

**Table I—Dissolution Values for Chlorpromazine Hydrochloride Tablets**

| T Value <sup>a</sup> | USP XVIII Method | Modified USP XVIII Method |
|----------------------|------------------|---------------------------|
| T <sub>10%</sub>     | 4.5 ± 1.3        | 6.7 ± 2.2                 |
| T <sub>40%</sub>     | 12.5 ± 4.4       | 20.5 ± 2.3                |
| T <sub>60%</sub>     | 23.4 ± 7.6       | 39.3 ± 1.8                |
| T <sub>80%</sub>     | 35.8 ± 10.3      | 60.6 ± 2.7                |

<sup>a</sup> Each T value (min.) is the mean of 10 determinations ± SD.

proximately 9 min. when a 10-mesh basket was used. Furthermore, variable results were not obtained when other brands of chlorpromazine hydrochloride tablets were tested or, if observed, the degree of variability was much less than that shown in Table I. This would appear to indicate that the inherent characteristics of the tablets tested led, in part, to the type of variability reported here.

The "correct" dissolution conditions are always difficult to establish, particularly in the absence of *in vivo* data. It is important, therefore, to standardize a procedure carefully in order to evaluate accurately various lots of the same drug product. From the results reported here, it appears that the time at which the rotation of the basket is commenced is important and that any variation from a standardized approach may yield variable results.

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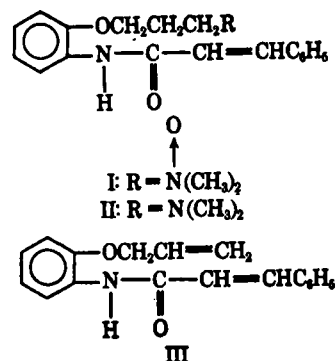
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## Identification of 2'-[3-(Dimethylamino)propoxy]cinnamanilide *N'*-Oxide by Mass Spectral Thermolysis

**Keyphrases** □ 2'-[3-(Dimethylamino)propoxy]cinnamanilide *N'*-oxide—identified using mass spectral thermolysis □ *N*-Oxides—identification of 2'-[3-(dimethylamino)propoxy]cinnamanilide *N'*-oxide using mass spectral thermolysis □ Mass spectral thermolysis—identification, *N'*-oxide of 2'-[3-(dimethylamino)propoxy]cinnamanilide

Sir:

The occurrence of *N*-oxides as natural products or as metabolites of pharmacologically active compounds



was reviewed previously (1). The only mass spectral studies of *N*-oxides have been those of aromatic *N*-oxides that usually exhibit the  $M^+ - 16$  ion, instead of the  $M^+$ , as the highest mass ion (2). Mass spectrometry was used to elucidate the structures of some thiopropyl-dimethylamino-*N*-oxide metabolites (3). In this report, these observations are extended to the thermolysis of 2'-[3-(dimethylamino)propoxy]cinnamanilide *N'*-oxide (I).

Since volatilization of the *N*-oxide base, I (mol. wt. 340), occurs very near its thermolysis point, the spectra obtained at temperatures below 150° were extremely weak and would not normally suffice to establish the structure of metabolites in the presence of the usual artifacts. Generally, the similarity in the mass spectra<sup>1</sup> of *N*-oxides and of free amines would make it difficult to assign structures to *N*-oxide metabolites. However, variation of the ion-source temperature does permit differentiation of amines and their *N*-oxides. At 155° or higher, I showed no  $M^+$ , and the  $M^+ - 16$  ion, though still present, was diminished in intensity relative to the  $m/e$  279 ion (Table I). The composition of the  $m/e$  279 ( $M^+ - 61$ ) ion corresponds to the olefin, III, formed by the Cope elimination of an *N*-oxide (5).

The *N*-oxide hydrochloride, I-HCl, shows the  $M^+ - 16$  ion, the  $m/e$  58 ion, and a temperature-dependent ion at  $m/e$  279. At 185°, fragment ions of I-HCl are present at  $M^+ - 18$  and  $M^+ - 30$  (the former being a dehydration product) but are absent at higher temperatures. At temperatures >185°, the  $m/e$  279 ion is more intense. However, the persistence of the  $M^+ - 16$  ion, coupled with the increase in intensity of the  $m/e$  58 ion, demonstrates that the thermolysis of I-HCl yields more II (mol. wt. 324) than does the thermolysis of I.

Differential thermal and thermal gravimetric analyses<sup>2</sup> also show the difference in the thermolysis of the hydrochloride and the free base of the *N*-oxide. The hydrochloride, I-HCl, melts in two exothermal steps at 186 and 191°, with a total loss of 7% of its weight. Since the loss of oxygen requires a weight loss of 4.3%, and the Cope elimination product requires a weight loss of 12%, the intermediate value for weight loss demonstrates that a mixed-product thermolysis can occur and substantiates the mass spectral results, which show that various thermolytic products were formed. But the free base of the *N*-oxide, I, showed an endotherm at

<sup>1</sup> The equipment and experimental technique for obtaining the electron-impact spectra were described in Reference 4.

<sup>2</sup> Performed on a Dupont analyzer.

Table I—Relative Intensities of Diagnostic Fragment Ions of I, II, and III

| Source Temperature <sup>a</sup> | Type <sup>b</sup> of Spectrum | Intensity Relative to the <i>m/e</i> 131 Ion (1.0) |                   |                   |       |                   |      |
|---------------------------------|-------------------------------|--|-------------------|-------------------|-------|-------------------|------|
|                                 |                               | 58   | 279               | 310               | 322   | 324               | 340  |
| <b>Compound I</b>               |                               |  |                   |                   |       |                   |      |
| 141°                            | E.I.                          | 3.6 <sup>c</sup>                                   | 0.49              | 0.05              | 0.07  | 0.10              | 0.03 |
| 145°                            | E.I.                          | 1.9 <sup>c</sup>                                   | 0.45              | 0.03              | 0.05  | 0.09              | 0.02 |
| 147°                            | E.I.                          | 1.0 <sup>c</sup>                                   | 0.22              | 0.01              | 0.02  | 0.04              | 0.0  |
| 152°                            | E.I.                          | 0.35   | 0.20              | 0.01              | 0.001 | 0.007             | 0.0  |
| 155° <sup>d</sup>               | E.I.                          | 0.25   | 0.21              | 0.005             | 0.0   | 0.02              | 0.0  |
| 160° <sup>d</sup>               | E.I.                          | 0.26   | 0.22              | 0.003             | 0.004 | 0.03              | 0.0  |
| 150°                            | C.I.                          | —  | 0.49 <sup>e</sup> | 0.03 <sup>e</sup> | 0.0   | 0.34 <sup>e</sup> | 0.0  |
| <b>Compound I-HCl</b>           |                               |  |                   |                   |       |                   |      |
| 185°                            | E.I.                          | 1.7  | 0.007             | 0.015             | 0.03  | 0.08              | 0.0  |
| 205°                            | E.I.                          | 1.5  | 0.11              | 0.0               | 0.0   | 0.05              | 0.0  |
| 235°                            | E.I.                          | 1.7  | 0.08              | 0.0               | 0.0   | 0.04              | 0.0  |
| <b>Compound II-HCl</b>          |                               |  |                   |                   |       |                   |      |
|                                 | E.I.                          | 7.7  | 0.02              | 0.0               | 0.0   | 0.27 <sup>f</sup> | —    |
|                                 | C.I.                          | —  | 0.0               | 0.0               | 0.0   | 8.8 <sup>e</sup>  | —    |
| <b>Compound III</b>             |                               |  |                   |                   |       |                   |      |
|                                 | E.I.                          | 0.05   | 0.15              | —                 | —     | —                 | —    |

<sup>a</sup> Room temperature (25°) plus increase in source temperature. <sup>b</sup> E.I. = electron impact (70 e.v.); C.I. = chemical ionization (isobutane). <sup>c</sup> Intensity includes acetone impurity. <sup>d</sup> Very volatile at this temperature. <sup>e</sup> Chemical ionization protonated ion 1 a.m.u. greater mass than mass indicated. <sup>f</sup> Molecular ion of the free base.

159° and a loss of 17.3% of its weight, results that agree extremely well with the loss of 18.2% corresponding to the elimination of dimethylhydroxylamine (mol. wt. 61) from I to form III (Cope elimination). Thus, it is advisable to study the mass spectra of the free base of the *N*-oxide rather than those of the hydrochloride salt.

The use of chemical ionization<sup>3</sup> with thermolysis provides a further means of distinguishing between the amine and the *N*-oxide of thiopropyl dimethylamino derivatives. In this series, the *m/e* 279 ion is completely absent in the chemical ionization spectrum of the oxypropyl dimethylamine, II, whereas the protonated molecular ion (MH<sup>+</sup>) of the thermolysis product (III) appears in the spectrum of I, along with the MH<sup>+</sup> of the thermolysis product, II, at *m/e* 325.

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