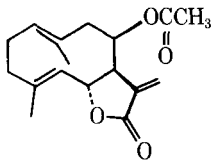

IX

This synthesis was accomplished by epoxidizing II in a two-phase system containing sodium bicarbonate (11). The presence of the latter prevented any cyclization and provided VI as the only product. As expected, VI underwent facile acid-catalyzed cyclization to VII and VIII. Moreover, it could be further epoxidized to III in the presence of excess peracid.

Since the absolute stereochemistry of C-1 in VII is *R* (7), it then followed that C-1 in VI must have the same absolute configuration. Also, the epoxide group of VI, being derived from the *trans*-1,10-double bond of II, must also have a *trans*-geometry. Therefore, the absolute stereochemistry of costunolide 1,10-epoxide should be as depicted in Structure VI. Consequently, III, which could be obtained by further epoxidation of VI, as mentioned before, must have similar chirality at C-1 and C-10.

Dihydrocostunolide was reported (12) to undergo epoxidation with perbenzoic acid to dihydrocostunolide diepoxide. In other words, epoxidation of dihydrocostunolide proceeded without cyclization. This behavior can be explained in terms of the poor acidity of perbenzoic acid and its reduction product, benzoic acid, relative to *m*-chloroperbenzoic acid and *m*-chlorobenzoic acid. However, there may be another explanation. The germacranolide sesquiterpene epitulipinolide (IX) can be epoxidized (1) with *m*-chloroperbenzoic acid to epitulipinolide 1,10-epoxide without cyclization. It appears, therefore, that the conformational factors affecting the transannular system of double bonds must play a significant role in deciding whether facile cyclization is to take place or not.

The root bark of *M. grandiflora* L. yielded, in addition to II, the two eudesmanolides VII and VIII. In view of the above discussion, these compounds must have been derived by the cyclization of biogenetically formed VI.

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Sustained Release from Inert Wax Matrixes I: Drug–Wax Combinations

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Abstract □ The melting and energy characteristics of several drug–wax combinations were investigated using differential scanning calorimetry. The phase diagrams of binary mixtures of tripelennamine hydrochloride and tolazoline hydrochloride with carnauba wax and castor wax showed no eutectic formation and gave no indication that a significant interaction was involved. However, in tripelennamine mixtures, a slight depression in the drug melting point was observed at around 50% concentration. For ternary systems, *i.e.*, drug, carnauba wax, and stearyl alcohol, thermograms of samples prepared by a fusion method differed slightly from those obtained with mixtures formulated by dissolving all ingredients in chloroform and evaporating the solvent. However, the location of the peak of each component remained essentially the same. A plot of melting point *versus* concentration of each compound showed insignificant changes in melting point and indicated that no interaction was occurring. The phase diagrams suggested that the combinations are strictly physical and that it is the physical characteristics, such as the hardness and composition of the core and drug particle size, that influence the release or dissolution of the drug from the waxy matrix.

Keyphrases □ Wax matrixes, inert—release of tripelennamine hydrochloride or tolazoline hydrochloride from mixtures with carnauba wax or castor wax □ Tripelennamine hydrochloride—release from inert carnauba or castor wax matrixes □ Tolazoline hydrochloride—release from inert carnauba or castor wax matrixes □ Dosage forms—inert wax matrixes, release of tripelennamine hydrochloride or tolazoline hydrochloride from mixtures with carnauba or castor wax □ Antihistaminics—tripelennamine hydrochloride, release from inert carnauba or castor wax matrixes □ Vasodilators, peripheral—tolazoline hydrochloride, release from inert carnauba or castor wax matrixes

The major factors influencing drug distribution in a sustained-release matrix (core) and drug release from the core include the particle size and drug solubility as well as core hardness and composition. Generally, the drug is physically incorporated into a wax matrix and compressed.

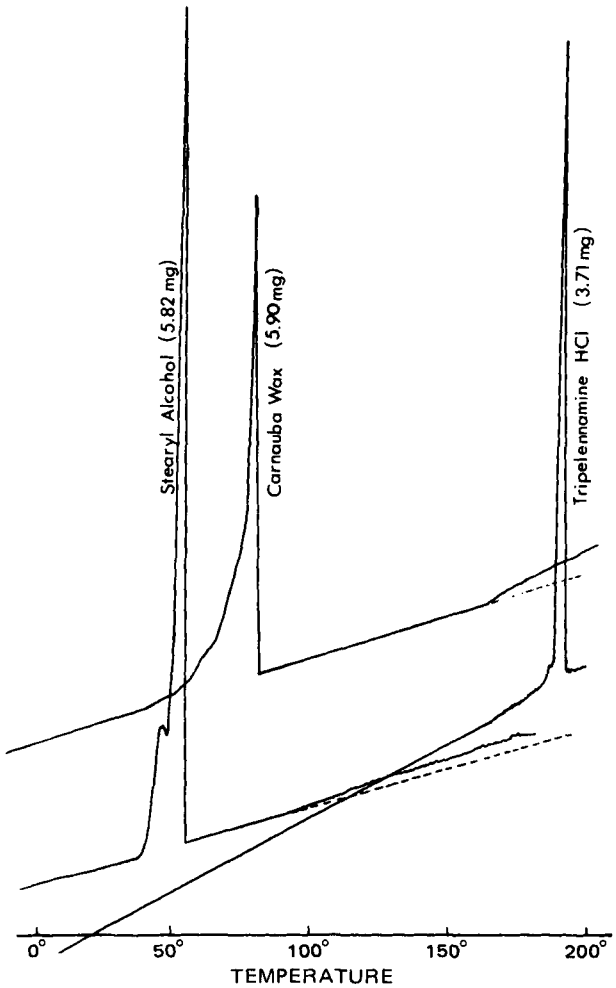

Figure 1—*DSC thermograms of tripelennamine hydrochloride, carnauba wax, and stearyl alcohol.*

BACKGROUND

Phase studies with sulfathiazole–urea combinations revealed that a eutectic mixture is formed (1) and that its physical properties differed significantly from the properties of mixtures at other compositions. The particle size of the drug crystals was smaller, and the increased surface area resulted in faster absorption and higher blood levels. A fused conglomerate of chloramphenicol and urea at the eutectic composition manifested no enhancement in the chloramphenicol dissolution rate as compared with the pure drug (2). However, in the presence of excess urea, a significant increase in drug release was reported.

Other investigators, after raising some theoretical questions concerning the proposed mechanism (2), postulated that the enhanced dissolution rate was attributable to the presence of solid solutions in the system rather than simple eutectic formation (3). This study (3) showed that dissolution rates from fused systems were greater than those from physical mixtures or pure drug. For example, evaluation of the dissolution rates of some griseofulvin–succinic acid samples indicated that the solid solution dissolved six to seven times faster than the pure material (4). Recently, the *in vitro* dissolution of tolbutamide was reported to be considerably increased by fusion with polyethylene glycol 6000 (5); enhanced bioavailability from such samples also was demonstrated (6).

Eutectic transformation, interactions resulting in the formation of monotectic or peritective compounds, formation of solid solution, and, possibly, stoichiometric compounds might be associated with a matrix solid dispersion system such as the drug–wax combination. The properties of a eutectic mixture would be expected to differ from those of a simple physical mixture. If the particle size and solubility of the drug were altered, then the dissolution characteristics and the *in vivo* availability could be influenced. Therefore, an investigation of the matrix-type sustained-release dosage form should commence with some basic phase studies to determine whether a drug–wax interaction occurs and at what composition a eutectic mixture exists.

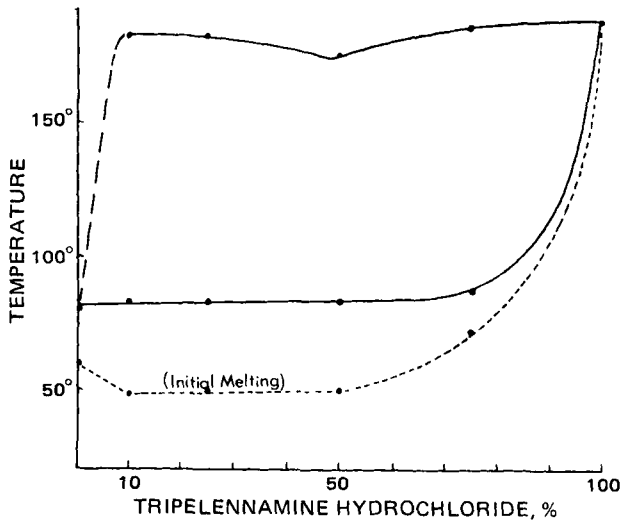

Figure 2—*Phase diagram for tripelennamine–carnauba wax binary system. The upper and lower solid curves correspond to the peak temperatures of the drug and wax, respectively. The broken line represents the temperature at which the initial deviation from the baseline in the thermogram occurred.*

In the present report, differential scanning calorimetry (DSC) was employed to investigate the melting and energy characteristics of various mixtures of drug (tripelennamine and tolazoline) and wax (carnauba wax, castor wax, and stearyl alcohol). A change in the these parameters would be indicative of component interactions. The information might be used to formulate a core with a better control of drug release.

EXPERIMENTAL

Materials[1]—Tripelennamine hydrochloride and tolazoline hydrochloride were used without further purification. Carnauba wax, castor wax, and stearyl alcohol were the wax bases used.

Fused Mixtures—The fused drug–wax binary mixtures were prepared by melting carnauba wax or castor wax to approximately 90°. Tripelennamine hydrochloride or tolazoline hydrochloride, after passing through a 40-mesh screen, was added in small portions while the mass was mixed. With constant stirring, the mixture was allowed to cool slowly to about 75°, and the entire mass was then immediately cast on cold glass plates. Subsequently, the congealed mass was crushed into a finely divided state and screened (40 mesh).

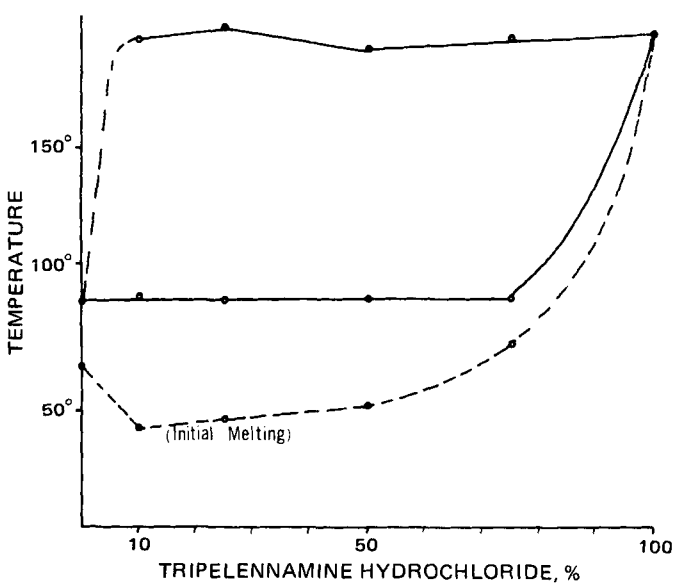

Figure 3—*Phase diagram for tripelennamine–castor wax binary system.*

[1] Supplied by Ciba-Geigy Corp., Summit, N.J.

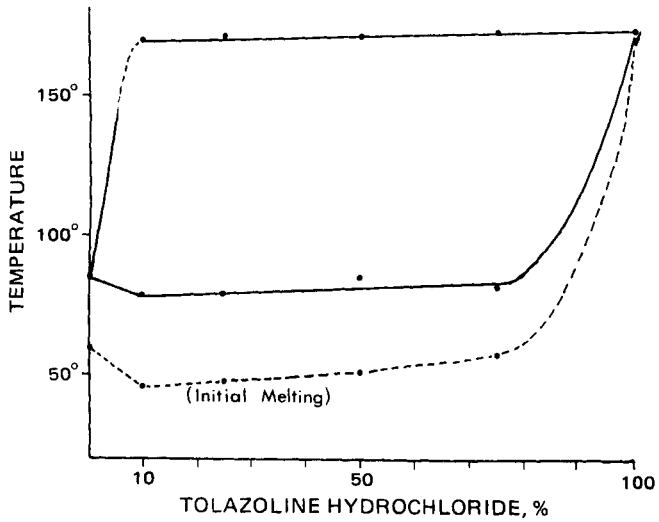

Figure 4—*Phase diagram for tolazoline–carnauba wax binary system.*

For the fused drug–carnauba wax–stearyl alcohol ternary mixtures, carnauba wax was first melted to approximately 90° and stearyl alcohol was then added. When a homogeneous mixture was attained, the drug was added. The mass was allowed to congeal and then powdered, following essentially the same procedure as already outlined.

Evaporated Mixtures—Carnauba wax and stearyl alcohol were dissolved in chloroform. A solution of the drug in the same vehicle was then added to the wax solution. After the system was mixed thoroughly, it was gently heated to evaporate the solvent. Subsequently, the solidified mass was crushed and passed through a 40-mesh screen.

Thermal Analysis—A differential scanning calorimeter[2] was used to determine the energy changes. The samples were placed in aluminum pans and scanned from 0 to 200° at 5°/min. To scan in the 0–40° range, the sample cover was filled with a methanol–dry ice mixture. Nitrogen purge at a rate of 30 ml/min was used constantly. Observed temperature values were corrected by using reference melting-point standards for calibration.

RESULTS AND DISCUSSION

One-Component Systems—The thermal stability of some individual substances was investigated. The DSC thermograms in Fig. 1 indicate that stearyl alcohol (mp 50–52°) and carnauba wax (mp 76–79°) undergo sublimation or degradation at elevated temperatures. Deviation from the baseline occurred at slightly above 100° for stearyl alcohol and at around 160° for carnauba wax. Tripelennamine hydrochloride (mp 188–190°) showed no sign of thermal decomposition in the 0–200° range.

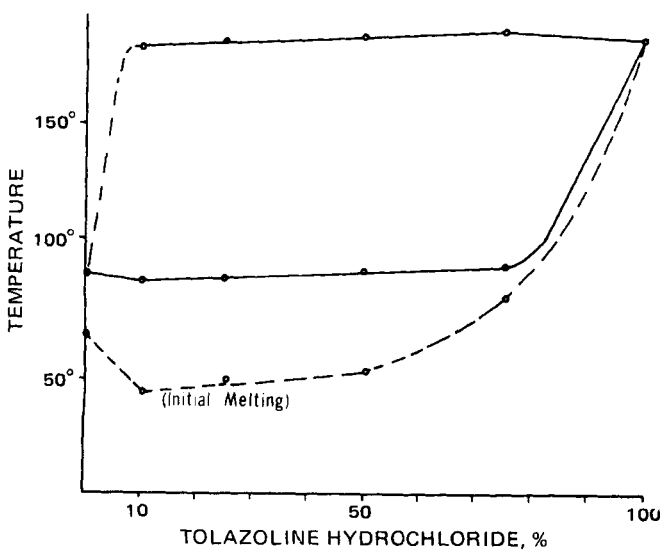

Figure 5—*Phase diagram for tolazoline–castor wax binary system.*

[2] Perkin-Elmer model DSC-1B.

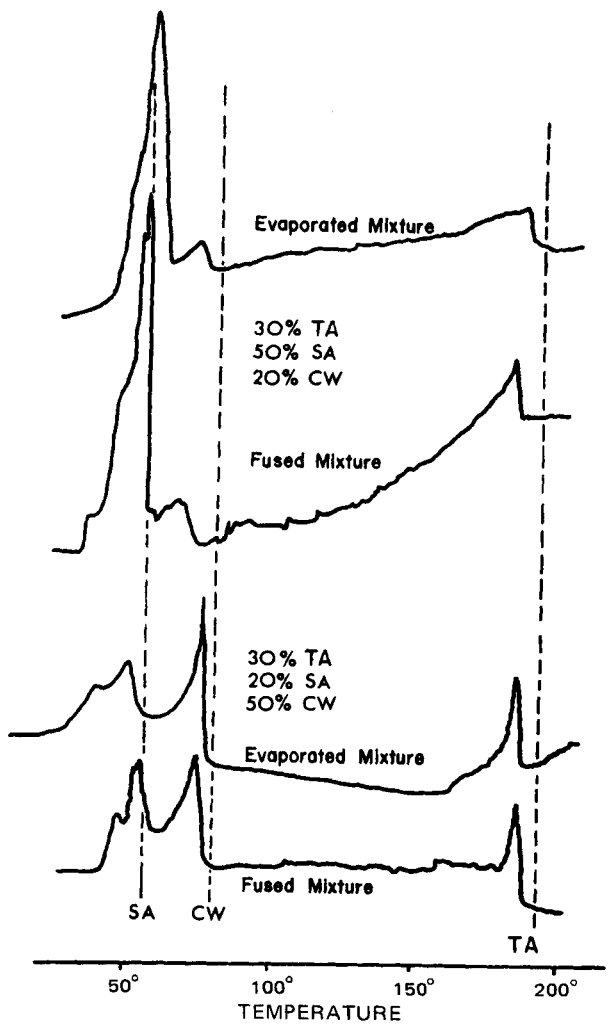

Figure 6—*DSC thermograms for two compositions of tripelennamine–carnauba wax–stearyl alcohol. Samples of each composition were prepared by dispersing tripelennamine in a melt of carnauba wax and stearyl alcohol (fused mixture) and by dissolving all ingredients in chloroform and evaporating the solvent (evaporated mixture). Key: SA, stearyl alcohol; CW, carnauba wax; and TA, tripelennamine hydrochloride.*

The fact that stearyl alcohol and carnauba wax undergo degradation or sublimation at elevated temperatures should be of no consequence since the preparation of the fused mixtures involved heating the components only to approximately 85–90°.

Two-Component Systems—Drug–wax mixtures were prepared at 0, 10, 25, 50, 75, and 100% (w/w) drug concentrations, and samples of these mixtures were heated in the differential scanning calorimeter. The locations of the peaks in each thermogram were plotted against the drug concentration to construct a phase diagram for each system. The tripelennamine–carnauba wax phase diagram is shown in Fig. 2. There was no indication of interaction or eutectic formation at above 10% drug concentration. The slight depression in the melting point of tripelennamine observed in the 50:50 combination is not unusual; it is well known that a slight change in the melting behavior of a substance occurs in the presence of another component.

Figure 3 shows the phase diagram for the tripelennamine–castor wax system. It is quite similar to that obtained for the tripelennamine–carnauba wax mixtures; once again, a slight depression in the melting point for the drug occurred at around 50% drug concentration. However, there was no indication that an interaction or eutectic formation was involved since the melting characteristics of the two components remained essentially unchanged.

For the tolazoline–carnauba wax and tolazoline–castor wax systems, the slight lowering in the melting point of the drug observed in the 50:50

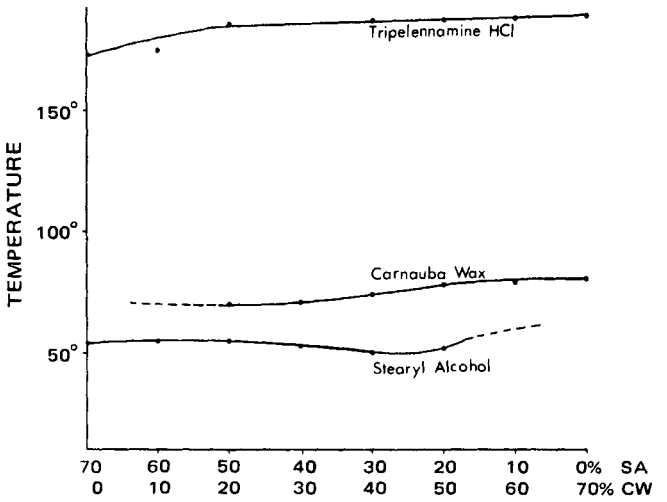

Figure 7—*Plot of the melting point (location of peak in the DSC thermogram) for each material in the tripelennamine–carnauba wax (CW)–stearyl alcohol (SA) system at various compositions. Tripelennamine concentration was kept constant at 30%, and the concentrations of the other two components were varied between 0 and 70%.*

tripelennamine–wax systems was absent. As shown in Figs. 4 and 5, the phase diagrams clearly indicated that an interaction between tolazoline and the waxes was nonexistent, although a slight decrease in the tolazoline melting point occurred as the wax composition increased.

Three-Component Systems—Ternary mixtures of tripelennamine, carnauba wax, and stearyl alcohol were prepared by two different methods to assess the effect of the preparation method on thermal behavior. The evaporated mixtures were selected for investigation to determine if the components would interact if combined in the dissolved state. Compounds that exhibit solid-state interactions frequently demonstrate interaction in solution. This phenomenon was observed with *N*-acetyl-*p*-aminophenol and urea (7) and niacinamide and ascorbic acid (8) and in griseofulvin–succinic acid (4) and chloramphenicol–urea (9) systems.

The concentration of tripelennamine hydrochloride was held constant at 30% (w/w), and the carnauba wax and stearyl alcohol concentrations were varied between 0 and 70%. Samples of the fused and evaporated mixtures were scanned. Thermograms for two compositions are shown in Fig. 6. While the curves for the evaporated samples differed slightly from thermograms of fused samples, the locations of the peak for each component remained essentially the same. From these results, it appears that an interaction between the components of the system does not occur even if they are dispersed at the molecular level.

Figure 7 shows a plot of the melting point *versus* concentration for each component. The slight variation in the melting points of the various components was considered to be insignificant. In addition, no interaction occurred in the three-component system.

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