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Degradation Mechanisms for Water-Soluble Drugs in Solid Dosage Forms

J. THURØ CARSTENSEN,* MODEST OSADCA, and S. H. RUBIN

Abstract □ Thiamine hydrochloride, when tableted with magnesium stearate and microcrystalline cellulose, degrades in a pattern whereby an apparent equilibrium is reached. The amount of intact thiamine at equilibrium depends on the amount of moisture present and exhibits a minimum at about 5.5 percent moisture content. A model is proposed to explain this phenomenon. Thiamine dissolved in the water present adsorbs on the microcrystalline cellulose and the thiamine present in the monolayer degrades totally, whereas the thiamine in layers beyond the monolayer does not degrade.

Keyphrases □ Solid dosage forms—water-soluble drug degradation □ Degradation, drug—solid dosage forms □ Thiamine degradation, tablets—moisture effect □ Model—thiamine degradation, tablets □ Mechanism—thiamine degradation, solid dosage forms

The manner in which drugs degrade in solid dosage forms is still rather obscure. Systematic investigations in this field have been made with pure drug by Leeson and Mattocks (1), Kornblum and Sciarrone (2, 3), Reinstein and Higuchi (4), and Garrett (5). Two phenomena seem to prevail in degradation of pure crystals: (*a*) the degradation is mostly zero order (2–5) although, at higher temperatures, three phases (induction period, acceleration period, and decay period) occur; (*b*) degradation is hypothetically confined to a liquid layer on the crystal (1, 4). Leeson and Mattocks (1) demonstrated that, in the presence of moisture in the vapor phase, the degradation of acetylsalicylic acid crystals took place in the sorbed moisture layer.

Publications dealing with degradation patterns in solid dosage forms are more plentiful, although by no means common. Tardif (6) and Carstensen *et al.* (7–9) have described the logarithmic decay patterns (*i.e.*, apparent first-order degradations) of vitamins in solid dosage forms, the effect of moisture, and the existence of equilibria and have pointed out that such data are amenable to Arrhenius (or Van't Hoff)-type treatment. These type investigations are of practical interest, in the sense that treatment is facilitated for those investigators primarily interested in product stability. The fact that many of these patterns are first-order types seems, however, to imply that phenomena other than those prevalent in degradation of the pure crystals are the determining factors. For, if the solid dosage form was to be considered a dry, noninteracting system, then zero-order patterns should prevail. If, on the other hand, sorbed moisture layers, saturated with drug, were the media of decomposition, then (drawing an analogy with a very concentrated "suspension") the degradation should also be a zero-order type.

The fundamental question then, is, what actual physical phenomena, aside from the purely chemical reaction, are involved? This has not been the subject of published reports in the case of solid dosage forms, and it is the intent of this study to examine whether some of the principles established for pure, solid drugs, by some model, might apply to solid dosage forms as well. In this type endeavor it is, of course, important to select a simple system, since, the more components are present, the more difficult the task of assigning effects to one particular species or interaction. For this reason, microcrystalline cellulose[1] was selected as the tablet base for the study.

The properties and uses of microcrystalline cellulose in tablet formulations have been described by Reier and Shangraw (10), Richman *et al.* (11), and Enezian (12), and the use of microcrystalline cellulose as a direct compression excipient is by now common practice in the pharmaceutical industry. The important feature here is that it is possible to prepare tablets consisting of only drug, the microcrystalline cellulose, a disintegrant, and a lubricant.

[1] Marketed as Avicel by the American Viscose Corp., Marcus Hook, Pa.

Microcrystalline cellulose has been the subject of previous publications with regard to both physical and chemical stability. Lee *et al.* (13) described the types of moisture adsorption (single layer *versus* multilayer) experienced with (*a*) ascorbic acid and (*b*) aspirin, tableted in matrices of microcrystalline cellulose. An interesting trend may be noted in their results in that aspirin exhibited minimal stability in the matrix when exposed to 45% relative humidity at 50°, *i.e.*, both higher and lower relative humidities at 50° gave rise to less decomposition. Of the formulas tested, the formula containing microcrystalline cellulose showed about the poorest stability at 45% relative humidity, but it exhibited better stability than the other formulas at 100% relative humidity.

Since, under pharmaceutical storage conditions, some moisture is always present, the conditions employed by Leeson and Mattocks (1) would be quite realistic. If, indeed, sorbed moisture layers, saturated with drug, are also the key to the mode of degradation in solid dosage forms, then it would be advantageous to select a water-soluble drug; for this reason, thiamine hydrochloride was chosen as test substance. The degradation mentioned in the following refers to the hydrolytic cleavage of the thiamine hydrochloride at the methylene group.

EXPERIMENTAL

Thiamine hydrochloride (5.5–6 mg.) was compressed into 300-mg. tablets with microcrystalline cellulose (291.5–291 mg.) and magnesium stearate (3 mg.). One batch of tablets, however, was made with a magnesium stearate content of only 1.5 mg./tablet. The tablets were stored at 25° in a desiccator containing water, and tablets were removed at various intervals and checked for (*a*) increase in weight and (*b*) moisture content. The tablets and a non-humidified control were placed in ampuls, flooded with nitrogen, sealed, and stored at 55°. Samples were then removed periodically and assayed for thiamine content by the USP method.

To check duplicability, thiamine hydrochloride tablets were removed from the desiccator after a weight gain of about 1%. A second set of tablets was removed after a weight gain of about 3%. A different batch of tablets of the identical composition and containing the same lots of raw materials was placed in the desiccator and the procedure repeated. Both duplicate sets were ampuled and stored at 55° as described above. Since the microcrystalline cellulose was used without prior drying, it contained some moisture, so that the unexposed tablets contained 2.7% moisture (by assay).

Other sets of tablets were removed from the desiccator at higher weight gains. Beyond 12% moisture the tablets lose their structure, and this moisture content, therefore, constitutes an upper limit of experimentation.

The tablets containing 1.5 mg. magnesium stearate were equilibrated at 9.5% moisture and compared with a set of tablets described above, which had approximately the same moisture content.

Slurries were made by dissolving 2.6 g. of thiamine hydrochloride in water, adding 139 g. of microcrystalline cellulose, 1.4 g. of magnesium stearate, and 1,000 ml. of water in a blender (Waring). After vigorous blending, the suspension was subdivided into bottles, which were then rotated in a constant-temperature water bath at 55°. Samples were removed periodically and assayed for thiamine.

The number of nitrogen molecules constituting a monolayer on the sample of microcrystalline cellulose used was determined by means of a sorptometer.[2] All moisture assays were performed by loss on drying *in vacuo* at 105°.

[2] Perkin-Elmer, Sorptometer 212D, manufactured by Perkin-Elmer Corp., Norway, Conn. 06852. The authors are indebted to Mr. Allan B. Larson for carrying out the surface area determination.

Table I—Stability of Thiamine in a Slurry of Microcrystalline Cellulose and Magnesium Stearate

	Thiamine Content, % w/w
Initial	0.235
1 day at 55°C.	0.240
2 days at 55°C.	0.235
5 days at 55°C.	0.235
7 days at 55°C.	0.215

RESULTS

Results from degradation studies of slurries of microcrystalline cellulose and magnesium stearate in an aqueous solution of thiamine hydrochloride at 55° are shown in Table I. As seen, the losses are negligible, especially in light of the results listed in Table II.

Thiamine and moisture contents of tablets from the two duplicate sets of tablets are shown in Table II and depicted graphically in Fig. 1. As will be discussed further, the thiamine content tapers off, and the value at which this occurs will be referred to in the following as the equilibrium content.

Equilibrium thiamine and initial moisture contents of tablets containing larger amounts of moisture are shown in Table III. Data from Table II are repeated in this table to facilitate the ensuing discussion.

The number of nitrogen molecules constituting a monolayer on 292 mg. of microcrystalline cellulose was found by the B.E.T. measurements to be 8.8×10^{18}.

Tablets containing 1.5 mg. magnesium stearate and 9.5% moisture and originally assaying 5.52 mg. thiamine per tablet exhibited an equilibrium content of 2.56 mg. of thiamine, and by comparison with the fifth column of Table III, it would appear that, at the levels used, the amount of magnesium stearate does not significantly affect the results.

DISCUSSION

It is apparent from Fig. 1 that the thiamine curve approaches an equilibrium level. If the logarithm of the amount of intact thiamine (A) is plotted as a function of time, a straight line does not result. However, if an equilibrium content (A_∞) of thiamine is estimated, then $\log [A - A_\infty] = -k \cdot t$, where t stands for time, yields a linear relationship, as shown in Table II, and in Figs. 2 and 3. The asymptote (A_∞), as mentioned earlier, will denote the equilibrium content of thiamine in the following. That this is not a true equilibrium is obvious from the fact that thiamine solutions (Table I) in contact with microcrystalline cellulose show much better stability than the solid dosage form.

The data from Lines 2 and 7 of Table III are shown graphically in Fig. 4; the graph shows a point of maximum instability between 4 and 5.5% moisture content.

It may be worthwhile to compare the system used in this study with the water vapor-acetylsalicylic acid system utilized by Leeson and Mattocks (1). Acetylsalicylic acid is only slightly water-soluble, and the authors demonstrated that the sorbed moisture on the acetylsalicylic acid crystals will behave like a saturated solution, which accounts wholly for the degradation. A similar situation might exist in a heterogeneous system such as the dosage form used here. If moisture were adsorbed by thiamine and microcrystalline cellulose both, then, at a certain moisture level there would be sufficient water to dissolve all the thiamine. Below this moisture level the two systems may be identical, but beyond it, the situation must be one in which a thiamine solution is adsorbed on the microcrystalline cellulose. At 55°, less than 1 g. of water is required to dissolve 1 g. of thiamine hydrochloride; therefore, when the percentage of water in the tablet is above 5%, deviation from the Leeson-Mattocks model may be expected. Thiamine hydrochloride was intentionally chosen so that this situation could be studied, since it would throw light on some aspects of the mode of degradation of drugs in solid dosage forms.

In the case of acetylsalicylic acid the sorbed layer behaved like a saturated bulk solution of the compound. In the case of thiamine tableted in microcrystalline cellulose, this viewpoint fails, because it would dictate the conclusion that thiamine reaches an equi-

Table II—Stability of Thiamine Hydrochloride in a Matrix of Microcrystalline Cellulose at Various Moisture Contents

Batch No.[a]	Days at 55°C.	% Moisture	mg. Thiamine per Tablet (A)	1 + log $[A - A_\infty]$	% Moisture	mg. Thiamine per Tablet (A)	1 + log $[A - A_\infty]$
1	0	3.91	5.64	1.375	5.49	5.50	1.556
1	0.33	4.73	5.45	1.338	5.69	5.15	1.512
1	0.67	4.30	5.29	1.305	5.03	4.50	1.415
1	1	4.33	5.22	1.290	5.78	3.42	1.182
1	1.33	4.40	5.00	1.238	5.80	2.89	0.996
1	1.67	4.28	4.68	1.149	5.78	2.86	0.982
1	2	4.01	4.81	1.188	5.65	2.57	0.826
2	1	4.10	5.02	1.243	5.35	3.90	1.301
2	2	—	4.38	1.045	—	2.52	0.792
2	3	—	4.24	0.986	—	2.24	0.532
2	4	—	4.14	0.940	—	2.24	0.532
2	5	—	3.71	0.644	—	2.24	0.532
2	6	—	3.62	0.544	—	2.07	0.230
2	7	—	3.48	0.323	—	1.94	0.602–1
2	10	3.90	3.27	—	5.50	1.90	—

[a] For differences in batches, see under *Experimental.*

Table III—Initial and Equilibrium Thiamine and Moisture Contents of Thiamine Hydrochloride Tablets (300 mg. Weight) in a Matrix of Microcrystalline Cellulose

Initial content thiamine, mg./tablet	5.64	5.50	5.60	5.60	5.70	6.20
Equilibrium thiamine content, mg./tablet	3.27	1.90	2.30	2.40	2.63	3.20
Percent thiamine retained at equilibrium	58	35	41	43	46	52
Amount of thiamine degraded, mg./tablet	2.37	3.60	3.30	3.20	3.07	3.00
Equilibrium content (C_T = molecules/tablet $\times 10^{-18}$)	5.82	3.38	4.09	4.27	4.69	5.69
Amount degraded (C_D = molecules/tablet $\times 10^{-18}$)	4.21	6.40	5.87	5.69	5.46	5.34
Percent Moisture (= number of molecules $\times 10^{-20}$)	4.0	5.5	7.5	7.8	9.8	11.4
$\frac{C_T}{C_D} - \frac{C_T}{n}$ $n = 10^{19}$		0.19	0.29	0.32	0.39	0.50
$n = 2 \cdot 10^{19}$		0.36	0.50	0.54	0.63	0.79
$n = 10^{20}$		0.49	0.66	0.71	0.81	1.01
		±0.02	±0.02	±0.02	±0.03	±0.03
$\frac{C_D^2}{C_T C_{H_2O}} 10^3$	8	22	11	10	7	4

librium with its degradation products, whereas the trend with increasing moisture content contradicts this view. If it is assumed that one molecule of thiamine reacts with one molecule of water to form two molecules of degradation product, and if C_T denotes the number of molecules of thiamine per tablet at equilibrium, C_D, the number of molecules of degradation product per tablet at equilibrium, and C_{H_2O} the number of molecules of water per tablet, then the ratio $(C_D^2)/C_T \cdot C_{H_2O}$ should be constant. In-

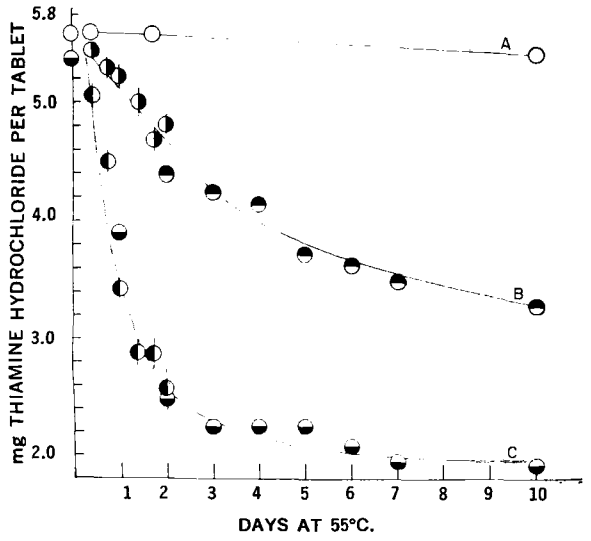

Figure 1—*Stability of thiamine hydrochloride in a cellulose-magnesium stearate tablet containing various amounts of moisture. Thiamine content of tablets of thiamine hydrochloride and microcrystalline cellulose of various moisture contents, at 55°C. storage. Key:* A, *no moisture added;* B, *1% moisture added;* C, *3% moisture added.*

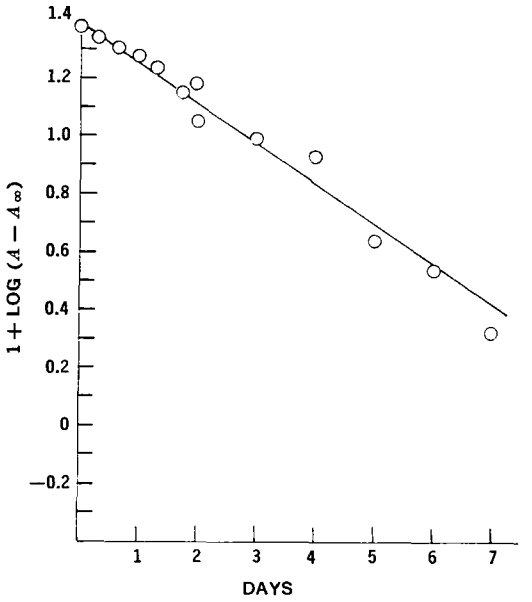

Figure 2—*Logarithm of thiamine content after subtraction of equilibrium content as a function of time (4% moisture). The fifth column of Table II is obtained by subtracting* A_∞ *(3.27 mg.) from all the thiamine contents* (A), *and taking the logarithm of the resulting figures. Log* (A − A_∞) *is then plotted as ordinate, and time (in days) plotted as abscissa.*

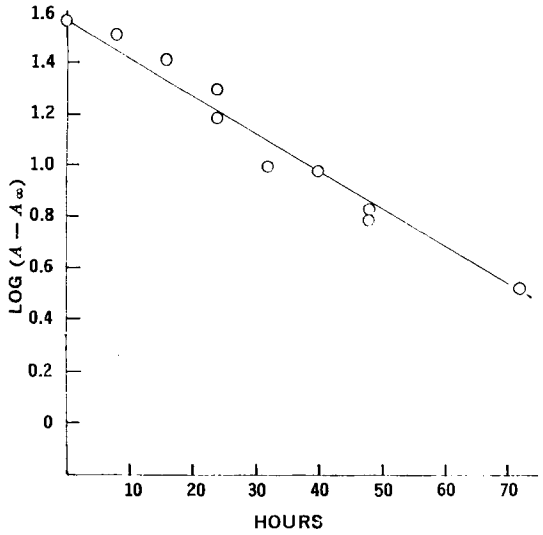

Figure 3—*Logarithm of thiamine content after subtraction of equilibrium content as a function of time (5.5% moisture). The eighth column of Table II is obtained by subtracting A_∞ (1.90 mg.) from all the thiamine contents* (A), *and taking the logarithm of the resulting figures. 1 + log (A − A_∞) is then plotted as ordinate, and time (in hours) plotted as abscissa.*

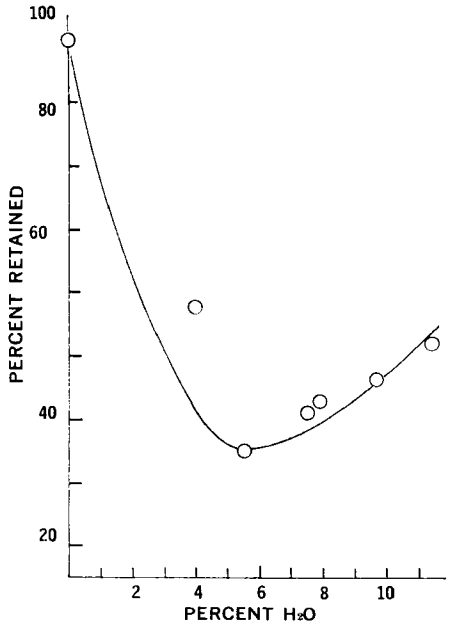

Figure 4—*Data from Table III are plotted as percent thiamine retained at equilibrium as a function of percent moisture in the tablet.*

creasing C_{H_2O} should then cause a decrease in C_T and an increase in C_D, contrary to the experimental data. The point is illustrated in the last line of Table III, and it is seen that the ratio is not constant.

In order to seek a model which would explain the trends in Fig. 4, assume that beyond 5% moisture, all the thiamine is in a dissolved state. Let it be further assumed that (provided a sufficient amount of solution is present to form at least a complete monolayer) all the thiamine in the monolayer decomposes rapidly, whereas the thiamine in the solution beyond the monolayer does not degrade rapidly. With these stipulations, the initial pattern of degradation will resemble an equilibrium, and the equilibrium ratio will be the ratio of adsorbed to nonadsorbed thiamine. There is then a situation of competitive adsorption, since water and thiamine molecules will compete for available sites. The amount of thiamine adsorbed (degraded) relates to the fractional coverage (θ) and the total number of sites (n) by the relationship:

$$C_D = n \cdot \theta$$

The number of molecules of nitrogen constituting a monolayer on 292 mg. of microcrystalline cellulose was found by B.E.T. measurement to be 8.8×10^{18}. The number of sites available to water molecules may be assumed to be larger by a proportion equal to the ratio of molecular cross-sectional areas of nitrogen to water. Under this assumption, n should be of the order of 10^{19}–10^{20} sites. It should be noted that the treatment to follow is not particularly sensitive to the magnitude of n (as shall be demonstrated by example).

In a competitive adsorption:

$$\theta = \frac{C_D}{n} = \frac{\zeta_T C_T}{1 + \zeta_T C_T + \zeta_{H_2O} C_{H_2O}} \qquad \text{(Eq. 1)}$$

The terms ζ are ratios of adsorption to desorption rate constants Equation 1[3] may be rearranged to read:

$$\frac{C_T}{C_D} - \frac{C_T}{n} = \frac{1}{n \cdot \zeta_T} + \frac{\zeta_{H_2O}}{n \cdot \zeta_T} \cdot C_{H_2O} \qquad \text{(Eq. 2)}$$

The parameter on the left-hand side of Eq. 2 is tabulated for $n = 10^{19}$, $n = 2 \cdot 10^{19}$, and $n = 10^{20}$ in Table III, and the three sets of values are plotted against C_{H_2O} in Fig. 5.

It is noted from Fig. 5 that the data exhibit good linearity (regardless of the value of n used). The slopes and intercepts obtained by weighted least-square fits are listed in Table IV. For $n = 10^{20}$ the equation is:

$$\frac{C_T}{C_D} - \frac{C_T}{10^{20}} = 8.7 \cdot 10^{-22} C_{H_2O} + 2 \cdot 10^{-3}$$

The value of the intercept is, of course, not very accurate, and at best it might be stated that it is close to zero. ζ-Values estimated from slope and intercept ($\zeta_T = 5 \cdot 10^{-17}$ and $\zeta_{H_2O} = 8.7 \cdot 10^{-19}$ for $n = 10^{20}$) are subject to a large standard deviation, but inspection of the figures show that, as pointed out in a footnote, $\zeta_T C_T$ and $\zeta_{H_2O} C_{H_2O}$ may well be of the same order of magnitude.

A further observation lends credence to the proposed model. If it is correct, then the maximum degradation should occur at just the point of one monolayer. Maximum instability, judging from

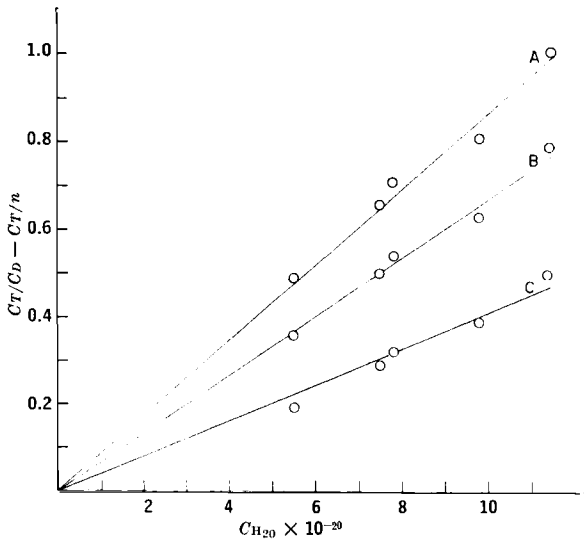

Figure 5—*Equilibrium ratio as a function of water content. A plot of the data in Table III as they apply to Eq. 2. For further detail refer to text. (C_T/C_D) − C_T/n is plotted as ordinate, and C_{H_2O} (number of water molecules per tablet) plotted as abscissa. The value of the intercept is $1/(n \cdot \zeta_T)$ and the slope is the intercept times ζ_{H_2O}. Key:* A, $n = 10^{20}$; B, $n = 2 \cdot 10^{19}$; C, $n = 10^{19}$.

[3] It is customary to assume either $\zeta_T C_T$ to be much larger or much smaller than $\zeta_{H_2O} C_{H_2O}$, in which case the equation may be simplified. This assumption should not be made here, since the two quantities might well be nearly equal.

Table IV—Least-Squares Fits of Data in Fig. 5

n-Estimate	Slope $\times 10^{-22}$	Intercept $\times 10^{3}$
10^{19}	4.1	−4.2
2×10^{19}	6.7	−0.7
10^{20}	8.7	+2.2

Fig. 4, should be about 5% moisture, which is equivalent to 5×10^{19} molecules of water per tablet. This is the same order of magnitude as the number of sites, *i.e.*, the point where exactly one monolayer would be expected. Again, this is not a sensitive comparison, but it demonstrates on a rough scale the fact that the data and the model are compatible.

It is thus seen that the experimental data fit the model, whereas simpler models fail to be consistent with the data. Selecting a water-soluble substance has made possible a study of the contribution to drug degradation of the interaction of the drug in dissolved state with the main excipient. Less water-soluble substances might exhibit the same behavior, but it would be difficult to separate the contribution from the solution sorbed on the excipient from the solution sorbed on the drug. Here one might expect a combination of the model proposed above and the Leeson-Mattocks model.

The specific data presented here, of course, can only be claimed to hold for the thiamine-microcrystalline cellulose system. It appears to hold in the case of lactose-thiamine also, but quantitation of data is difficult in this system. It is believed that the type phenomenon described here is part of the overall mode of degradation in solid-dosage form.

SUMMARY

1. Thiamine, when tableted in a matrix of microcrystalline cellulose, initially will be less stable the more moisture is present. However, a point is reached where this trend reverses, and beyond this moisture content stability is enhanced with increased moisture content.

2. A model is proposed, which is believed to apply to many systems, whereby solutions of the drug are adsorbed on the main excipient and degradation is then confined to the first monolayer of the adsorbed solution.

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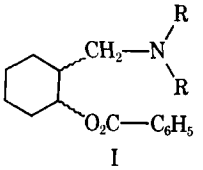
Conformational Aspects of Local Anesthetics

MARVIN R. BOOTS and SHARON G. BOOTS

Abstract □ The syntheses of two epimers of 3-*exo*-(*N*,*N*-dimethylaminomethyl-2-norbornanyl)4-*n*-butoxybenzoate are described. The results of several assays of local anesthetic activity are discussed.

Keyphrases □ Anesthetics, local—conformational aspects □ 3-*exo*-(*N*,*N*-Dimethylaminomethyl-2-norbornanyl)4-*n*-butoxybenzoate epimers—synthesis □ Pharmacological screening—local anesthetics □ UV spectrophotometry—structure □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Evidence in support of the concept of a receptor(s) being involved in blockage of nerve impulses by local anesthetics has been generated in recent years (1, 2). Numerous investigations have attempted to correlate a variety of physicochemical properties of the drug such as lipid solubility (3, 4), pKa′ values (5), electronic (4, 6), and steric factors (7, 8).



I

Mannich and Hong (9) evaluated a series of α-dialkylaminomethylcyclohexyl benzoates (I) and found one isomer (*cis* or *trans*?) to be very active.

This system (I) may exist as *cis-trans* isomers, conformational (axial or equatorial) isomers, and optical