the absorption of digoxin from the elixir and Tablet I was not statistically significant. Similar findings were demonstrated previously for tablets with rapid dissolution rates (12).

Both the elixir and I were better absorbed than the slow dissolution tablet. Using the *AUC*, however, the absorption of the two tablets was not significantly different despite differences in the peak serum digoxin concentrations. The discrepancy between the urine and serum data is due to a decreased absorption estimate for I using the *AUC* parameter. Since the coefficient of variation for the urine data was 16% as compared with 21% for the serum data, the cumulative excretion of digoxin is the more reliable estimate for determining the bioavailability of orally administered digoxin preparations.

Ideally, all digoxin excreted following the dose should be collected. With the assumption that the pharmacokinetics of digoxin fit a

**Table II**—Area under Concentration *versus* Time Curves (ng × 24 hr/ml)[a]

| Subject | I | II | III | IV |
|---|---|---|---|---|
| 1 | 17.2 | 14.0 | 20.6 | 27.5 |
| 2 | 15.7 | 14.2 | 29.6 | 32.7 |
| 3 | 22.8 | 20.0 | 39.1 | 24.3 |
| 4 | 23.5 | 19.5 | 22.2 | 33.8 |
| 5 | 14.3 | 15.4 | 15.7 | 19.6 |
| 6 | 20.3 | 18.7 | 19.8 | 21.2 |
| 7 | 19.4 | 18.9 | 25.9 | 30.7 |
| 8 | 23.9 | 16.8 | 21.8 | 30.7 |
| 9 | 16.7 | 21.6 | 23.0 | 24.0 |
| 10 | 20.8 | 20.6 | 19.7 | 30.5 |
| 11 | 14.7 | 13.4 | 23.0 | 27.0 |
| 12 | 21.2 | 21.0 | 21.4 | 27.8 |
| 13 | 15.8 | 11.9 | 20.7 | 22.6 |
| 14 | 17.7 | 21.4 | 20.1 | 21.1 |
| 15 | 18.2 | 19.2 | 18.5 | 22.1 |
| 16 | 11.1 | 28.4 | 26.4 | 19.4 |
| Mean | 18.4 | 18.4 | 22.9 | 25.9 |
| *SE* | 0.9 | 1.02 | 1.35 | 1.18 |
| *SD* | 3.5 | 3.96 | 5.25 | 4.58 |
| Percent of IV | 71.0 | 71.0 | 88.0 | 100.0 |

**Analysis of Variance (*AUC*)**

| Source of Variation | *df* | Sum of Squares | Mean of Squares | *F* Ratio | *p* |
|---|---|---|---|---|---|
| Between individuals | 15 | 529.3 | 35.3 | 2.08 | $p < 0.05$ |
| Between formulations | 3 | 601.4 | 200.5 | 11.82 | $p < 0.001$ |
| Between periods | 3 | 88.4 | 29.5 | 1.73 | $p > 0.05$, NS[b] |
| Error | 42 | 712.5 | 16.9 | — | — |
| Total | 63 | 1931.6 | — | — | — |

**Multiple Range Analysis**

| Drug | I | II | III | IV |
|---|---|---|---|---|
| *AUC* | 18.3 | 19.1 | 23.0 | 25.9 |

IV *versus* III, $p > 0.05$, NS
IV *versus* I, $p < 0.005$
IV *versus* II, $p < 0.005$
III *versus* I, $p < 0.05$
III *versus* II, $p < 0.05$
I *versus* II, $p > 0.05$, NS

[a] The area under the serum concentration *versus* time curve (*AUC*) was determined by the trapezoidal rule for the first 24 hr after drug administration. [b] NS = not significant.

**Table III**—Area under Serum Digoxin Concentration *versus* Time Curves Corrected for Subjects 3 and 16 (ng × 24 hr/ml)[a]

| Drug | I | II | III | IV |
|---|---|---|---|---|
| Mean | 18.5 | 17.6 | 21.6 | 26.5 |
| Percent of IV | 69.8 | 66.4 | 81.5 | 100.0 |

**Analysis of Variance**

| Source of Variation | *df* | Sum of Squares | Mean of Squares | *F* Ratio | *p* |
|---|---|---|---|---|---|
| Between subjects | 15 | 310.0 | 20.67 | 2.309 | $p < 0.05$ |
| Between formulations | 3 | 767.1 | 255.7 | 28.562 | $p < 0.001$ |
| Between periods | 3 | 11.5 | 3.83 | 0.428 | $p > 0.05$, NS[b] |
| Error | 42 | 376.0 | 8.95 | — | — |
| Total | 63 | 1464.00 | — | — | — |

**Multiple Range Analysis**

IV *versus* III, $p < 0.005$
IV *versus* I, $p < 0.001$
IV *versus* II, $p < 0.001$
III *versus* I, $p < 0.05$
III *versus* II, $p < 0.05$
I *versus* II, $p > 0.05$, NS

[a] The area under the concentration *versus* time curve (*AUC*) was determined by the trapezoidal rule for the first 24 hr after drug administration. [b] NS = not significant.

two-compartment open model, urine was collected for 4.2 half-lives and accounted for over 95% of the total drug eliminated. Since there was a highly significant correlation between the excretion of digoxin for the first 2 days and the 7-day cumulative excretion, a 2-day urine collection appears to be satisfactory. It is suggested that urine be collected for a minimum of 2 or preferably 3 days following the administration of digoxin. The longer collection period will be particularly important when evaluating the bioavailability of digoxin from tablets with slow absorption. In this manner, the 748 serum and 448 urine digoxin assays necessary to complete this four-way crossover study can be reduced to a mere 64.

Although bioavailability studies have not been performed in pa-

tients who are receiving digoxin, steady-state studies in normal volunteers (7) correlate with the single-dose studies, suggesting that either protocol may be used.

The dose of digoxin appears to be important with regard to its absorption. Greenblatt *et al.* (12) used a single dose of 0.75 mg and found that the absolute bioavailability relative to an intravenous infusion of digoxin was 65% for the elixir and 55% for a digoxin tablet. Both of these values are considerably lower than the findings in this study. They administered the intravenous digoxin by a 1-hr infusion and found a slightly higher percent of the intravenous dose of digoxin in the urine, which may explain these differences.

Recent studies by Greenblatt *et al.* (13) indicate that the cumulative excretion of digoxin in the urine is 7% greater following a 1-hr intravenous infusion of digoxin when compared to an intravenous injection over 3 min. This finding accounts for the difference between the 66% cumulative excretion of digoxin following the intravenous dose in this study as compared with 76% in their study (12). When this difference is considered, however, there still remains an unexplained 13% difference in the bioavailability of digoxin in the two studies. Steady-state studies suggest that the bioavailability of oral digoxin may be dose dependent (7). The differences between this study and the earlier one (5) support this possibility. Therefore, a standard dose of digoxin should be chosen for future digoxin bioavailability studies.

## REFERENCES


(1) J. Lindenbaum, M. H. Mellow, M. O. Blackstone, and V. P. Butler, Jr., *N. Engl. J. Med.*, **285**, 1344(1971).

(2) V. Manninen, J. Melin, and G. Hartel, *Lancet*, **2**, 934(1971).

(3) T. R. D. Shaw, M. R. Howard, and J. Hamer, *ibid.*, **2**, 303(1971).

(4) J. G. Wagner, M. Christensen, E. Sakmar, D. Blair, J. P. Yates, P. W. Willis, III, A. J. Sedman, and R. G. Stol, *J. Amer. Med. Ass.*, **224**, 199(1973).

(5) D. J. Greenblatt, D. W. Duhme, J. Koch-Weser, and T. W. Smith, *N. Engl. J. Med.*, **289**, 651(1973).

(6) D. H. Huffman and D. L. Azarnoff, *J. Amer. Med. Ass.*, **222**, 957(1972).

(7) D. H. Huffman, C. V. Manion, and D. L. Azarnoff, *Clin. Pharmacol. Ther.*, **16**, 310(1974).

(8) J. Lindenbaum, V. P. Butler, Jr., J. E. Murphy, and R. M. Cresswell, *Lancet*, **1**, 1215(1973).

(9) T. W. Smith, V. P. Butler, Jr., and E. Haber, *N. Engl. J. Med.*, **281**, 1212(1969).

(10) D. B. Duncan, *Biometrics*, **11**, 1(1955).

(11) H. L. Harter, *ibid.*, **16**, 671(1960).

(12) D. J. Greenblatt, D. W. Duhme, J. Koch-Weser, and T. W. Smith, *Clin. Res.*, **22**, 318(1974).

(13) D. J. Greenblatt, D. W. Duhme, J. Koch-Weser, and T. W. Smith, *Clin. Pharmacol. Ther.*, **15**, 510(1974).


## ACKNOWLEDGMENTS AND ADDRESSES


Received May 6, 1974, from the **Medical Service, Veterans Administration Hospital, Kansas City, MO 64128,* and the *‡Clinical Pharmacology and Toxicology Center, Departments of Medicine and Pharmacology, University of Kansas Medical Center, Kansas City, KS 66103*

Accepted for publication September 26, 1974.

Supported in part by grants from the U.S. Public Health Service (GM 15956) and Burroughs Wellcome.

§ Postdoctoral trainee in clinical pharmacology (GM 01342).



ˣ To whom inquiries should be directed.


# Alcoholysis of Medicinally Active 5-Aminodibenzo[*a,d*]cycloheptenes


**J. NALLY, J. NAZARENO, J. POLESUK, and H. V. MAULDING ˣ**



**Abstract** □ The rate constants for alcoholic solvolysis of the hydrochloride salts of diethylaminodibenzo[*a,d*]cycloheptene and related amino congeners were determined. The objective was a study of the comparative ease of cleavage of the C—N amino linkage by various aliphatic alcohols. The interaction of protonated amines of this series with alcoholic hydroxyls presumably leads to formation of the corresponding ethers in a manner somewhat analogous to alkoxide reaction with alkyl bromides. The methyl ether produced from solvolysis of diethylaminodibenzocycloheptene hydrochloride was isolated and identified. Methanol appears to react somewhat more rapidly with the amine hydrochlorides than other aliphatic alcohols. The latter produce almost invariant velocity constants with a given amine hydrochloride. The exception was *tert*-butanol, which resulted in $k_{obs}$ values about one-third of those given by the other alcohols. Some velocity constants in formic and acetic acids were evaluated. Generation of carbonium ions of appreciable lifetime was indicated in formic acid by the formation of a highly colored (red-violet) solution. This color may be a manifestation of the dibenzotropylium ion.



**Keyphrases** □ 5-Aminodibenzo[*a,d*]cycloheptenes—alcoholic solvolysis, rate constants □ Solvolysis, alcoholic—medicinally active 5-aminodibenzo[*a,d*]cycloheptenes, rate constants □ Alcohols—solvolysis of hydrochloride salts of diethylaminodibenzo[*a,d*]cycloheptene and related amino congeners, rate constants


Protonated members of the 5-aminodibenzo[*a,d*]-cycloheptane series (I) were found to be relatively unstable in aqueous solution, with rupture of the C—N linkage being the pertinent reaction (1). Insertion of a double bond between positions 10 and 11 of the cycloheptane moiety produced 5-aminodibenzo[*a,d*]cycloheptenes (II) and led to a nearly two-magnitude enhancement of the hydrolytic velocity constant. Velocity increases in each series were dependent upon the amino substituent at C-5. The rate constants for hydrolysis of these 5-amino compounds (I and II) were invariant with pH (where pH < pKa), being only a function of the nature of the various protonated amines and the specified temperature (1).