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REVIEW ARTICLE

Mechanisms of Solid-State Reactions of Drugs

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During the past few years, substantial advances in the knowledge of the chemical and physical factors governing solid-state reactions of molecular crystals have occurred. Surprisingly, little of this knowledge has been applied to the study of the decompositions of drugs and related compounds.

The purposes of this review are to classify and discuss representative solid-state reactions of medicinal agents in terms of this knowledge and to support the idea that a thorough knowledge of the mechanism of solid-state reactions and the effect of crystal structure on solid-state reactions of drugs can suggest rational approaches to drug stabilization. This latter point is particularly important in the pharmaceutical industry, where a knowledge of solid-state chemistry could be used to develop methods of stabilizing drugs and solid dosage forms.

There have been recent reviews of solid-state photochemical (1), thermal (2), and solid–gas (3) reactions of organic compounds and the stability of solids and solid dosage forms (4), but none of these has treated the chemical and mechanistic aspects of solid-state reactions of pharmaceuticals. This review will emphasize the mechanistic and chemical aspects of solid-state reactions of drugs and will, in general, be restricted to solid-state reactions of pure compounds. It is divided into four general sections: (*a*) solid-state photochemical reactions, (*b*) solid-state thermal reactions, (*c*) solid–gas reactions, and (*d*) applications.

Before proceeding, it is important to attempt to define a solid-state reaction. The simplest definition of a solid-state reaction is one that proceeds below the eutectic melting point of the components of the system (2). However, such a definition automatically excludes all reactions that have a liquid as one of their products. For reactions of solids yielding both a solid and a liquid product, the criteria of Morawetz (5) may be more appropriate; *i.e.*, a reaction occurs in the solid state when: (*a*) pronounced differences are found in the reactivities of closely related compounds, (*b*) different reaction products are obtained from those formed when the reaction is carried out in the liquid state, or (*c*) different crystalline modifications of the compound have different reactivities or form different products.

SOLID-STATE PHOTOCHEMICAL REACTIONS

These reactions were reviewed recently (1, 6), and only selected studies related to solid-state reactions of biologically important compounds will be summarized here. Many solid-state photochemical reactions can be explained in terms of the topochemical postulate (1, 6), which states that solid-state reactions proceed with a minimum of atomic and molecular movement. Thus, the stereochemistry of the product depends upon the packing of the reactants in the crystal. The topochemical postulate permits prediction of the stereochemistry of many solid-state cycloaddition reactions including those of quinones, anthracenes,

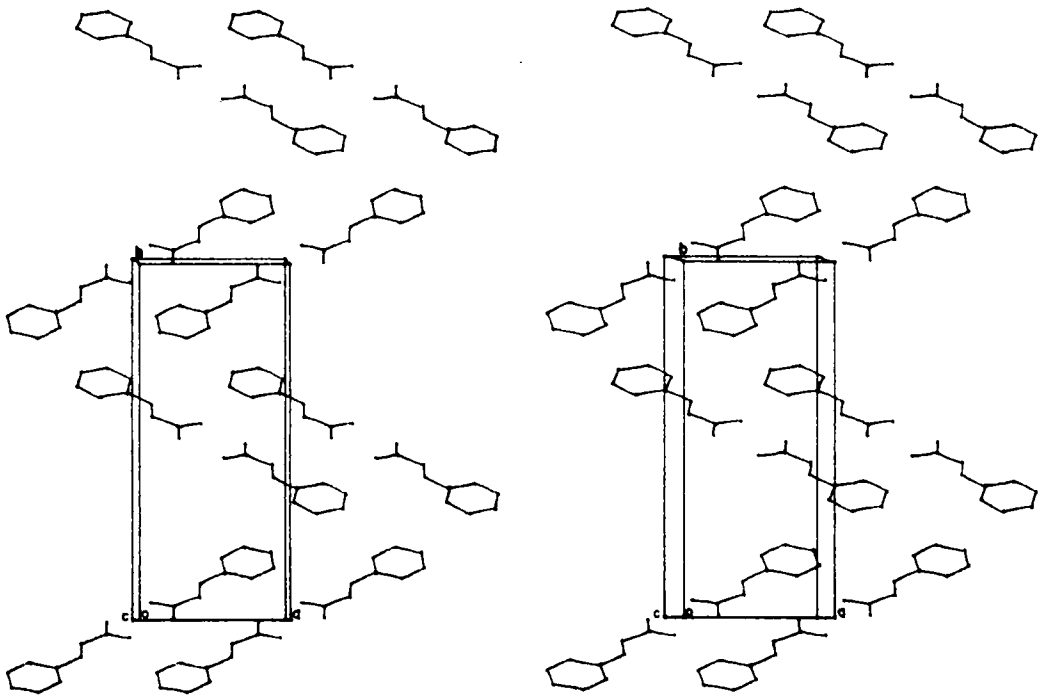


Figure 1—*Stereo pair view of the packing of the α-form of cinnamic acid.*

α,β-unsaturated ketones, chalcones, dienes, and cinnamic acids. The application of the topochemical postulate to these reactions will be illustrated using cinnamic acids.

However, several solid-state photochemical cycloaddition reactions do not obey the topochemical postulate. Careful study of these reactions has shown that they occur at defects, yielding products with stereochemistries different from those predicted from the crystal packing (7). Further discussion of this important topic is beyond the scope of this review.

Photodimerizations of Solid *trans*-Cinnamic Acids—The solid-state photochemistry of the *trans*-cinnamic acids can be generalized as follows. *trans*-Cinnamic acids solidify in three forms (polymorphs), α, β, and γ, which can be distinguished by their crystallographic cell dimensions. The shortest cell dimensions of 38 cinnamic acid polymorphs fall into three ranges: (*a*) >5.1 Å (α-type), (*b*) 3.9 ± 0.2 Å (β-type), and (*c*) 4.9 ± 0.2 Å (γ-type) (1, 6). Upon photolysis, each form yields characteristic cyclobutane products with the symmetries indicated in Table I. These products have been rationalized in terms of the relationship of the monomers in the crystal and the separation between neighboring double bonds.

In α-type crystals (Fig. 1[1]), the double bonds of the monomers are parallel, centrosymmetrically related, and 3.6–4.1 Å apart. The crystal packing of the α-form of cinnamic acid is shown in Fig. 1. The packing of molecules in the α-crystal is quite interesting, since there are pairs of molecules centrosymmetrically related.

In the β-type crystals, *e.g.*, *p*-chlorocinnamic acid (Fig. 2), the double bonds of the monomers are separated by about 4.0 Å and the molecules are arranged in stacks and are related only by translational symmetry. Both *trans*-α-bromocinnamic acid and *trans*-*m*-chlorocinnamic acid belong to the γ-type, with monomers related by translational symmetry but with their double bonds more than 5.1 Å apart. This correlation of the packing geometry and separation of the double bonds with the shortest cell dimension is surprising, since the choice of unit cell is somewhat arbitrary in many of the crystals studied. However, the significance of the correlation is underscored by the specificity of the solid-state photodimerizations.

Topochemical control of these solid-state photochemical reactions is illustrated by the dimerization of the two (α and β) polymorphic forms of *trans*-cinnamic acid whose crystal packing is shown in Figs. 1 and 2. The dimerization reaction is illustrated in Schemes I and II. Upon exposure to sunlight in cellophane-covered petri dishes or Pyrex cylinders, the centrosymmetric α-form (I) gives the centrosymmetric dimer α-truxillic acid (II) (74% yield). The unstable β-form (III) gives pure β-truxillic acid (IV) upon irradiation, provided care is taken to ensure that the photolysis is run below the α to β transition temperature.

It has been suggested that solid-state photodimeri-

Table I—*trans*-Cinnamic Acid Polymorphs and Cyclobutane Products

Crystal Type Packing	Shortest Cell Dimension, Å	Crystallographic Relationship of Monomers	Double Bond Separation, Å	Symmetry of Product
α	>5.1	$\bar{1}$ (centric)	3.6–4.1	$\bar{1}$ (centric)
β	3.9 ± 0.2	Translation	3.9–4.1	m (mirror)
γ	4.9 ± 0.2	Translation	4.2–5.1	No reaction

[1] The author thanks J. Ladell, Phillips Electronic Instruments, for making the atomic coordinates available through Dr. I. C. Paul. Glasses for viewing such drawings can be ordered from Hubbard Scientific Co., P.O. Box 105, Northbrook, Ill.

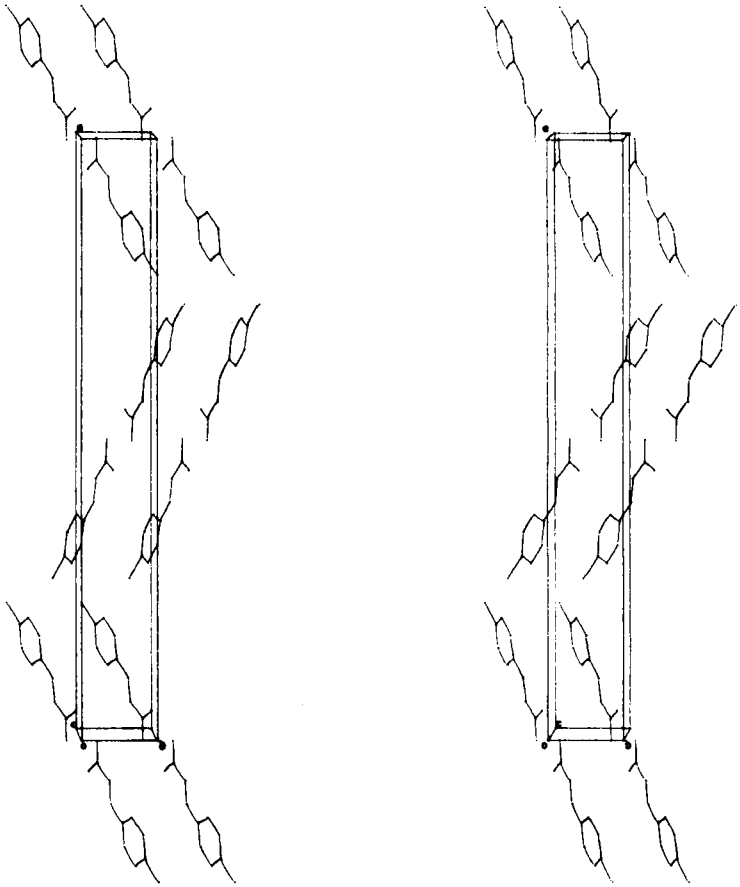


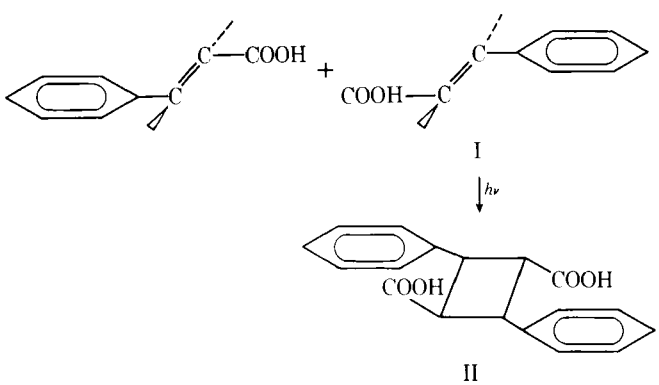
Figure 2—*Stereo pair view of the packing of the β-form of* p-*chlorocinnamic acid (8). This structure is isomorphous with the β-form of cinnamic acid.*

zation usually proceeds from the singlet state (6). This suggestion is based on experiments on solid solutions of cinnamides, for which the products indicate that the dimerization is faster than energy transfer, and on studies of thymine dimerization in frozen solution. However, none of these experiments rules out the possibility that the photodimerization of cinnamic acids proceeds through the triplet state.

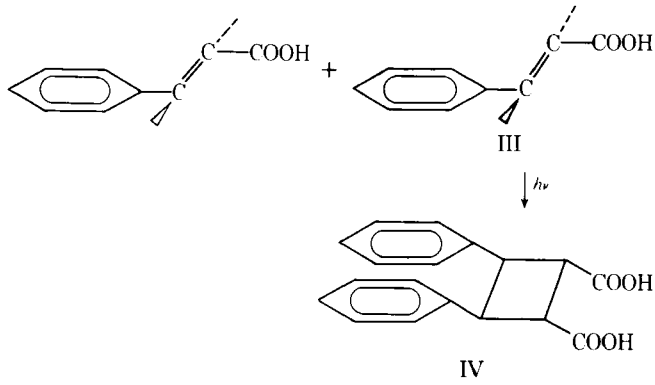
The striking observation that the reacting double bonds of cinnamic acids must be not only within 4 Å but also aligned and parallel for cycloaddition to occur has been made (6). For example, *trans*-methyl *m*-bromocinnamate does not photodimerize over long periods of irradiation. This ester has its double bonds 3.93 Å from each other but nonparallel. (The double bonds are related by a glide plane.)

Recently, the concept of crystal engineering was introduced (6). The introduction of a dichlorophenyl group into unsaturated systems usually causes crystallization in a unit cell of the β-type with a 4-Å axis (Table I). Irradiation of such crystals yields a dimer with mirror symmetry. Thus, crystal engineering involves controlling the course of solid-state reactions by controlling crystal packing with appropriate functional groups.

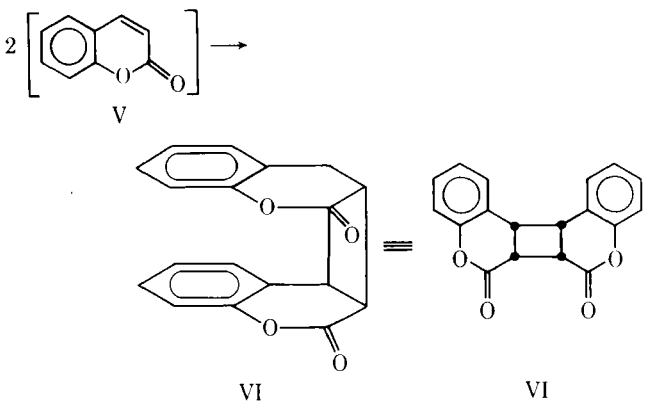
Photodimerizations of Solid *cis*-Cinnamic Acids—The photochemistry of solid *cis*-cinnamic acids is complicated by the possibility of *cis–trans* isomerization (9). Many of the *cis*-acids studied by single-crystal X-ray techniques crystallized with their double bonds within 4 Å of each other and in position to yield *cis*-dimers; however, irradiation



Scheme I



Scheme II



Scheme III

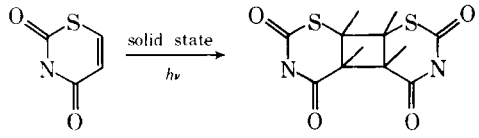
yielded either the *trans*-cinnamic acids or photoproducts derived from *trans*-acids. These products contained microcrystallites of the respective acids. Powder X-ray experiments indicated that the *cis*-acids isomerized to *trans*-acids, which then dimerized to give *trans*-type products (9). For the *trans*-acids that crystallized in several polymorphic forms, dimers expected from all of the polymorphs were often obtained. In contrast, coumarin (V), a *cis*-cinnamic acid derivative pinned in the *cis*-configuration, and the coumarin–mercuric chloride complex, crystallized with the double bonds 4 Å apart and gave upon irradiation the *cis–syn*-dimer (VI), as expected from the topochemical postulate (Scheme III).

Careful study of the solid-state photochemistry of *cis-o*-methoxycinnamic acid showed that mainly *o*-methoxy-α-truxillic acid (a derivative of II) was formed upon irradiation at room temperature while the *trans-o*-methoxycinnamic acid accumulated at low temperatures (between −80 and −180°) but no dimer was formed. Control experiments showed that the dimerization of *trans*-cinnamic acids was not temperature dependent (between 25 and −180°). On the basis of this evidence, the reaction of *cis*-cinnamic acids was explained as follows. Crystals of the *cis*-acid, upon irradiation, are transformed to a solid solution of *trans*-acid (formed by *cis* → *trans* photoisomerization) in the *cis*-host crystal. Then the *trans*-acid crystallizes out of the solid solution and these crystals dimerize to *trans*-products. At low temperatures, the crystallization of *trans*-crystals from the solid solution is slowed or stopped, allowing the *trans*-acid to accumulate.

In conclusion, solid-state photochemical reactions offer distinct synthetic advantages over the corresponding solution reactions since they allow control of the stereochemistry of the product (truxillic acids) and the course of the reaction. For example, *trans*-cinnamic acid yields 98% polymer when irradiated in solution.

Solid-State Photochemical Polymerizations—This area has been widely studied, and this brief discussion will only emphasize that these reactions also appear to obey the topochemical postulate.

Irradiation of crystals of 5-bromo-2-methoxy-*cis*-cinnamic acid yielded a polymer with a structure consistent with the topochemical postulate (10) along with other products. This cinnamic acid did not crys-



Scheme IV

tallize in either the α- or β-type (Table I) but had the double bonds related by both translation and screw-axis symmetry. Polymerization along the screw axis is consistent with the structure of the polymer obtained.

In several cases, topotaxy was observed in solid-state polymerizations. In the polymerization of trioxane (11, 12) induced by ionizing radiation and the photochemical polymerization of crystalline 2,5-distyrylpyrazines and 1,4-bis[β-pyridyl-2-vinyl]-benzene (13–17), chains of the polymer grew in the monomer crystal with the same orientation as the stacks of monomer (topotaxy).

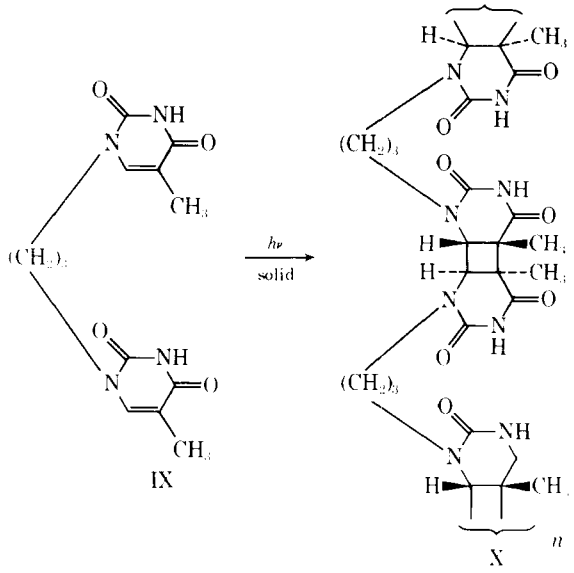
SOLID-STATE PHOTOCHEMICAL REACTIONS OF BIOLOGICALLY IMPORTANT COMPOUNDS

Only unequivocal photochemical reactions are included in this section. The photochemical reactions of crystalline fumagillin, ergocalciferol (vitamin D_2), and vitamin A, which probably involve photochemical solid–gas reactions, are discussed later.

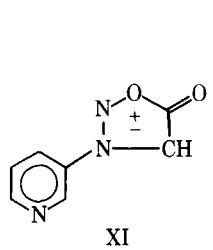
Nucleic Acids—The solution and frozen-state photochemical reactions of nucleotides, nucleosides, purines, and pyrimidines have been extensively reviewed (18–20) and will be briefly discussed here.

The solid-state photochemical reactions of pyrimidines obey the topochemical postulate. For example, irradiation of crystals of the thio analog of uracil (VII) yielded the *cis–syn*-dimer (VIII), as predicted from the crystal packing (21) (Scheme IV). Similarly, the irradiation of crystalline thymine, 1-methylthymine, 3-methylthymine, and 1,3-dimethylthymine gave the topochemically expected product (22, 23).

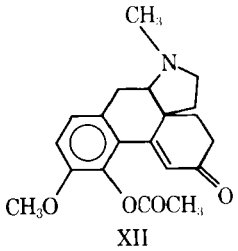
The irradiation of dinucleotides in the solid has not been extensively studied; however, irradiation of



Scheme V



XI



XII

crystals of the dinucleotide analog, trimethylene dithymine (IX), gave polymer X rather than the dimer which might have been expected from a casual glance at the crystal-packing arrangement (24, 25) (Scheme V). Closer examination of the molecular packing of IX shows that the double bonds are not perfectly aligned for intramolecular dimer formation; therefore, polymerization occurs. This observation, along with the observation that perfect double bond alignment is required before cinnamic acid dimerization will occur, indicates a surprisingly rigid requirement for π-bond overlap in these reactions. These observations are consistent with the idea that these reactions occur from the singlet state and are concerted, photochemically allowed [2 + 2] dimerizations.

Although none of these compounds is a medicinal agent, the principles discussed could be used to stabilize nucleic acid analogs that are anticancer agents. The fact that these reactions obey the topochemical postulate is also important in understanding the mechanisms of radiation damage of DNA.

Photochromic and Thermochromic Drugs—Photochromism and thermochromism, in general, involve light-induced or heat-induced color changes. They are not commonly observed phenomena in medicinal chemistry; however some sydnones are photochromic and at least one derivative of morphine has thermochromic properties. *N*-(3-Pyridyl)sydnone (XI) gives colorless crystals which almost instantly turn blue on exposure to sunlight. The blue crystals rapidly become colorless when heated to 80° and bleach more slowly at room temperature (26). The IR spectra of the blue and colorless crystals are identical.

The failure to observe different spectra and structures for the blue and colorless crystals is consistent with studies of the photochromic and thermochromic salicylideneanilines. No crystallographic differences between the colored and colorless forms of these anilines were observed (27, 28). Apparently, the color change in these crystals is due to a small concentration of a highly colored species. Recently, the blue sydnone color was suggested to be due to a small concentration of a charge-transfer complex of unknown structure (29). On the other hand, the photochromic properties of bicyclic ethylenimines were explained in terms of the formation of a structurally distinct, colored, azomethine ylide. These ylides had different IR spectra from the bicyclic ethylenimines (30).

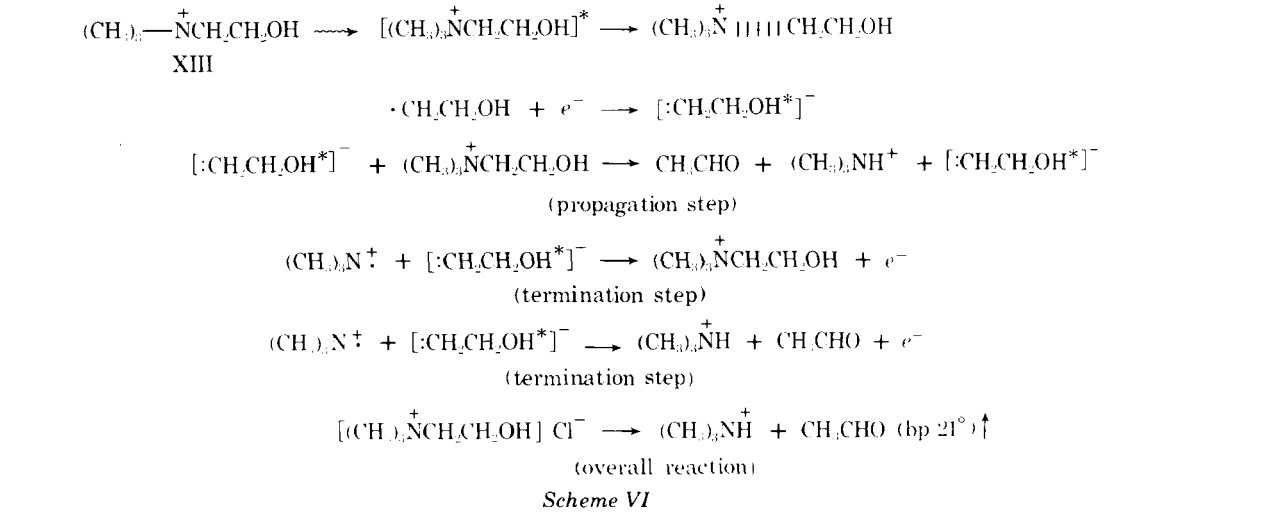
The morphine derivative acetyl metathebainol (XII) is thermochromic in solution and near its melting point (31). A solution of acetyl metathebainol turns pink upon heating, and crystals turn pink at 143° before melting to a red liquid at 150°.

Since both photochromism and thermochromism are usually reversible phenomena, these color changes may cause substantial concern to the unaware observer, even though the drug is not degraded.

Other Biologically Important Molecules—Choline chloride (XIII) is a particularly interesting example of the effect of radiation on crystals of biologically important molecules. Choline chloride crystallizes in a stable α-form and an unstable β-form, which is present at temperatures greater than 78° (5, 32, 33). The α-form is the most ionizing-radiation-sensitive compound known (33). The G factor for radical formation (radicals produced per 100 ev) is about 2, while the G factor for radiolysis (molecules destroyed per 100 ev) is as high as 55,000.

In contrast, the high temperature β-form is not abnormally radiation sensitive. The difference in radiation sensitivity of these polymorphs is probably related to the crystal packing of the two forms. The choline molecules in the crystals of the α-form are apparently in a geometry favoring the propagation step in radiolysis (Scheme VI). This step involves the attack of an excited carbanion on a ground-state choline cation.

Examination of packing in the α-polymorph (Fig. 3) indicates that the abnormal radiation sensitivity of α-choline chloride may be due to the fact that the



Scheme VI

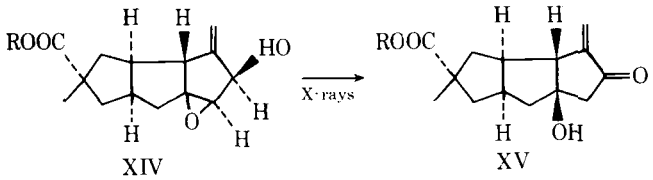
Figure 3—*Stereo pair view of the packing of the α-form of choline chloride. The chloride ions are represented as dots, and the hydrogen atoms are not drawn. The atom coordinates were taken from the literature (34, 35).*

propagation step proceeds rapidly through the stacks of choline molecules, much like a topochemically controlled polymerization. A knowledge of the structure of the β-polymorph of choline chloride would be of interest, and a comparison of the packing in the two polymorphs might provide insight into this reaction.

Hirsutic acid (XIV) rearranges in the solid state upon exposure to X-rays (Scheme VII) (36). This sesquiterpenoid acid is an antibiotic isolated from *Stereun hirsutun,* and its *p*-bromophenacyl ester rearranges during crystallographic data collection. This reaction proceeded to the extent of 60% with the product dissolved in the crystal lattice of the starting material. Thus, the observed structure in the crystal is the weighted average of XIV and XV. The structure of the product was proved by chemical means, ruling out the possibility that disorder or some other crystallographic artifact was responsible for the observed structure in the crystal.

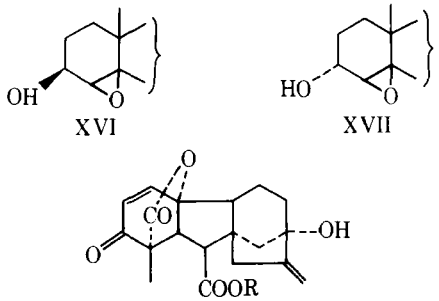
The observation of a solid solution containing nearly equal proportions of two materials is surprising when, in general, most solid solutions only exist for small amounts of guest molecule in the host lattice (2). The possibility of mixed crystal formation containing one molecule of XIV and one molecule of XV is also ruled out, since such mixed crystals would contain two molecules per asymmetric unit rather than one molecule as observed. Other hirsutic acid esters also rearrange on exposure to X-rays; however, unesterified hirsutic acid and other epoxy alcohols do not rearrange. For example, steroids containing either XVI or XVII epoxy alcohol groups are stable to X-irradiation. These observations suggest that rigid packing and structural requirements must be met before rearrangement will occur.

The solid-state photochemistry of 3-ketogibberellin (XVIII) is sensitive to packing influences (37). The methyl ester of 3-ketogibberellin (XVIII*a*) dimerizes to a cyclobutane (XIX) upon irradiation in the crystalline state (Scheme VIII), while the free acid, 3-ketogibberellic acid (XVIII*b*), photoaromatizes to XX (Scheme IX). Presumably, the acid functionality causes crystallization in a geometry unfavorable for dimerization.



R = *p*-bromophenacyl

Scheme VII



XVIII*a*: R = CH_3

XVIII*b*: R = H

The sodium salt of the antibiotic novobiocin (XXI) is light sensitive (38). It is possible that this light sensitivity is due to solid-state photodimerization of the coumarin functionality in novobiocin; however, air oxidation has not been ruled out.

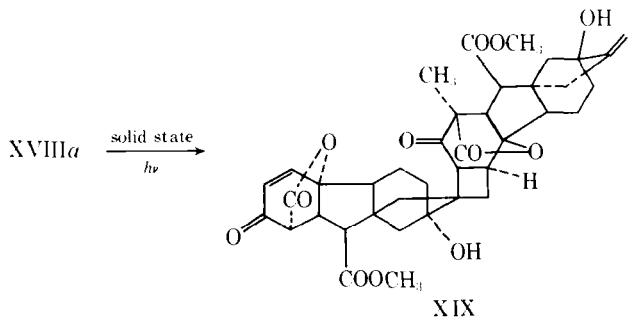
In conclusion, it is clear that the packing of crystals can control their reactivity, and this control can potentially be used to advantage when one wishes to prepare a more stable form of a drug.

SOLID-STATE THERMAL REACTIONS

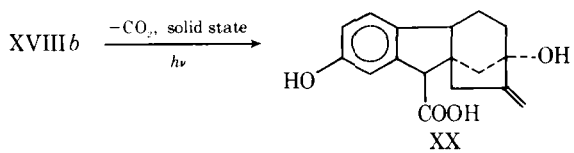
The scope of solid-state thermal reactions is broad, but several reviews are available (2, 5). One can expect that a reaction occurring in an inert solvent at a reasonable rate at 60–100° below the melting point of the substances present will occur in the solid (2), although this fact is not generally recognized.

A solid-state thermal reaction can be divided into four stages: (*a*) molecular loosening, (*b*) molecular change, (*c*) solid solution formation, and (*d*) separation of the product (2). Stages *b*, *c*, and *d* are very similar to the proposed steps of the photochemical reactions of *cis*-cinnamic acids (discussed previously). The first stage involves loosening or disordering of the reacting crystal at the reaction site. This step is required to allow the tightly packed reactant molecules sufficient space in which to react.

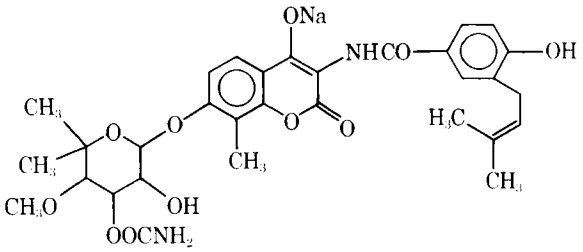
The second step involves conversion of the reactants to products. Few comparisons of the mecha-



Scheme VIII



Scheme IX



XXI

nisms of solid-state and solution thermal reactions have been made. However, the rates of solid-state thermal reactions apparently are two to 100 times slower than the corresponding solution reactions (2). Paul and Curtin (2) also pointed out that some solid-state thermal reactions proceed more cleanly than the corresponding solution reaction, just as do some solid-state photolyses (already discussed).

As the first molecules of product are formed, they probably appear as a solid solution of product molecules in the reactant crystals. Solid-solution formation has been studied (2), and it was noted that the range of solubility of one solid in another is surprisingly small, even when the two compounds have nearly the same shape. For example, the maximum solubility of acridine in anthracene is only 12%. The 60:40 solid solution of hirsutic acid (XIV) and its rearrangement product (XV) is an apparent exception to this generalization, although the solid solution is formed *in situ* by a chemical reaction. The existence of the 1:1 molecular complex of ergocalciferol and a thermal rearrangement product, pyrocalciferol, suggests that solid ergocalciferol could thermally rearrange to pyrocalciferol *via* this 1:1 complex.

After the solubility of the product in the reactant crystal is exceeded, it begins to crystallize out of the solid solution. Usually the crystalline product is highly disordered, since crystallization of this product occurs at many sites, each giving microcrystallites. However, several topotactic reactions are also known. In these reactions, single crystals of product are obtained from single crystals of starting material (39).

Almost all solid-state reactions begin at nucleation sites. The importance of defects in solid-state photochemical and thermal reactions has been discussed (1–3, 40). For example, the phase transition of the α-form of *p*-dichlorobenzene to the β-form begins at visually observable defects. Perfect crystals of the α-form are resistant to reaction. However, when these crystals are pricked with a pin, the reaction nucleates at this site (41, 42). In the phase transitions of the β-form of *p*-dichlorobenzene (41, 42) and the α-form of *p*-nitrophenol (43, 44), well-defined fronts between the starting phases and the product phases were observed.

Upon heating, the crystalline yellow isomer (Y-XXII) of dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate is transformed to the white (W-XXII) isomer (Scheme X), nucleating at variable sites in the crystal (45). The formation of the white isomer proceeds through the crystal in a "front" moving along the long morphological axis. This highly anisotropic spread of the reaction can be explained in terms of

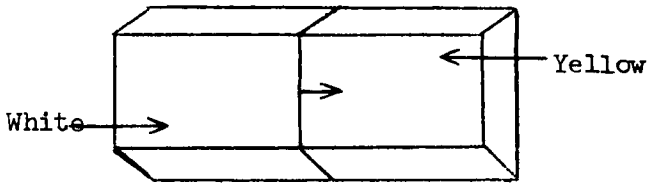


Figure 4—*Schematic drawing of the reaction spreading through the crystal.*

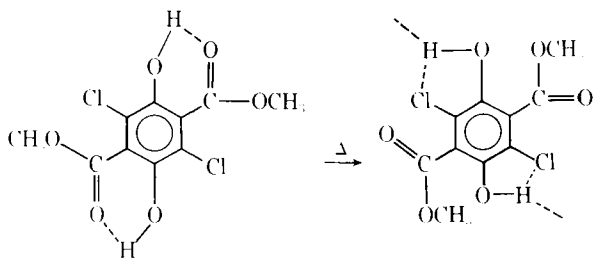
the packing and crystal structures of the yellow and white forms. Goniometric and crystal-packing studies showed that there were stacks of yellow molecules perpendicular to the plane of the paper in Fig. 4 and that each stack was associated with adjacent stacks in a direction perpendicular to the long morphological axis and relatively isolated from the stacks along the long morphological axis.

The relationship between the packing of crystals of Y-XXII and W-XXII showed that the white form could be obtained from the yellow form if every other molecule in a stack was "flipped" or rotated 180° about the Cl- - - Cl axis. The rapid spread of the reaction in both directions perpendicular to the long morphological axis is consistent with closer association of molecules in these directions and the relative isolation of molecules along the long morphological axis. One would expect that once the molecules in a stack are disrupted and loosened enough to allow one to flip, the rate of rearrangement would be rapid in that stack and would quickly spread to the closely associated adjacent stack. The rate of spread of the reaction to the relatively isolated adjacent stack would be slower.

The studies on dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate emphasize the valuable information that can be obtained when data from crystallographic, photomicrographic, and goniometric experiments are combined to explain solid-state reactions (45).

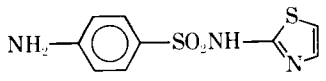
SOLID-STATE THERMAL REACTIONS IN MEDICINAL CHEMISTRY

Phase Transitions of Drugs—Polymorphism of drugs is an important subject, much too large for detailed discussion in this review. A review of polymorphs in pharmacy has appeared (46). Here, studies of the transformations of polymorphs of medicinal agents will be briefly discussed as examples of the simplest solid-state thermal transformations. Although none of the polymorphic transformations discussed here has been studied using photomicrogra-

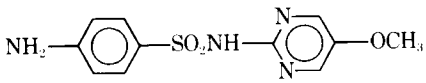


Y-XXII W-XXII

Scheme X



XXIII



XXIV

phy, it is likely that these transformations nucleate at defects and proceed by a mechanism related to that for the phase transition of *p*-dichlorobenzene and *p*-nitrophenol (discussed previously).

Several studies of the crystal structures of polymorphs of drugs have been performed. One definitive series of studies concerned sulfathiazole (XXIII) (Table II) (47, 48). In these studies, the crystal structures of three polymorphs (I, II, and III) were determined. These polymorphs had different rates of dissolution; however, visual examination of the packing from the crystal structures revealed differences in hydrogen bonding but allowed no definite conclusions about the relative stability of the polymorphs. The densities of Polymorph I and either II or III could be correlated with their rates of solution; the denser polymorphs (II or III, mp 200–202°) had the slower rates of dissolution. Also, heating I yielded the more dense polymorphic forms. This correlation is consistent with Kitaigorodskii's (49) closest packing theory which states, in part, that the most dense crystal is the most stable, since it has the highest packing energy. On the other hand, the more stable polymorph of resorcinol has the lower density (1.33 *versus* 1.28 g/ml) (50).

Sulfameter (XXIV) exists in three polymorphs (I, II, and III), two solvates (IV and V), and an amorphous form (VI). All forms are transformed to Polymorph I upon heating. Grinding converts all forms to III. Forms IV and V were suggested to be solvates containing dioxane and chloroform, respectively (51). Powder patterns and IR spectra confirmed the crystallographic differences among all five forms. Studies of dissolution rates indicated that Form II had the fastest dissolution rate and yielded a solution, from which Form I slowly crystallized. However, the relative stabilities of these polymorphs are not known, although these experiments indicated that Form I is the most stable.

Table II—Polymorphs of Sulfathiazole

Polymorph	I[a]	II[a]	III[a]
Melting point	200–202°	200–202°	200–202°
Transition point (to I)	—	173–175°	173–175°
Habit	Rods	Prisms	Plates
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a, Å	10.554 (5)	8.235 (4)	17.570 (9)
b, Å	13.220 (7)	8.550 (4)	8.574 (4)
c, Å	17.050 (9)	15.558 (8)	15.583 (8)
β, °	108.06 (1)	93.67 (1)	112.93 (1)
Molecules per asymmetric unit	8	4	4
Observed density, g/ml	1.50	1.55	1.57
Calculated density, g/ml	1.499	1.550	1.567

[a] Numbers in parentheses designate the error in the least-significant digit.

A convenient method of determining the relative stabilities of polymorphs involves equilibration of crystals of two forms in a solvent in which these polymorphs are relatively insoluble (46). Under these conditions, the crystals of the more stable polymorph grow while those of the less stable one disappear. In an apparently related observation, the crystalline transformation of an unspecified antihypertensive drug was observed when crystals were bathed in 0.1 *N* HCl (52).

Since the polymorph present can affect the rate of dissolution and, to some extent, bioavailability, care must be taken during the manufacturing process to assure that no polymorphic transition occurs. A particularly disturbing transformation could occur when the solid is subjected to the relatively high pressures of tablet machines, which can range up to 2812 kg/cm^2 (4000 lb/sq in.) or 281 bar. These pressures might favor transformation to a denser polymorphic form. However, few, if any, documented cases showing that compression during tablet preparation can alter the polymorphic form have appeared (53).

A recent study of the effect of compressional force on the polymorphs of succinylsulfathiazole showed that compressional force did not cause a polymorphic transition (53). While this study involved pressures up to about 15 kbar, studies at much higher pressures, but of different compounds, resulted in chemical reactions (54, 55). Aromatic hydrocarbons such as pentacene condensed when subjected to pressures of 150–300 kbar (54, 55). It is rather unlikely that pressures in tableting machines could cause a large number of chemical reactions.

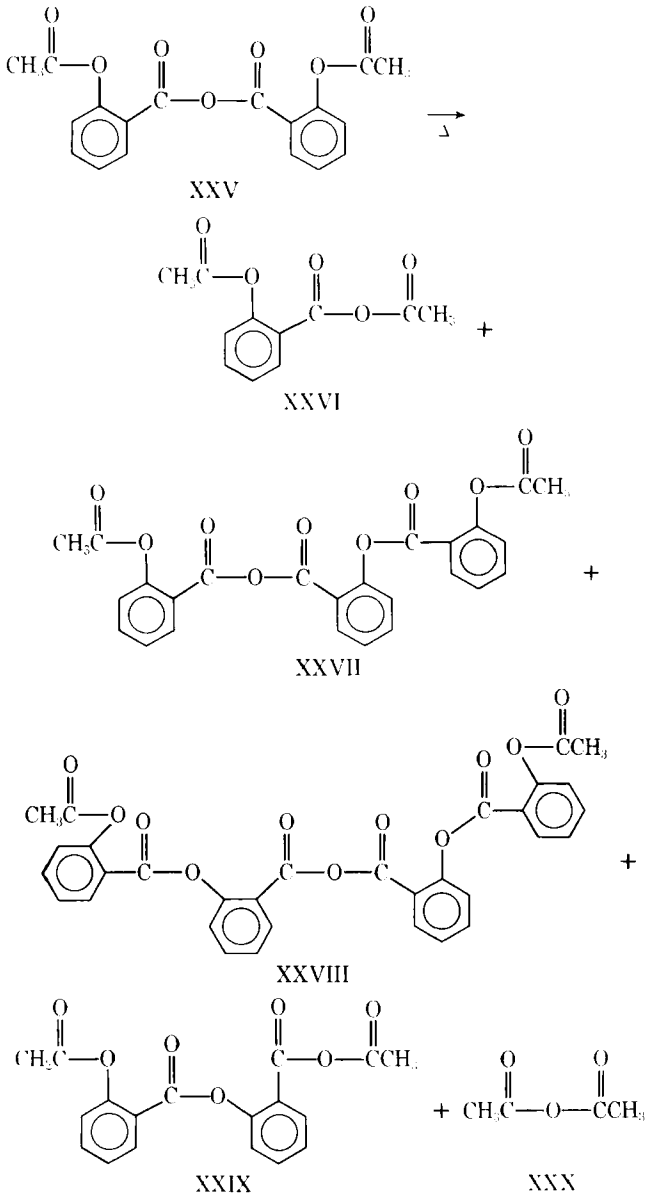
Aspirin Anhydride—Garrett *et al.* (56) reported an extremely interesting study of the solid-state decomposition of aspirin anhydride (XXV) (Scheme XI), which may be a superior form for the oral administration of aspirin.

Aspirin anhydride (mp 83–85°) decomposed in the solid state at temperatures ranging from 40 to 70°. At 70°, the starting crystals were completely liquefied after 24 hr and the rate of decomposition increased significantly after liquefaction. Even at the lower temperatures, liquefaction was noticeable after longer times. However, the rates of decomposition at 50° varied as much as 10 times from lot to lot of crystals. Samples containing moisture decomposed more rapidly than dried samples and, most important, crystals from ethyl acetate–hexane[2] were more stable than crystals from ethanol. It was suggested that the unstable crystals contain ethanol of solvation which, like moisture, accelerates the reaction. However, elemental analysis showed that crystals from ethanol do not contain solvent of crystallization[3]. This finding suggests that the reaction having the slower rate of decomposition might be a true solid-state reaction.

The solution thermal decomposition of aspirin anhydride has apparently not been studied. However,

[2] Skelly B.

[3] *Anal.*—Calc. for $C_{18}H_{14}O_7$: C, 63.16; H, 4.12. Found: C, 63.36; H, 4.35. These crystals belong to space group $P4_2\,2_12$ $a = b = 8.457$ (1), $c = 23.116$ (3) with four molecules per unit cell. S. R. Byrn, J. L. Killian, and P. Y. Siew, unpublished observations.

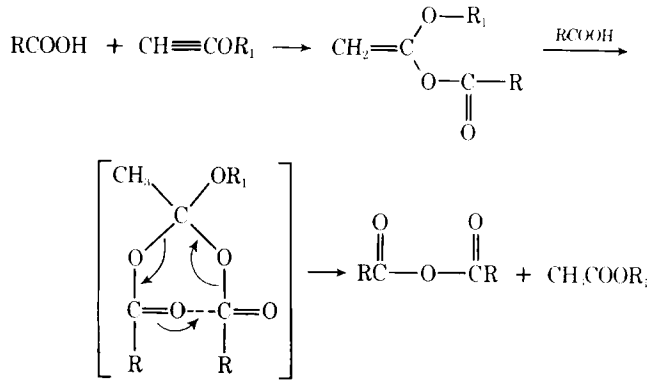


Scheme XI—Solid-state decomposition of aspirin anhydride. The products shown are those suggested by Garrett et al. *(56) and include all possible mixed anhydrides.*

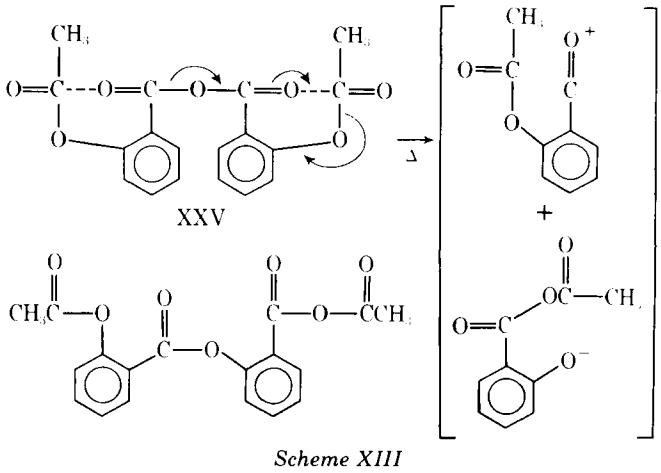
the oxygen to oxygen acyl and benzoyl migrations observed are related to the reaction shown in Scheme XII (57) and solid-state nitrogen to oxygen benzoyl migrations of phenylazotribenzoylmethanes (58–60).

Studies of the crystal structures of the starting and product crystals of these azotribenzoylmethanes revealed that the benzoyl groups appeared to pack preferentially in a conformation that places the carbonyl oxygen of one group near the back side of the carbonyl carbon of an adjacent benzoyl group as shown in the hypothetical reaction in Scheme XIII. Such a packing arrangement in aspirin anhydride would be geometrically quite favorable to acyl and benzoyl migrations. Solid-state benzoyl migrations also have been found to yield different product ratios from the corresponding reaction in solution (58–60).

Solid-State Nucleophilic Cyclizations—Recently, two solid-state cyclization reactions of anticancer agents have been reported. These reactions render



Scheme XII



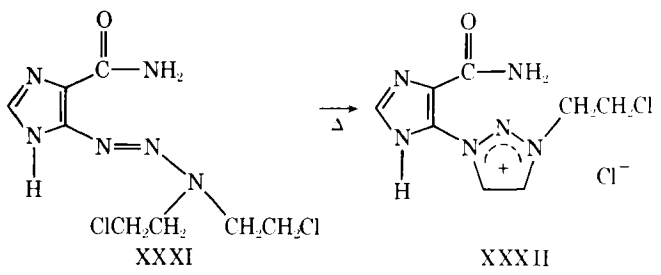
Scheme XIII

these compounds nearly useless as clinical agents because of the difficulty involved in stabilizing these materials during storage.

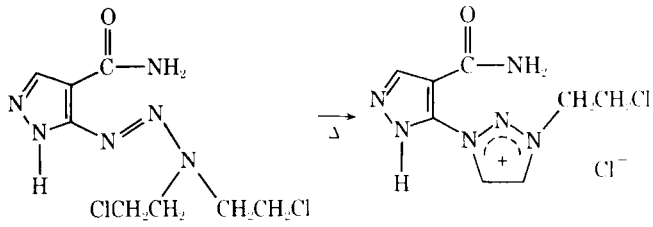
The nitrogen mustard 5(4)-[3,3-bis(2-chloroethyl)-1-triazeno]imidazole-4(5)-carboxamide (NSC-82196) (XXXI) is an antileukemic agent, which spontaneously cyclizes in the solid state at room temperature (Scheme XIV) (61–63). The structure of the product (XXXII) was unequivocally confirmed by crystal structure determination (64).

Similarly, 5-[3,3-bis(2-chloroethyl)-1-triazeno]pyrazole-4-carboxamide (XXXIII) spontaneously cyclizes (Scheme XV). The structure of the triazolium chloride (XXXIV) was determined by single-crystal X-ray techniques (65).

These reactions raise the question of whether the bis-2-chloroethyl-1-triazenes crystallize with one chloroethyl group in a conformation favorable to cyclization. Thus, the most important crystal structure in this series is that of the starting material rather



Scheme XIV



XXXIII XXXIV

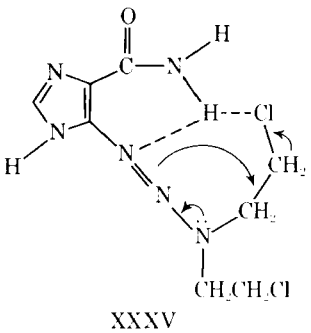
Scheme XV

than the product. Of particular interest is the possibility that N····CH_2Cl atoms in the crystal are in a trigonal bipyrimidal geometry favorable to an S_N2 reaction. A packing arrangement favorable to this cyclization (XXXV) was recently proposed in connection with crystallographic studies of dacarbazine [5-(3,3-dimethyl- 1-triazeno)imidazole-4-carboxamide (NSC-45388)] (66). However, the geometry at the reaction center of XXXV is not perfectly trigonal bipyrimidal with the chloride anion leaving as the nitrogen attacks because of the proposed N—H- - -Cl hydrogen bond. Whether the solid-state geometry is that in XXXV or a trigonal bipyrimidal arrangement can only be resolved by the determination of the crystal structure of this compound.

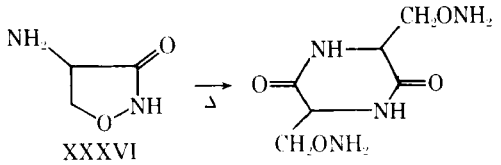
Of practical importance are experiments directed toward crystallizing these bis-2-chloroethyltriazenes in unreactive solid-state conformations.

An interesting solid-state reaction involving nucleophilic addition of an amine to an amide (transamidation) was observed when crystals of cycloserine (XXXVI) were heated (Scheme XVI) (67). This reaction was studied in a humid atmosphere and may occur in solution. A similar dimerization was observed in concentrated solutions. Unfortunately, the crystal structure of cycloserine has not been determined. However, if a solid-state reaction is involved, the relationship of the crystal packing to dimerization would be of interest.

Decomposition of 3-Amino-4-hydroxybenzenearsonous Acid (XXXVII)—This acid, which was used to treat syphilis, quantitatively decomposed in the absence of oxygen at 100° (Scheme XVII) in 7 days (68–70). (After 5 years, essentially no decomposition was observed at room temperature.) In contrast, after 5 days at 100° under anaerobic conditions, the hydrochloride salt of the anhydride of 3-amino-4-hydroxybenzenearsonous acid (XXXVIII) decomposed only slightly and only 15% decomposition was observed under aerobic conditions. The pentahydrate of this anhydride (XXXVIII) liquefied

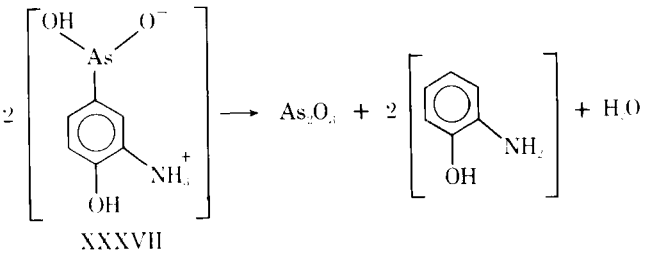


XXXV



XXXVI

Scheme XVI



XXXVII

Scheme XVII

after only 24 hr at 100°, and after 48 hr an essentially quantitative yield of *m*-aminophenol was obtained. This pentahydrate, like other derivatives of 3-amino-4-hydroxybenzenearsonous acid, gave oxidation products (*e.g.*, XXXIX) of an aminophenol when heated in the air.

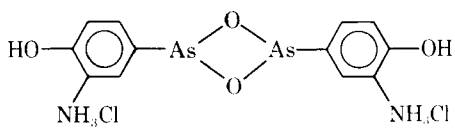
The lack of reactivity of the anhydride (XXXVIII) relative to the acid (XXXVII) may be related to packing in the crystal.

SOLID–GAS REACTIONS

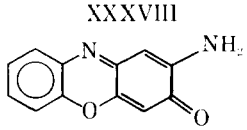
A review of solid–gas reactions of molecular crystals recently appeared (3). Only some important points will be summarized here.

Sensitivity to Minor Structural Changes—One striking feature of solid–gas reactions is their sensitivity to minor changes in the structure of the solid. For example, solid tetramethylrubrene in the presence of light readily adds oxygen while the parent dye, rubrene, does not (71).

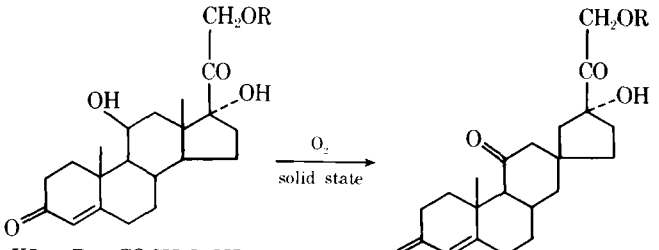
Similarly, hydrocortisone-21-*tert*-butylacetate (XL*a*) yielded, upon standing at room temperature for 1–2 years, 40% of the 11-one (XLI) (Scheme XVIII) (72, 73). In contrast, other esters, including the ethyl ester (XL*b*), were completely resistant to air oxidation even after 15 years at room temperature. The oxidation of XL*a* was accelerated by heat and greatly accelerated by free radical initiators and UV light. The reactivity of crystals of these esters was apparently related to the nonstoichiometric incorporation of solvent into the crystal lattice. The inert crystals were either stoichiometric solvates or unsolvated crystals. Unfortunately, the structure of these nonsolvated crystals was not studied further.



XXXVIII



XXXIX



XL*a*: R = $COCH_2C(CH_3)_3$
XL*b*: R = COC_2H_5

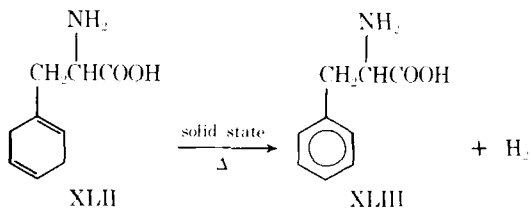
XLI: R = $COCH_2C(CH_3)_3$

Scheme XVIII

A related but more dramatic observation was made during studies of the biological properties of dihydrophenylalanine (*l*-1,4-cyclohexadiene-1-alanine, XLII) (74, 75). Dihydrophenylalanine is an effective antagonist of phenylalanine and is obtained from a one-step Birch reduction of phenylalanine. Crystallization of XLII from a dilute 80% ethanol solution yielded stable prisms (mp 235–236°), while crystallization from a saturated 80% ethanol solution or methanol–ethyl acetate yielded unstable needles. After 10 min at 100°, these unstable needles contained 70% phenylalanine (XLIII) (Scheme XIX). In aqueous solution the dihydrophenylalanine was recovered unchanged after 5 hr at 100°. Elemental analysis and NMR studies showed that the unstable crystals were hydrates (three water molecules associated with four molecules of XLII). The stable prisms, however, contained no water of hydration. Furthermore, the rate of the solid-state dehydrogenation was obviously much faster than the rate in solution (70% decomposition in 10 min in the solid state at 100° and 0% decomposition in 300 min at 100° in solution).

A possible explanation of this observation is that the dehydrogenation is preceded by loss of the water of crystallization and that the dehydrated crystal form is very reactive, perhaps because of the large number of defects left after water evaporation. This explanation is inconsistent with studies of the loss of solvent from crystals of phenylazotribenzoylmethane hemietherate. While phenylazotribenzoylmethane (XLIV) rearranged in the solid state, the crystals formed after loss of ether of crystallization were no more reactive than unsolvated crystals (76). In fact, in this case, microcrystallites of the unsolvated crystalline form were obtained when ether was lost, as shown by X-ray diffraction studies[4].

Reactions of Acids and Anhydrides with Ammonia—Photomicrographic investigations of these reactions show that the penetration of ammonia into the crystal is highly anisotropic. The different reactivity of the crystal faces can be explained in terms of the crystal packing (3). For example, *p*-chlorobenzoic acid upon crystallization forms carboxylic acid dimers which pack, giving layers of nonpolar phenyl rings and polar carboxyl groups parallel to the (100)



XLII XLIII

Scheme XIX

crystal face (the top or bottom face in Fig. 5). Ammonia can easily penetrate the faces of the crystal nearly perpendicular to the (100) face, since the polar NH_3 molecules can proceed down the polar stacks of carboxyl groups. However, ammonia molecules reacting with the (100) face encounter layers of polar and nonpolar material, which significantly retards the rate of reaction of gas with this face and leads to the observed anisotropy.

The anisotropic reactivity of crystals of at least six other acids and anhydrides was explained in terms of similar concepts related to the crystalline packing (3). Most of the reactions were ditropic (two pairs of faces were reactive); however, the crystals of the cyclopropane carboxylic acid (XLV) showed unitropic reactivity (one pair of faces was reactive). The unitropic reactivity of XLV may be related to the crystal packing. Crystals of XLV contained chains of carboxyl groups rather than dimers.

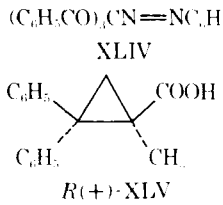
As for many solid-state photochemical and thermal reactions, defects appear to play an important role in the initiation of solid–gas reactions. These reactions often begin at a crystal edge and move inward in "fingers" toward the middle. All crystals retain their original shape for a substantial part of the reaction. In some cases, particularly the reaction of adipic acid with ammonia, the crystals were observed to crack and break apart (77). The reaction of ammonia with acenaphthylene-1-carboxylic acid was found to occur at relatively unreactive faces in the presence of certain slip defects (78).

SOLID-GAS REACTIONS OF MEDICINAL AGENTS

Solid–gas reactions are probably the most common solid-state reactions of medicinal agents, since solid-state hydrolysis with water vapor and solid-state oxidations by oxygen belong to this group. Solid–gas addition reactions and solid-state reactions involving elimination of a gas or elimination of a solvent from crystals are included in this section.

Photofading of Dyes Used in Coating Tablets—This area has been reviewed (79) and only selected examples will be treated.

Tablets were coated with the following dyes: FD&C Red No. 1, FD&C Red No. 3, FD&C Green No. 5, FD&C Green No. 3, FD&C Blue No. 2, FD&C



XLIV

R(+)-XLV

[4] *Added in proof:* Recently a second example of a solid-state reaction faster than the corresponding solution reaction was reported [C. N. Sukenik, J. A. P. Bonapace, N. S. Mandel, R. G. Bergman, P.-Y. Lau, and G. Wood, *J. Amer. Chem. Soc.*, **97**, 5290(1975). The X-ray crystallographic study of the reactive crystals showed that the crystal packing was particularly favorable to reaction.

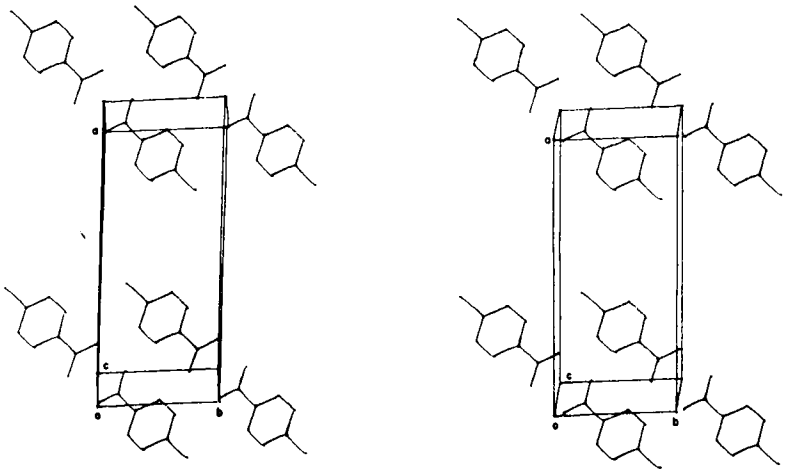
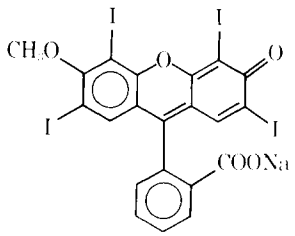


Figure 5—*Stereo pair view of the packing of* p-*chlorobenzoic acid (77).*

Blue No. 1, FD&C Yellow No. 5, FD&C Yellow No. 10, D&C Orange No. 3, and FD&C Violet No. 1. The dye erythrosine (XLVI) (FD&C Red No. 3) was the most reactive (80, 81). The decompositions of these dyes probably involve photochemical solid–oxygen reactions. Such an explanation is supported by the observation that erythrosine undergoes oxidative bleaching in solution (82). The triplet state of fluorescein also is reported to react with oxygen to yield a semioxidized dye (83).

The solid-state oxidation of these dyes may be mechanistically related to the photochemical oxidation of tetramethylrubrene and could involve addition of oxygen to an excited state of the dye. A plausible alternative explanation is that these reactions involve singlet oxygen addition to ground-state dye molecules. Rose bengal and eosin are fluorescein derivatives and are used as photosensitizers for the production of singlet oxygen in solution (84). As was the case for tetramethylrubrene and rubrene, different derivatives of fluorescein have different reactivities. A third mechanism involving free radical-initiated oxidation, similar to that postulated for β-carotene (discussed later), cannot be ruled out.

Indigo and triphenylmethane dyes are also oxidized in the solid state. Brilliant indigo 4B (XLVII) is oxidized and dehalogenated to give bromoisatin (XLVIII) (Scheme XX) (85), while FD&C Blue No. 2 (XLIX) decomposes in the presence of light and reducing agents to a leuco form (L) (86). In the presence of tablet excipients containing reducing sugars, this reaction is facile (86) and may proceed by a mechanism similar to the one shown in Scheme XXI. This mechanism was proposed for the corresponding solution reaction.



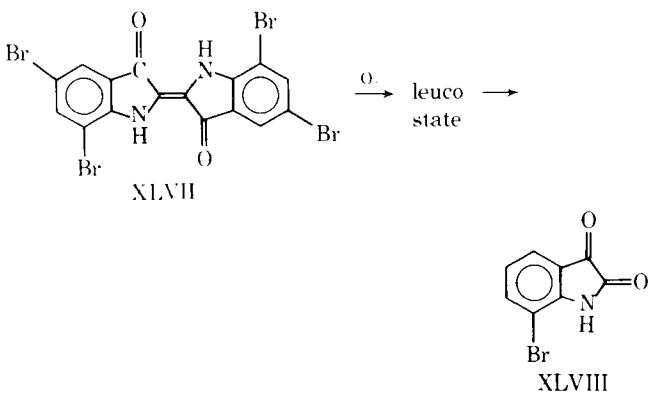
XLVI

Loss of Solvent of Crystallization—Whether the crystal form contains solvent of crystallization can affect the stability and bioavailability of a drug. The loss of solvent of crystallization, while not a chemical reaction, has several features in common with solid–gas reactions since considerable intermolecular interaction can be involved.

The loss of water of crystallization from theophylline monohydrate (LI) and ampicillin trihydrate (LII) was studied (87, 88). The kinetics of desolvation of theophylline monohydrate were followed using X-ray powder photography, since the powder patterns of the monohydrate and anhydrous forms are substantially different. The reaction obeyed zero-order kinetics from 38 to 54° and had an activation energy of 33 kcal/mole. Caffeine monohydrate also desolvated in the solid state and the hydrated and anhydrous forms had different powder patterns (87).

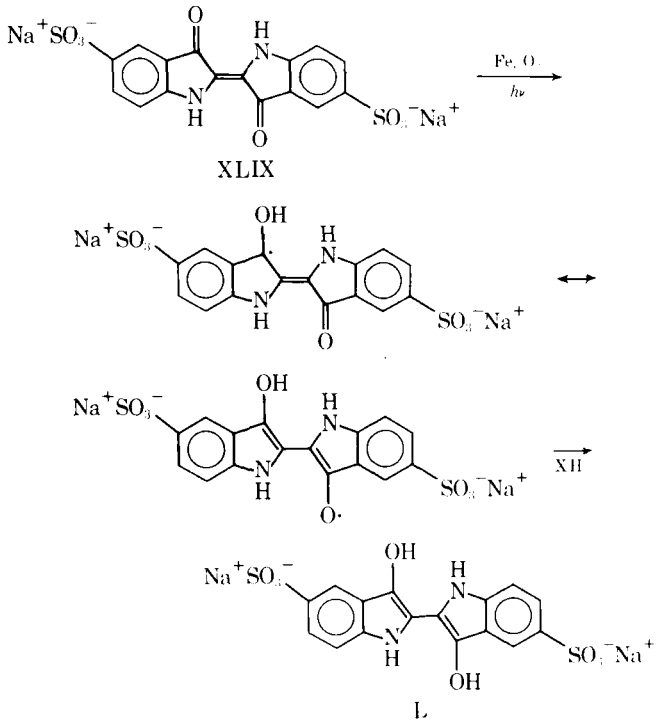
Similarly, ampicillin trihydrate (LII) lost water at temperatures ranging from 68 to 95°. This reaction was also followed using X-ray powder diffractometry. This reaction obeyed zero-order kinetics and had an energy of activation of about 23 kcal/mole. The zero-order kinetics of these reactions indicate that solvent loss proceeds from nuclei according to the diminishing-sphere model (87, 88).

In contrast to these studies, the powder patterns of the solvates and unsolvated crystal forms of cephaloglycin (LIII) and cephalexin (LIV) are virtually iden-



XLVII XLVIII

Scheme XX

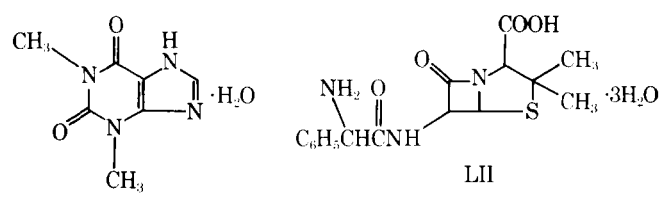


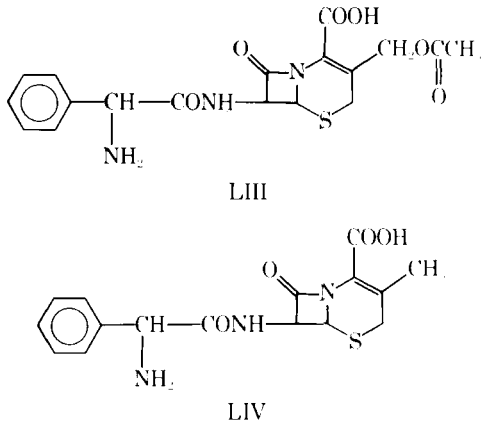
Scheme XXI

tical (89). Cephaloglycin forms solvates with water (1:2), formamide (1:1), methanol–water (1:1:1), acetonitrile–water (1:1:1), acetic acid–water (1:1:1), acetic acid (1:2), acetic acid–methanol (1:1:1), ethanol–water (1:1:1), and *N*-methylformamide (1:1). Cephalexin forms solvates with water (1:2 and 1:1), formamide (1:1), methanol (1:1), acetonitrile (1:2), acetonitrile–water (1:1:1), *N*-methylformamide (1:1), and *N*-ethylformamide (1:1). Drying of many of these solvates under normal conditions reportedly yielded a "desolvated" crystal with a powder pattern very similar to that of the solvated crystal form.

Although the powder patterns of the desolvated crystals were not identical to the patterns of the solvated forms, only minor differences such as a general loss of diffraction intensity and a change in the intensities at one or two reflections were reported. Exposure of the desolvated crystal to solvent vapor yielded the original solvate. This behavior has been termed crystal pseudopolymorphism and is perhaps related to the behavior of solvates of cyclodextrins, although no structural reasons for the presence of large cavities in the crystal are apparent. It would be interesting to determine the crystal structure of some of these solvates to find how the solvent molecules are packed in the lattice and to compare the theoretical powder pattern calculated from the atom positions in the single crystal to that observed.

Solid-State Hydrolysis of Aspirin (LV)—This



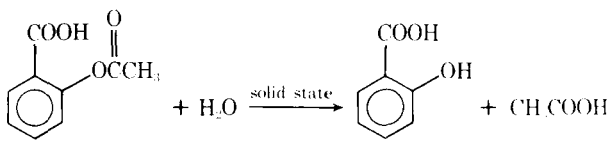


LIV

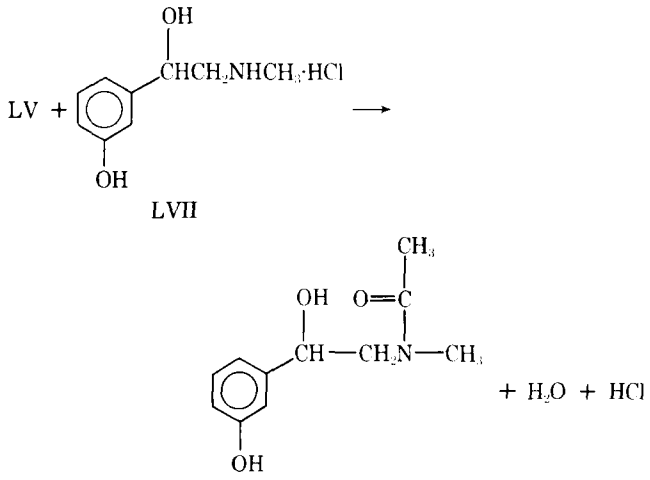
reaction (Scheme XXII) was studied in the presence and absence of moisture at 50–80° (90). As the humidity increased, the rate of reaction increased. The kinetics of this reaction were treated in terms of a solution reaction in which water was adsorbed onto the surface of the aspirin, with the amount of water adsorbed assumed to be proportional to the pressure of water. However, all experiments reported were run at a water pressure substantially below the vapor pressure (91); furthermore, aspirin is not hygroscopic. The reliability of these kinetic studies is probably poor, since a later study showed that sublimation of salicylic acid (LVI) from a cellulose-coated aspirin tablet caused appreciable errors in the measurement of the percent decomposition (92).

The observation of sublimed salicylic acid (LVI) on the surface of cellulose-coated aspirin tablets is also difficult to interpret in terms of a solution reaction on the surface of the solid, since it is unlikely that salicylic acid would sublime out of a water solution. However, it is quite likely that if the hydrolysis proceeds rapidly, the acetic acid produced will be unable to evaporate and the reaction will proceed in an acetic acid solution. The vapor pressure of acetic acid is 100 mm at 63°, indicating the substantial volatility of this acid. The eutectic point of mixtures of aspirin (mp 143–144°) and salicylic acid (mp 157–159°) has not been determined, but aspirin crystals containing 60.0, 23.9, 17.7, and 1.3% salicylic acid had melting points of 115, 115, 114, and 136.6°, respectively. These findings indicate that the eutectic point is probably much greater than 80° and rule out the possibility of reaction in a melt of these compounds in the absence of acetic acid.

Studies of aspirin crystals heated on a hot stage would perhaps provide a definitive solution to this problem. Our preliminary studies on aspirin crystals grown from benzene heated at 95, 87, and 68° on a hot stage in air showed that the crystal edges softened and liquid appeared after a few minutes, 24 hr, and 48 hr, respectively, although the crystals did not



Scheme XXII



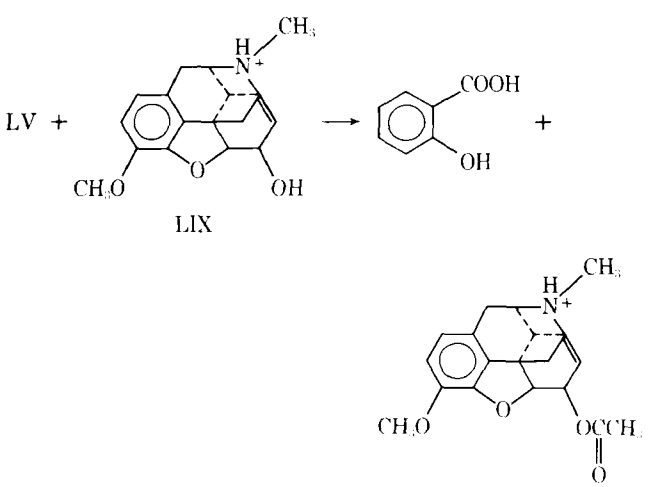
Scheme XXIII

melt. These observations substantiate the suggestion that this reaction proceeds in solution, at least at high temperatures. The solution may result because acetic acid does not evaporate rapidly enough.

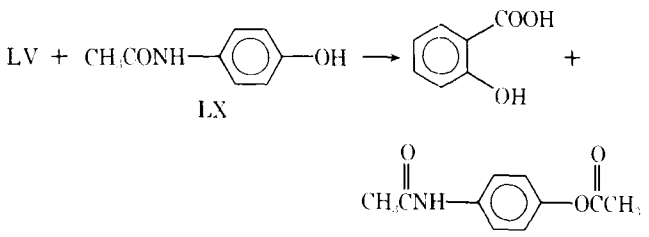
Excipients and antacids accelerated the decomposition of aspirin. A study was made of the effect of antacids on the decomposition of aspirin after 1 year. In the presence of some antacids, such as calcium carbonate, aspirin was 4.4% decomposed; in the presence of others, such as sodium bicarbonate, there was complete decomposition in 44 weeks (93). Diluents also affected the stability of aspirin tablets, cellulose and calcium sulfate conferring substantially more stability than mannitol–starch or amylase (94). The decomposition of aspirin in the presence of these compounds was related to the amount of moisture sorption and to the tablet hardness (94).

A comparison of aspirin decomposition in suspensions and in tablets in the presence of diluents and antacids showed that the rates of decomposition were nearly the same (95). Of the compounds studied, hexanoic acid conferred the most stability to aspirin and magnesium trisilicate conferred the least.

Tablet mixtures containing aspirin and drugs with easily acylated functionalities react to give acyl compounds (LVIII) and salicylic acid (Scheme XXIII). For example, mixtures of phenylephrine hydrochloride (LVII) and aspirin (LV) contained 80% of acylated phenylephrine after 34 days at 70° (96). A mixture of starch and magnesium stearate slowed this acylation to only about 1% after 34 days, while magnesium stearate without starch caused complete decomposition after 16 days. Some diacylated product was also obtained. This reaction may proceed by direct acylation.



Scheme XXIV



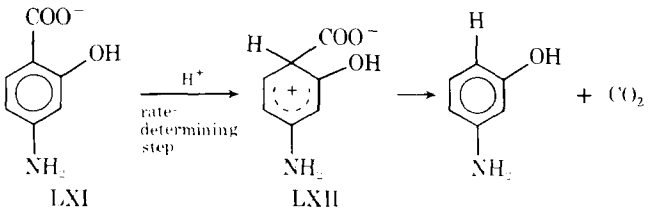
Scheme XXV

Similarly, tablets containing aspirin and codeine (LIX) (Scheme XXIV) and aspirin and acetaminophen (LX) (Scheme XXV) also yielded acylated drugs upon heating (97, 98).

Thermal Decarboxylation of *p*-Aminosalicylic Acid (LXI)—The solid-state and solution decarboxylations of the antituberculosis drug aminosalicylic acid have been carefully studied (99, 100). In buffered aqueous solution, the rate-determining step of the general-acid-catalyzed decarboxylation reaction apparently involves addition of a proton to the carboxylate anion (Scheme XXVI).

Crystals of aminosalicylic acid (mp 220° dec.) decarboxylated upon heating at 70, 75, or 80° to yield *m*-aminophenol (mp 122–123°). Photomicrographs showed that the crystals cracked and broke upon reaction (99). Kornblum and Sciarrone (99) also found that a carbon dioxide atmosphere did not retard the rate of solid-state decomposition, and the reaction was about 10 times as fast in moist atmospheres as in dry atmospheres. The rate of the reaction was apparently controlled by nucleus formation and was zero order. Recently, another study of the kinetics of decomposition of aminosalicylic acid in the solid state was reported (101). First-order kinetics were observed and interpreted in terms of competing solid-state and solution reactions (101). The solution reaction was suggested to occur in a sorbed moisture layer approximately 60 Å thick.

The decarboxylation of aminosalicylic acid was studied at 65, 68, and 72°[5,6]. Mixed melting-point studies showed that the eutectic point for a 1:1 mixture of aminosalicylic acid and *m*-aminophenol was



Scheme XXVI

[5] S. R. Byrn and J. L. Killian, unpublished observations.

[6] The atomic coordinates used for this drawing were recently determined by Dr. P. Y. Siew in our laboratories and correct those reported in the literature (102). Full details will be reported shortly.

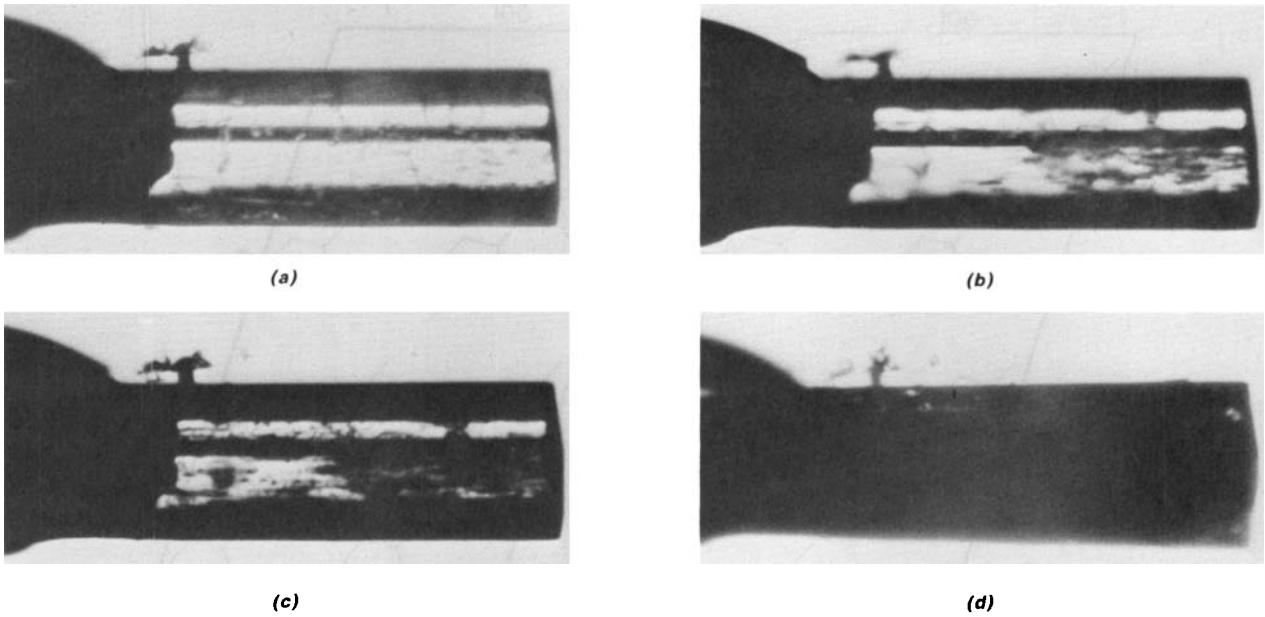


Figure 6—*View of a crystal of aminosalicylic acid after heating on a hot stage at 68° for* (a) *50 hr,* (b) *12 days,* (c) *21 days, and* (d) *33 days. The faces of the crystal were determined by optical goniometry and precession photography. The "crystal" shown in* (d) *was a mixture of pure* m*-aminophenol and aminosalicylic acid.*

about 110°. Figure 6 shows the behavior of a single crystal of aminosalicylic acid at 68° as photographed in air[7]. The decarboxylation reaction appears to occur on the 10$\bar{2}$ face, leaving the 001 face relatively unreacted.

The crystal packing of aminosalicylic acid is shown in Fig. 7[6]. An examination of these diagrams indicates that there are layers of polar carboxyl groups and nonpolar aromatic groups parallel to the 001 face and somewhat perpendicular to the 10$\bar{2}$ face. One possible explanation of the surface behavior of the crystal faces is that the carbon dioxide formed exits from the 10$\bar{2}$ face rather than passing through alternating planes of polar and nonpolar functionalities to exit from the 001 face. However, other explanations involving preferential sublimation of aminosalicylic acid or the more volatile *m*-aminophenol from the 10$\bar{2}$ face cannot be ruled out.

Furthermore, the relationship between the solid-state and solution reactions of aminosalicylic acid and the source of the proton for catalysis of the solid-state reaction (if the mechanisms of the solid-state and solution reactions are similar) is not known. Since the rate-determining step of the reaction is almost certainly not the exit of carbon dioxide from the crystal, the progress of the reaction through the crystal must be explained in terms of other processes. For example, the direction of migration of catalyzing protons through the crystal might be related to the progress of the reaction. We are presently studying this and other possible mechanisms as well as the surface behavior of the faces of these crystals.

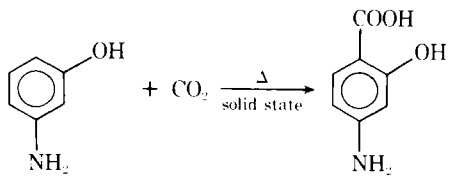
[7] A Mettler FP-5 hot stage and a Zeiss microscope equipped with camera were used.

The reverse reaction also was reported to occur upon heating a mixture of *m*-aminophenol (mp 122–123°), potassium carbonate, and carbon dioxide at 175° in a ball mill (Scheme XXVII) (103). The melting point of *m*-aminophenol (122°) and the eutectic points of *m*-aminophenol and aminosalicylic acid (110°) indicate that this reaction probably occurs in the liquid state.

The decomposition reaction of solid benzoic acid derivatives to give carbon dioxide gas and a liquid product also was studied (104). The kinetics of these reactions were interpreted in terms of competing solid-state and liquid reactions. Interestingly, the rate of the solid-state reaction was inversely related to the melting point of the starting acid. (See section on vitamin A for a discussion of the effect of the melting point on reactivity.)

SOLID-STATE REACTIONS OF MEDICINAL AGENTS CONTAINING POLYENE FUNCTIONALITIES

These reactions are difficult to classify since polyene functionalities have been reported to undergo solid–gas reactions, thermal reactions, and photochemical reactions. Therefore, they have been placed in a section by themselves.



LXIII

Scheme XXVII

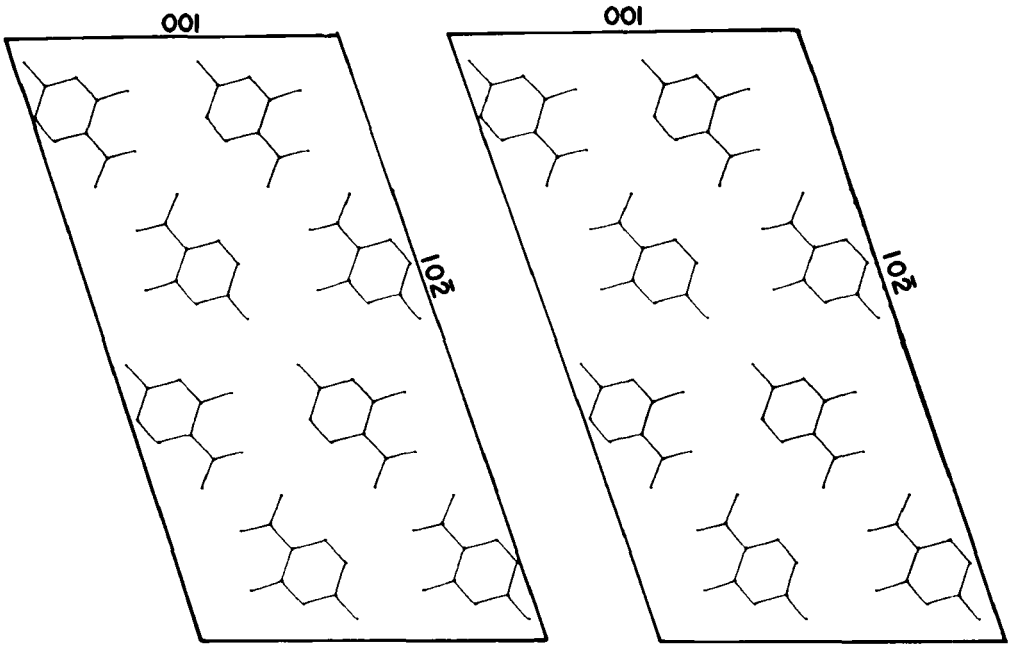
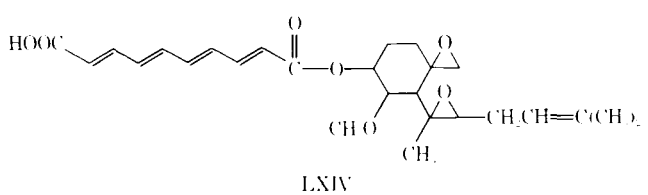


Figure 7—*Stereo pair view of the crystal packing of aminosalicylic acid as viewed from a direction parallel to the 001 and 10$\bar{2}$ planes.*

Thermal and Photochemical Degradation of Fumagillin—Fumagillin (LXIV) undergoes both solution and solid-state photochemical reactions, and the solid decomposes thermally (105–107). Irradiation of fumagillin with a fadeometer[8] (light about twice as intense as sunlight) in ethanol solution yielded neofumagillin (structure unknown). The rate and products of this reaction were the same whether the reaction was run in air or nitrogen. Experiments with filters indicated that the photoreaction of fumagillin (λ_{max} 351 and 366 nm, shoulder at 315 nm) required light of a wavelength greater than 280 nm.

Although Garrett and Eble (105) suggested that the polyene side chain of fumagillin might cyclize to yield the cyclohexadiene species neofumagillin (LXV), these workers also indicated that neofumagillin was photolabile and decomposed shortly after formation. It was also suggested that neofumagillin solvolytically rearranged, which hampered any further attempts to determine its structure.

The course of solid-state photolysis of fumagillin depends upon the atmosphere (106). In the presence of air, an oxidized product is obtained upon photolysis in a fadeometer; but in the absence of air, an oxygen-sensitive product is obtained. After the first 5 hr, the first-order rate constant of the solid-state photolysis in air is of the same order of magnitude as the solution photolysis (0.14 hr^{-1}). During the first 5 hr, the reaction is definitely not first order and it may involve a kinetically important intermediate (106). The relationship between the products of the solid-state and the solution reactions has not been studied, but some of the products are probably the same (106).

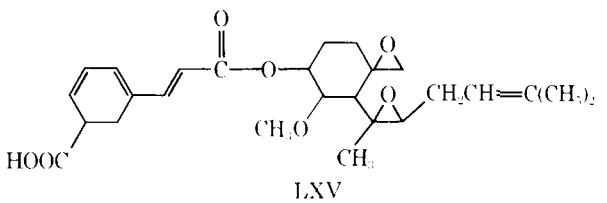


LXIV

The solid-state thermal reaction of fumagillin proceeds by different but unknown mechanisms in the presence and in the absence of air (107). The reaction in the presence of air was interpreted as a thermally induced oxidation. The solid-state thermal reaction is poorly understood but is slower than the photolytic reaction and should not interfere with photolytic studies. Fumagillin is thermally stable in ethanol solution. Further studies of the products and of the influence of crystal packing on this reaction are needed.

Thermal and Photochemical Degradation of Ergocalciferol (Vitamin D_2)—Ergocalciferol (LXVI) has an extensive series of solution, photochemical, and thermal reactions (Schemes XXVIII–XXX) [R = —$CH(CH_3)CH{=}CHCH(CH_3)CH(CH_3)_2$] (108, 109). Crystalline ergocalciferol is light, air, and heat sensitive and gives a number of products whose structures have not been determined (110, 111). Furthermore, although crystalline ergocalciferol is unstable and was deemed unsuitable for crystallographic studies, crystals of the 3,20-bisethylenedioxy (112) and the 4-iodo-5-nitrobenzoate (113) derivative are more stable and their crystal structures have been determined.

We found that crystalline ergocalciferol ($C_{28}H_{44}O$, mol. wt. 396.6; calc.: C, 84.8%; H, 11.2%) completely



LXV

[8] Atlas.

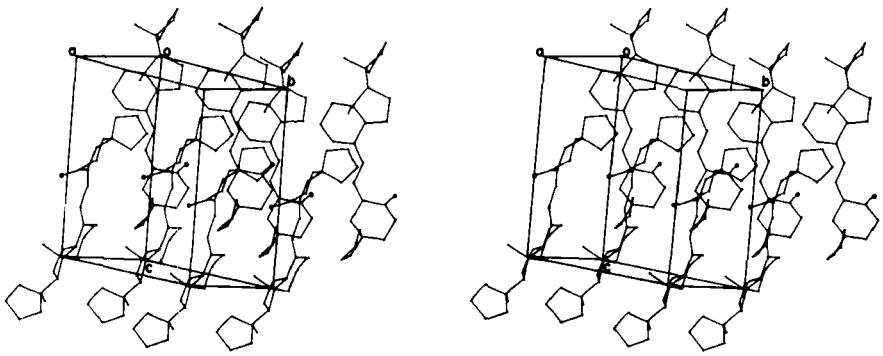


Figure 8—*Stereo pair packing drawing of 3,20-bisethylenedioxycalciferol (112). Contacts of less than 5.5 Å between the triene functionalities involved only C(19), which is designated by the heavy dot. These are: C(19)–C(5), 4.70 Å; C(19)–C(6), 4.24 Å; C(19)–C(7), 5.12 Å; and C(19)–C(8), 5.18 Å. (See Scheme XXVIII for numbering.)*

decomposed to a yellow powder (mp 58–100°) after 6 months at room temperature in air, although the "crystals" retained their original shape. TLC showed that at least five products were formed. Elemental analysis of this powder indicated extensive oxidation; observed: C, 66.0%; H, 7.7%; calc. for $C_{28}H_{44}O_8$: C, 66.12%; H, 8.72%[9]. Mass spectra indicated degradation since the highest molecular ion observed had a mass of 276. We also found that crystals of ergocalciferol decomposed and eventually melted when heated at 80° in air in the presence and absence of light. Elemental analysis of these melts indicated oxidation. Crystals were stable when heated for 1 week at 80° in the absence of oxygen[9].

These thermal and photochemical solid-state reactions in air apparently do not involve formation of cyclized ergocalciferol derivatives such as ergosterol (LXVIII), lumisterol (LXX), or suprasterols (LXXIII and LXXIV). Furthermore, the mass spectral data indicate that ergocalciferol does not undergo photochemical dimerization in the solid state. This finding is consistent with the packing (Fig. 8) of the bisethylenedioxy derivatives of ergocalciferol. No close contacts between double bonds are apparent in Fig. 8. In fact, the only intermolecular contacts less than 5.5 Å between atoms in the triene functionality involve only atom C(19). Topochemically controlled dimerization reactions do not seem possible. A topochemically controlled polymerization of bisethylenedioxy calciferol involving successive linkage of C(19) to C(6) is possible but is not consistent with the melting point and mass spectral studies discussed previously. An intramolecular photocyclization of ergocalciferol to suprasterol is possible; but if it is occurring, its rate must be substantially slower than the air oxidation.

Thus, the solid-state oxidation of ergocalciferol is much less specific than oxidations of the cortisone derivatives. However the ethylenedioxy and 4-iodo-5-nitrobenzoate derivatives are more stable than vitamin D itself. It is not known whether these compounds undergo any solid-state reactions.

The mechanism of the solid-state oxidation of ergocalciferol is unknown but may involve one or more of the following paths: (*a*) singlet-oxygen addition to the diene or triene group of ergocalciferol, (*b*) reaction of an excited state of ergocalciferol with ground-state oxygen (as in the rubrene reaction), and (*c*) free-radical reactions initiated by heat or light involving formation of hydroperoxides alpha to the double bond system. The singlet-oxygen path and the addition of ground-state oxygen to an excited state of ergocalciferol cannot be the only pathways, since oxidation was observed when ergocalciferol was heated in the dark.

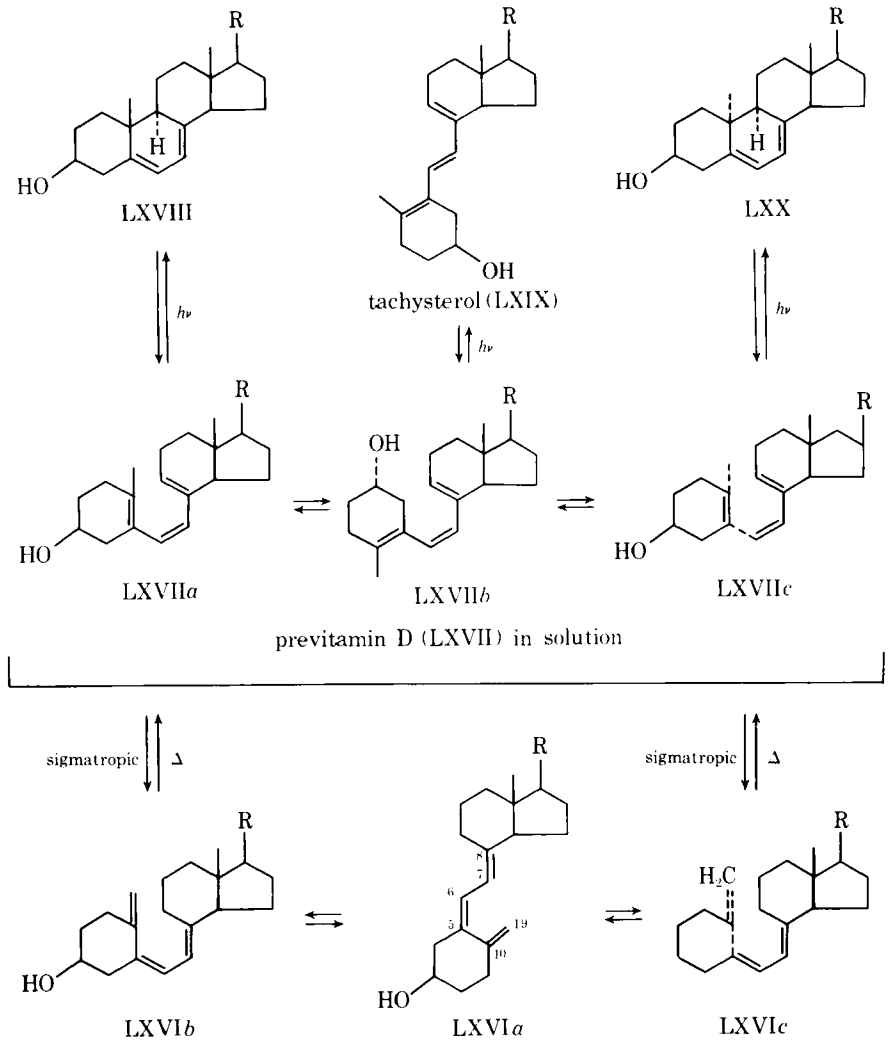
Decomposition of Vitamin A and Derivatives—Crystalline esters of vitamin A (LXXV) (including the succinate half-ester, the nicotinate, and the 3,4,5-trimethoxybenzoate) decompose by both polymerization and oxidation pathways (114, 115). Vitamin A, exposed to air at room temperatures for several years or heated at 100° for 5 hr, gave at least five ketones on TLC plates treated with 2,4-dinitrophenylhydrazine (116).

β-Carotene (LXXVI) autooxidizes in the solid state at 25 and 35° (117). The rate of this oxidation depends on oxygen pressure and temperature, and a free radical mechanism was proposed for this reaction (Scheme XXXI) (117).

Diluents with antioxidant properties stabilize vitamin A palmitate in vitamin preparations (118). Aluminum salts of fatty acids such as stearic acid stabilize vitamin A, as does combination with gelatin and dextrin, which probably contain reducing sugars (119). In solution, vitamin A and its derivatives undergo several oxidation and isomerization reactions. For example, cobalt(II) stearate oxidized vitamin A to an epoxide with the postulated structure LXXVII. A hexane solution of vitamin A acetate was converted to peroxides in hexane in the presence of oxygen (120). Vitamin A gave 35% of the peroxide LXXVIII upon irradiation of a hexane solution (121) and a 50% yield of LXXVIII when irradiated in methanol in the presence of rose bengal (a singlet-oxygen sensitizer) (Scheme XXXII) (122).

It is impossible to predict the products of the solid-state oxidation on the basis of the solution studies discussed. These oxidation products probably can result from singlet-oxygen reactions, free-radical reactions, and perhaps even excited states of vitamin A. In this regard, the polymerization of vitamin A in the solid state could possibly be topochemically controlled. However, from the packing of vitamin A acetate in the solid state (Figs. 9 and 10), it is clear that there are no stacks of molecules that could undergo topochemically controlled polymerization. Two molecules have the C(11)–C(12) double bond parallel (di-

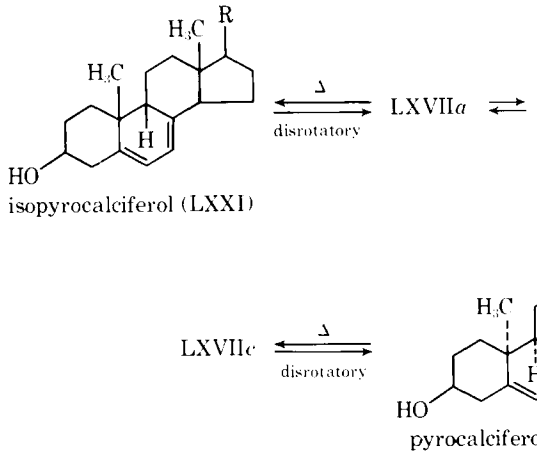
[9] S. R. Byrn and S. L. Midland, unpublished observations.



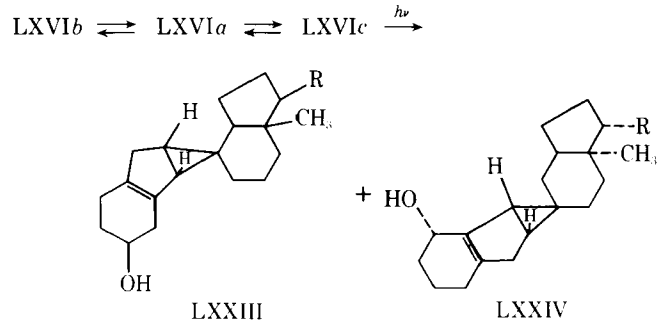
Scheme XXVIII

hedral angle = 0.0°) and related by a center of symmetry, but they are 5.41 Å apart, which is probably too far for dimerization, according to Schmidt's topochemical postulate (6).

An interesting correlation of the melting points of the vitamin A esters with their zero-order rate of solid-state decomposition was observed (114). The solution rates of decomposition of these esters were virtually identical. These results were interpreted in terms of crystal lattice energy. It was argued that the higher melting esters had more crystal lattice energy and thus were more stable to the solid–gas oxidation reaction. A much better measure of lattice energy in a series of compounds is the heat of sublimation (124). If the melting point is proportional to the heat of sublimation in this series, then the higher the melting point the more efficient is the packing and, conceivably, the less permeable is the crystal to reacting gas. The rates of reaction of acid crystals with ammonia do not correlate with the melting point of the acid (125). Whether this failure is due to the fact that the melting point does not correlate with the heat of sub-



Scheme XXIX



Scheme XXX

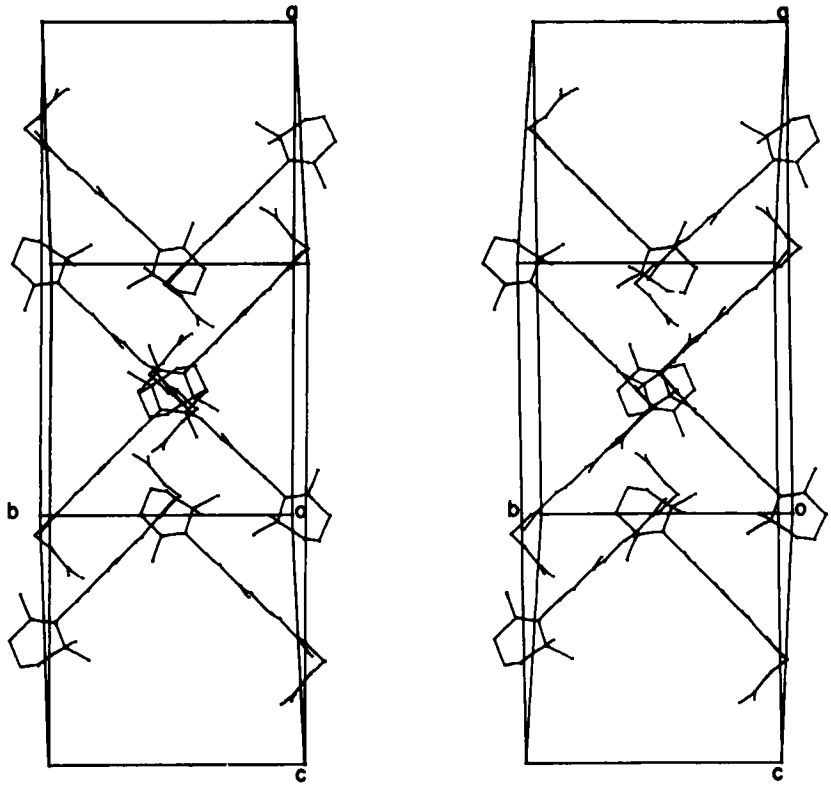


Figure 9—*Stereo pair drawing of the contents of the unit cell of vitamin A acetate, space group C2/c (123). A consideration of this drawing indicates that there are no stacks of molecules that could undergo topochemically controlled polymerization reactions.*

limation or other factors is not known.

In conclusion, it should be noted that the polyene antibiotics pimaricin (natamycin) (126) and filipin (127) are also oxidized in the solid state.

The degradation of solid polyenes apparently involves a complex series of reactions which can include: (*a*) polymerization, (*b*) oxidation by singlet oxygen, (*c*) free-radical-initiated oxidation, (*d*) reaction of oxygen with electronically excited drug molecules, and even (*e*) thermal rearrangement reactions.

APPLICATIONS: POTENTIAL FOR STABILIZATION OF DRUGS BY RATIONAL APPROACHES

In many of the solid-state reactions discussed, the derivative or crystal form present plays an important role in the reactivity. In the gibberellins, replacement of the ester by an acid changes the course of the photochemical reaction. Similarly, derivatives of ergocalciferol are more stable than the parent compound, and vitamin A esters with high melting points are more stable than those with lower melting points. Choline chloride crystallizes in two forms, one with unusually high radiation sensitivity and the other with normal radiation sensitivity. Cortisone derivatives containing nonstoichiometric quantities of solvent in the crystal are oxidized in air, while crystals containing stoichiometric amounts of solvent are unreactive as are unsolvated crystals. Crystals of the hydrate of dihydrophenylalanine dehydrogenate while the anhydrous crystals are thermally stable, and the crystalline hydrate of arsenous acid anhydride is more reactive than the anhydrous form.

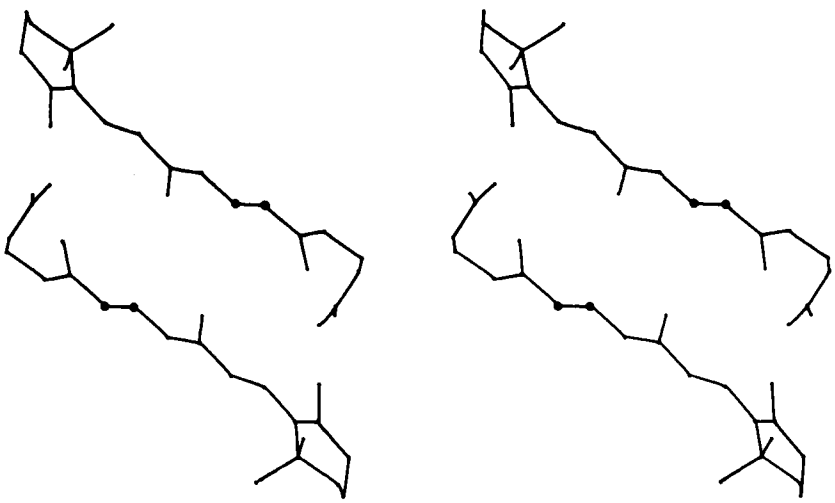
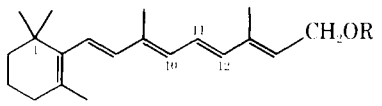
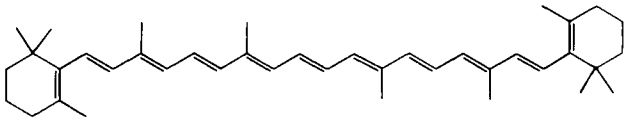


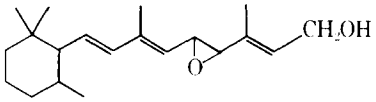
Figure 10—*Stereo pair view of two vitamin A acetate molecules. The atoms designated by heavy dots are C(11) and C(12), which are parallel and related by a center of symmetry. The C(11)–C(12) and C(12)–C(11) distance was 5.41 Å.*



LXXV



LXXVI



LXXVII

Recent studies on organic solid-state reactions have shown that a knowledge of crystal packing may explain the course of these reactions and the stereochemistry of the products. Furthermore, a knowledge of the factors influencing crystal packing is developing. In an example of the application of the concept called crystal engineering, Schmidt (6) was able to control the packing type of olefins using a 2,4-dichlorophenyl group. The presence of this group in a variety of olefins caused crystallization in the β-packing type. Irradiation of these crystals yielded the dimer with mirror symmetry, as expected from the topochemical postulate. Recently, Paul and Curtin (3) discussed the packing of carboxylic acids and showed the influence of this packing on solid–gas ammonia reactions.

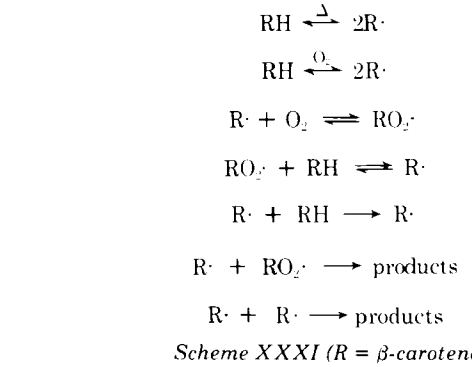
Thus, many solid-state reactions can be explained in terms of crystal packing. An obvious corollary of this principle is that changing crystals packing can change the solid-state reactivity. The application of this idea to pharmaceutical problems will hopefully lead to more efficient and effective methods of drug stabilization.

In particular, once the mechanism of the decomposition process has been established, it is, in principle, possible to apply the concept of crystal engineering to the development of a more stable drug and dosage form. Attractive approaches involve the following:

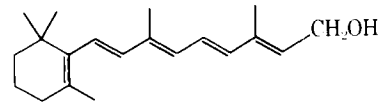
1. Preparation of an equally active but more stable derivative of an unstable drug, in analogy with the attachment of a 2,4-dichlorophenyl group to olefins to control their packing. For example, esters of vitamin A have the same biological activity after correction for molecular weight differences but substantially different solid-state reactivity (115).

2. Crystallization of solvates or polymorphs with less solid-state reactivity, in analogy with the steroid and cinnamic acid reactions previously discussed.

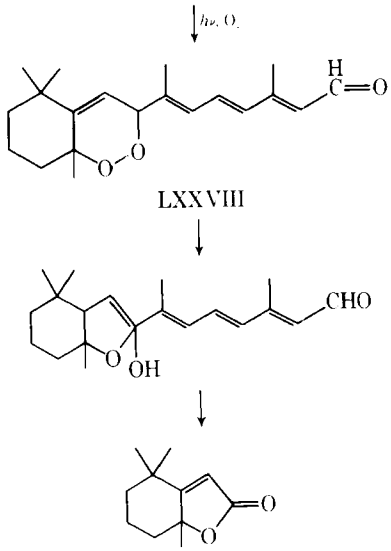
These approaches will hopefully lead to more rational methods for stabilizing drugs in the solid state and the production of safer and more efficient products.



Scheme XXXI (R = β-carotene)



LXXV



LXXVIII

LXXIX

Scheme XXXII

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RESEARCH ARTICLES

Glass for Parenteral Products: A Surface View Using the Scanning Electron Microscope

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Abstract □ The scanning electron microscope was utilized to explore the internal surface of glass ampuls and vials used in parenteral products. The surface topography of USP Type I borosilicate glass containers was viewed after exposure to "sulfur," ammonium bifluoride, and sulfuric acid treatments. The scanning electron micrographs showed startling differences in the appearance of the surface regions. "Sulfur treatment" of ampuls was associated with a pitting of the surface and the presence of sodium sulfate crystals. The sulfur treatment of vials altered the glass surface in a characteristically different manner. The dissimilarity between the surface appearances was attributed to the method of sulfur treatment. Ampuls exposed to sulfuric acid solutions at room temperature did not show the pitting associated with the sulfur treatment. Scanning electron micrographs of ammonium bifluoride-treated ampuls showed a relief effect, suggesting that the glass was affected by the bifluoride solution but that sufficient stripping of the surface layer did not occur to remove the pits associated with the sulfur treatment. Flakes emanating from the glass were identified with the aid of the electron microprobe. Scanning electron micrographs showed that these vitreous flakes resulted from a delamination of a thin layer of the glass surface. It is concluded that the scanning electron microscope, in conjunction with other analytical techniques, is a valuable tool in assessing the quality of glass used for parenteral products. The techniques studied should be of particular importance to the pharmaceutical industry where efforts are being made to reduce the levels of particulate matter in parenteral dosage forms.

Keyphrases □ Glass—ampuls and vials, internal surface, effect of sulfur, ammonium bifluoride, and sulfuric acid treatments, scanning electron micrographs □ Scanning electron microscopy—internal surface, glass ampuls and vials, effect of sulfur, ammonium bifluoride, and sulfuric acid treatments □ Parenteral containers—glass, scanning electron micrographs, surface view □ Containers, glass—surface, effects of sulfur, ammonium bifluoride, and sulfuric acid treatments, scanning electron micrographs

Glass vials and ampuls are the primary containers for parenteral products. The general inertness of glass has been the basis for its use since it is desirable for pharmaceutical products to have acceptable physical and chemical stability for extended periods, *i.e.*, up to 5 years. This report is concerned with the quali-