(4) G. G. Birch, in "Olfaction and Taste," 6th ed., J. Le Magnen and P. MacLeod, Eds., IRL, London, England, 1977, p. 27.
(5) R. S. Shallenberger and M. G. Lindley, *Food Chem.*, **2**, 145 (1977).
(6) G. G. Birch and C. K. Lee, *J. Food Sci.*, **39**, 947 (1974).
(7) R. U. Lemieux and J. T. Brewer, in "Carbohydrates in Solution," H. S. Isbell, Ed., Advances in Chemistry Series 117, American Chemical Society, Washington, D.C., 1973, p. 121.
(8) H. D. Holtje and L. B. Kier, *J. Pharm. Sci.*, **63**, 1722 (1974).
(9) G. G. Birch and C. K. Lee, in "Developments in Sweeteners," C. A. M. Hough, K. J. Parker, and A. J. Vlitos, Eds., Applied Science, London, England, 1979, p. 165.
(10) G. G. Birch, in "Carbohydrate Sweeteners in Foods and Nutrition," P. Koivistoinen and L. Hyvönen, Eds., Academic, London, England, 1980, pp. 61–75.
(11) H. W. Spencer, in "Sweetness and Sweeteners," G. G. Birch, L. F. Green, and C. B. Coulson, Eds., Applied Science, London, England, 1971, p. 112.
(12) N. Larson-Powers and R. M. Pangborn, *J. Food Sci.*, **43**, 41 (1978).

Crystal Structure and Solid-State Behavior of Aspirin Anhydride Crystals

STEPHEN R. BYRN ˣ **and P. Y. SIEW**

Received May 2, 1980, from the *Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, IN 47906.* Accepted for publication August 15, 1980.

Abstract □ The crystal structure and solid-state behavior of aspirin anhydride were determined using single-crystal X-ray techniques and microscopic examination of the reacting crystals. The crystal structure and solid-state conformation of aspirin anhydride were similar to those of related compounds. The crystal packing of aspirin anhydride allows the initial product of the solid-state reaction to be predicted; however, this prediction could not be tested because the thermal degradation products reported in the literature appear to be those obtained from reaction in a liquid state.

Keyphrases □ Aspirin anhydride—determination of crystal structure and solid-state behavior, X-ray crystallography and microscopy of reacting crystals □ Crystal structure—aspirin anhydride, determination of solid-state behavior of crystals □ Degradation, thermal—aspirin anhydride end-products, crystal structure and solid-state behavior of aspirin anhydride determined

The use of crystallographic data to explain the products of solid-state reactions has provided insight into these reactions and the factors controlling them (1–3). However, few studies have been conducted to determine the relationship between the crystal structure and the degradation products of pharmaceuticals. The aim of this study was to investigate the products of the true solid-state reaction of aspirin anhydride in terms of the crystal packing. It is hoped that such studies will lay the groundwork for understanding drug degradation in the solid state and how to prevent this degradation.

This investigation involved a microscopic study of the behavior of solid aspirin anhydride during heating and determined the crystal structure of aspirin anhydride using single-crystal X-ray techniques. It was found that solid aspirin anhydride liquefies during reaction even at 50°.

EXPERIMENTAL

Preparation of Aspirin Anhydride—Aspirin anhydride was prepared following literature procedures for the reaction of acetylsalicylic acid with ethyl chloroformate (4, 5). When 10 g of acetylsalicylic acid was mixed with 6.2 g of ethyl chloroformate with cooling, ~4 g of crystals formed, mp 79–81°. Subsequent structure determination showed these crystals to be aspirin anhydride.

Crystal Properties of Aspirin Anhydride ($C_{18}H_{14}O_7$, mol. wt. = 342.31)—The crystals were tetragonal with a = 8.457(1), c = 23.166(6) Å, V = 1656.85 Å^3, z = 4, ρ_{calc} = 1.372 g/cm^3, μ (20°, CuKα, λ = 1.5418 Å) = 9.176 cm^{-1}; systematic absences $00l$, $l \neq 4n$; $h00$ $(0k0)$, $h \neq 2n$ $(k \neq 2n)$; space group $P4_12_12$ or $P4_32_12$. The structure was determined assuming space group $P4_12_12$.

Data Collection—A crystal of 0.49 × 0.48 × 0.20 mm^3 was obtained from absolute ethanol by cooling and was aligned with its long axis parallel to the ϕ direction of a Picker four-angle diffractometer. The ϕ direction thus was parallel to the a axis. Intensity data were collected with CuKα radiation and a scintillation counter for the reciprocal octant hkl to a 2θ maximum of 133.85° using a $\theta/2\theta$ scan of 2.4° and a scan speed of 30 sec/degree. Background readings were taken for 10 sec at each end of the scan range. During the data collection (120 hr), the decay of two reference reflections was only 6.7%.

Equivalent reflections in the two semioctants hkl $(h > k)$ and khl $(h < k)$ were averaged using a discrepancy factor R of 0.067. If:

$$\frac{|I(hkl) - I(khl)|}{[I(hkl)I(khl)]^{1/2}} \leq R$$

the average was taken; otherwise, the reflection with the larger net count was retained. The total number of independent reflections was 946, 645 of which satisfied the criterion $F > 3\sigma(F)$ and were considered to be observed. Lorentz polarization corrections were applied to all data. No absorption correction was made.

Structure Determination and Refinement—The 100 reflections of the largest E-forming 843 Σ_2 relationships were sorted with respect to the strength of the phase reliability given by the equation $\sigma_h = 2\sigma_3\sigma_2^{-3/2}|E_h|(s_k^2 + c_k^2)^{1/2}$, where the symbols are defined by Karle and Karle (6). The convergence method was applied to generate 64 starting sets which, upon multiple-tangent refinement, yielded sets of phases with various figures of merit (7). An E-map calculated from the set of phases with the highest figure of merit revealed the positions of 12 of the 13 nonhydrogen atoms. The remaining atom was the oxygen atom.

Full matrix least-squares techniques were used to refine the structure. A weighting scheme ($w^{-1} = (|F_{obs} - B|/A)^2 + 1$, where A = 2.5 and B = 11.3) was also used. Refinement with nonhydrogen atoms proceeded smoothly to an R of 0.105 and a wR of 0.080. A difference Fourier map then revealed the positions of five of the seven hydrogen atoms, and the other two methyl hydrogen atom positions were calculated. The refinement holding the hydrogen atoms invariant with a temperature factor of $B_{overall}$ + 1 then proceeded smoothly to an R of 0.085 and a wR of 0.074. Release of the constraints on the hydrogen atoms resulted in improvement of the R factor to 0.082 and chemically reasonable positions for the aromatic hydrogen atoms but unreasonable positions for the methyl hydrogen atoms; thus, these positions were recalculated, and the final

0022-3549/81/0300-0280$01.00/0

Table I—Final Parameters (Estimated Standard Deviation) x,y,z × 10^4, U_{ij} × 10^3 Å^2, Temperature Factors = exp[$-2\pi^2(a^{*2}h^2U\cdots + \cdots + 2b^*c^*klU_{23})$]

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	u_{23}
O-1	1516 (4)	x	0	56 (2)	u_{11}	115 (4)	−5 (3)	$-u_{23}$	19 (2)
O-2	3471 (5)	2484 (5)	552 (2)	69 (2)	58 (2)	100 (3)	−1 (2)	1 (2)	−13 (2)
O-3	4499 (4)	261 (5)	1356 (2)	48 (2)	96 (3)	67 (2)	−2 (2)	2 (2)	−17 (2)
O-4	6920 (5)	649 (6)	1014 (2)	65 (3)	95 (3)	99 (3)	−12 (3)	19 (3)	−11 (2)
C-1	3240 (6)	−305 (6)	446 (2)	49 (3)	55 (3)	57 (3)	−11 (3)	2 (2)	−4 (3)
C-2	4136 (6)	−806 (7)	913 (2)	51 (3)	73 (4)	49 (3)	−11 (3)	3 (3)	−7 (3)
C-3	4616 (7)	−2355 (7)	979 (2)	59 (3)	70 (4)	74 (3)	−3 (4)	2 (3)	10 (3)
C-4	4154 (8)	−3464 (7)	580 (3)	78 (4)	61 (4)	91 (4)	7 (3)	8 (4)	4 (4)
C-5	3233 (8)	−3030 (6)	119 (3)	78 (4)	52 (3)	72 (4)	−9 (3)	1 (3)	−7 (3)
C-6	2780 (6)	−1464 (7)	60 (2)	62 (3)	68 (4)	56 (3)	−4 (3)	−3 (3)	−3 (3)
C-7	2824 (6)	1347 (7)	351 (2)	47 (3)	51 (3)	74 (4)	−13 (3)	10 (3)	−10 (3)
C-8	5947 (7)	957 (7)	1356 (3)	65 (4)	69 (4)	62 (3)	13 (3)	−1 (3)	1 (3)
C-9	6083 (8)	2086 (9)	1843 (3)	84 (5)	104 (5)	86 (4)	−24 (4)	1 (4)	−26 (4)

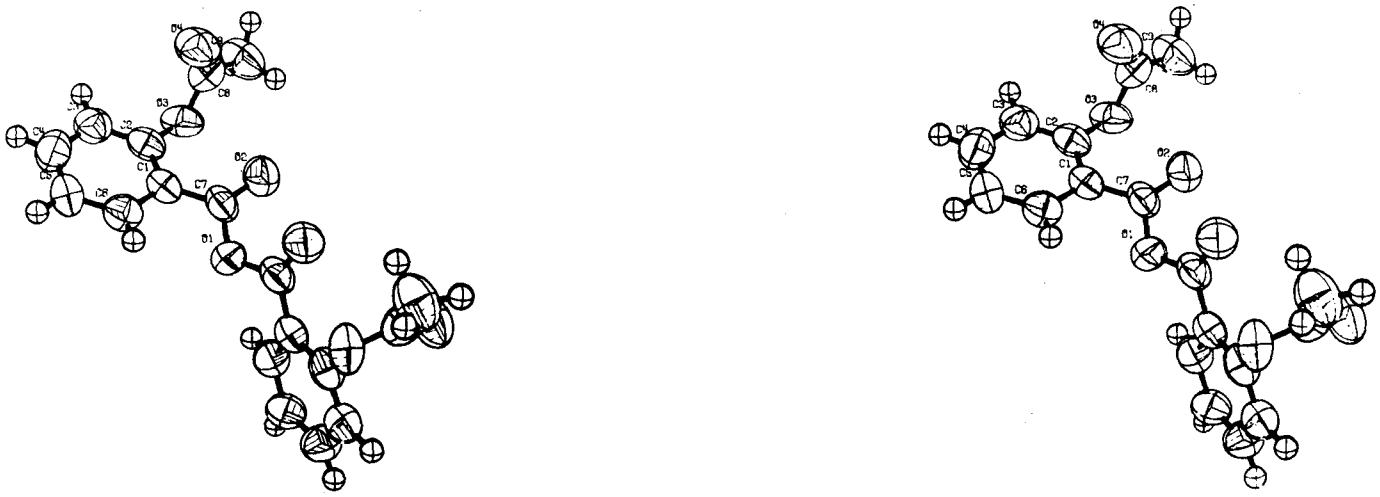


Figure 1—*View of aspirin anhydride along the (018) direction. The ellipsoids are drawn with a probability of 60% and the isotropic spheres of the hydrogen atoms with the arbitrary radius of 0.147 Å.*

refinement was performed holding the hydrogen atom positions and temperature factors constant. The final R was 0.082 and wR was 0.065. Table I lists the final atomic positions and temperature factors.

Figure 1 gives a stereoscopic view of the aspirin anhydride molecule along the (018) direction. The molecule has point group symmetry C-2 with the unique oxygen atom situated on the diad axis of the crystal structure.

Figure 2 shows a stereoscopic drawing of the crystal packing of aspirin anhydride.

Tables II and III list the bond lengths and angles in aspirin anhydride.

Table IV describes the deviation of atoms C-7, O-2, O-3, and O-1 from the best plane through the ring atoms C-1 through C-6. The plane through these six ring atoms gives a χ^2 of 14.94, indicating a probability of <0.01 that these atoms are planar.

Table V lists the dihedral angles for the various atoms. In addition, the angle of twist of the anhydride, *i.e.*, the angle between the plane through C-7, O-1, and O-2 and the plane through C-7′, O-2′, and O-1 was 54°. Table VI lists the contacts of less than 3.5 Å.

The solid-state behavior of aspirin anhydride crystals grown from ethanol was studied. Single crystals were heated on a hot stage at various temperatures. Liquefication was observed at all temperatures. Even at the lowest temperature (50°), liquefication occurred after 11 days.

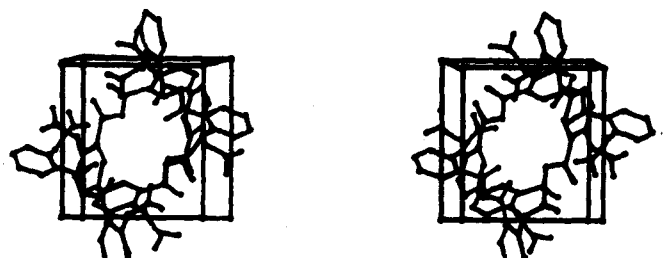


Figure 2—*Stereoscopic view of the crystal packing of aspirin anhydride. The origin is at the bottom left with a across and b vertical.*

DISCUSSION

The general molecular geometry of aspirin anhydride is consistent with that of other anhydrides such as *p*-bromobenzoic anhydride (8) in that

Table II—Bond Lengths and Important Intramolecular Contacts in Aspirin Anhydride with Standard Deviations in Parentheses

Atom	Bond	Atom	Bond
O-1–C-7	1.380 (6)	C-2–C-3	1.380 (9)
O-2–C-7	1.202 (7)	C-3–C-4	1.374 (9)
O-3–C-2	1.400 (7)	C-4–C-5	1.371 (9)
O-3–C-8	1.359 (7)	C-5–C-6	1.385 (8)
O-4–O-8	1.172 (7)	C-8–C-9	1.483 (9)
C-1–C-2	1.387 (7)	C-7–O-4	3.835 (7)
C-1–C-6	1.382 (7)	C-8–O-2	3.084 (7)
C-1–C-7	1.457 (8)	O-2–C-7′	2.772 (7)

Table III—Bond Angles in Aspirin Anhydride with Standard Deviations in Parentheses

Atom	Bond	Atom	Bond
C-7′–O-1–C-7	120.9 (4)	C-1–C-2–C-3	122.5 (5)
O-1–C-7–O-2	120.7 (5)	C-3–C-2–O-3	117.8 (5)
O-1–C-7–C-1	112.5 (4)	C-2–O-3–C-8	118.5 (4)
O-2–C-7–C-1	126.8 (5)	C-2–C-3–C-4	119.3 (5)
C-7–C-1–C-2	122.9 (5)	C-3–C-4–C-5	120.2 (6)
C-7–C-1–C-6	121.0 (5)	C-4–C-5–C-6	119.3 (5)
C-2–C-1–C-6	116.1 (5)	C-5–C-6–C-1	122.5 (5)
C-1–C-2–O-3	119.6 (5)		

Table IV—Deviation of All Atoms of Aspirin Anhydride from the Best Plane through the Ring Atoms C-1 through C-6

Atom	Deviation from Plane, Å
C-1	−0.015
C-2	0.013
C-3	−0.004
C-4	−0.004
C-5	0.002
C-6	0.007
O-1	0.360
O-2	−0.471
O-3	0.144
O-4	2.030
C-7	−0.095
C-8	−0.974
C-9	−0.639

Table V—Dihedral Angles in Degrees for Aspirin Anhydride

Atom	Angle
O-3–C-2–C-1–C-7	8.5 (8)
C-2–C-1–C-7–O-2	19.9 (9)
C-2–C-1–C-7–O-1	−158.4 (5)
C-6–C-1–C-7–O-1	23.1 (7)
C-6–C-1–C-7–O-2	−158.6 (5)
C-2–O-3–C-8–C-9	177.9 (5)
C-2–O-3–C-8–O-4	−3.2 (8)
C-1–C-2–O-3–C-8	−99.4 (6)
C-3–C-2–O-3–C-8	84.4 (6)
C-6–C-1–C-2–O-3	−172.9 (5)
C-3–C-2–C-1–C-6	3.2 (8)
C-3–C-2–C-1–C-7	−175.4 (5)

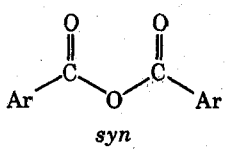
Table VI—Contact Distances ≤3.5 Å Involving Nonhydrogen Atoms

Atoms	Distance
O-2···C-3 ($\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{4} - z$)	3.446 (7)
O-2···C-4 (x, y + 1, z)	3.476 (7)
O-2···C-5 (y + 1, x, $\bar{z}$)	3.402 (7)
O-4···C-5 (y + 1, x, $\bar{z}$)	3.414 (8)
O-4···C-6 (y + 1, x, $\bar{z}$)	3.362 (7)

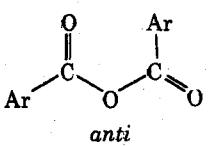
the geometry is *syn* rather than *anti*. However, the crystal packing of aspirin anhydride is different from that of *p*-bromobenzoic anhydride. The bond lengths, angles, and torsion angles are consistent with those of the related acetylsalicylic acid and salicylic acid. The crystal packing indicates that a particular product should predominate during solid-state reaction; however, published studies indicate that numerous products are formed (4), probably because liquefication occurs during the reaction.

Bond Lengths and Angles—The bond lengths (Table II) are within 2σ of those of acetylsalicylic acid (9) except for the bond lengths involving the carboxyl group of the anhydride: C-7–O-1 is 1.380(6) in aspirin anhydride *versus* 1.29 in aspirin; C-7–O-2 is 1.202(7) in aspirin anhydride *versus* 1.24 in aspirin; and C-7–C-1 is 1.457(8) in aspirin anhydride *versus* 1.50 in aspirin. Similarly, the bond lengths of aspirin anhydride are within 2σ of those for salicylic acid (10), except for C-7–O-2 and C-7–O-1, which are 1.23 and 1.31 in salicylic acid, respectively.

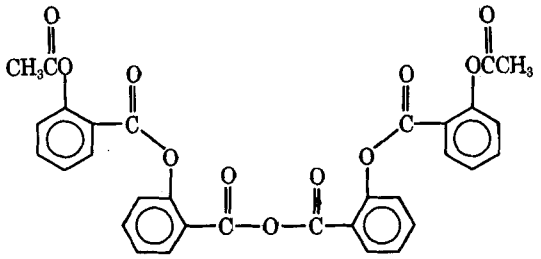
The bond angles in aspirin anhydride differ from those in aspirin and salicylic acid only around the anhydride and acetyl groups. The angles in aspirin anhydride *versus* aspirin that differ by more than 2° (2σ) are: C-7–C-1–C-2, 122.9 *versus* 125; O-2–C-7–C-1, 126.8 *versus* 118; O-2–C-7–O-1, 120.7 *versus* 123; and O-1–C-7–C-1, 112.5 *versus* 119. For aspirin anhydride *versus* salicylic acid, the angles that differ by more than 2° (2σ) are: C-7–C-1–C-2, 122.9 *versus* 120; C-6–C-1–C-2, 116.1 *versus* 119; C-1–C-2–C-3, 122.5 *versus* 120; O-2–C-7–C-1, 126.8 *versus* 123; and O-1–C-7–C-1, 112.5 *versus* 116.



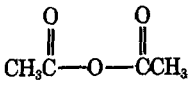
syn



anti



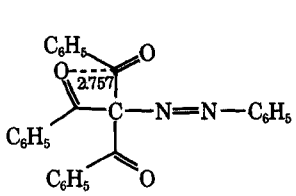
I



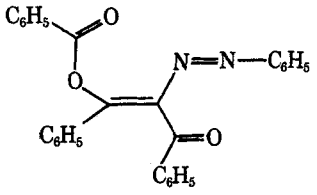
II

None of these differences in bond lengths or angles are major, and they probably reflect the slightly different electronic and steric requirements of the anhydride *versus* the acid functionality.

Molecular Conformation and Torsion Angles—Aspirin anhydride adapts a nonplanar *syn*-conformation instead of the *anti*-conformation that might be expected to be more planar. The angle of twist of the car-

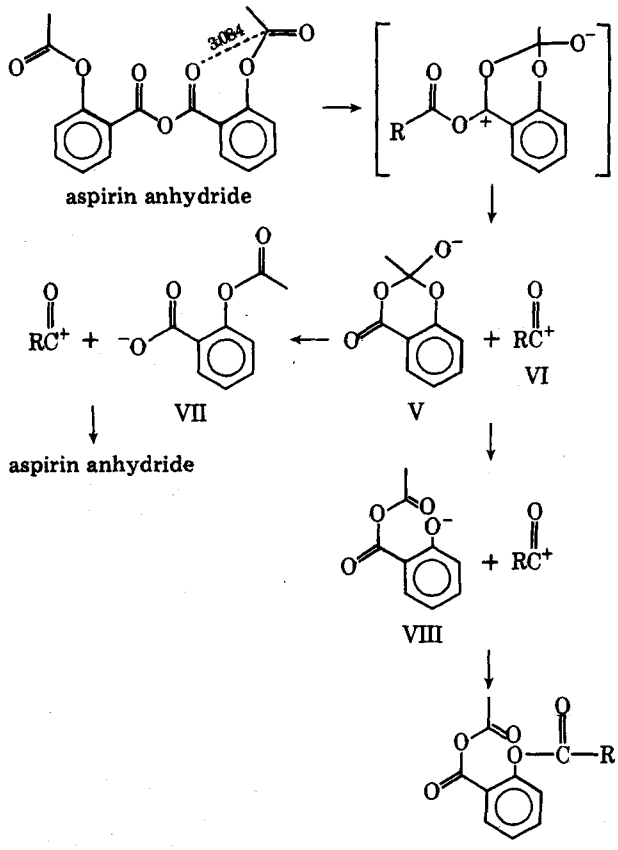


III



IV

Scheme I—Benzoyl transfer reactions of phenylazotribenzoylmethane (III).



Scheme II—Possible acyl transfer reaction in solid aspirin anhydride.

bonyl groups with respect to each other is 54°. A similar *syn*-conformation is observed in *p*-bromobenzoic anhydride crystals. The anhydride group in aspirin anhydride is twisted from the plane of the benzene ring significantly more than is the acid group in either acetylsalicylic acid or salicylic acid. In aspirin, the C-2–C-1–C-7–O-2 torsion angle is −2°; in salicylic acid, it is 1°, in aspirin anhydride, it is 19.9(9)°. The acetyl group is rotated about the C-2–O-3 bond in both aspirin anhydride and acetylsalicylic acid. The torsion angle C-1–C-2–O-3–C-8 is 99.4° in aspirin anhydride and 86° in aspirin.

Solid-State Reactions and Crystal Packing—The following generalizations can be made concerning the solid-state thermal reactions of aspirin anhydride (4):

1. Water contamination increases the thermal instability of aspirin anhydride.

2. Thoroughly dried, high-purity aspirin anhydride has enhanced thermal stability.

3. Removal of the aspirin anhydride degradation products (*i.e.*, acetic acid and acetic anhydride) by a stream of heated air inhibits liquefication and stabilizes aspirin anhydride.

4. The thermal degradation products include all possible mixed anhydrides from acyl and benzoyl transfer reactions; however, the end-products are I and II (4). It is likely that the end-products observed are due to the reaction in both the solid and liquid states.

The crystal packing of aspirin anhydride was investigated to see if any predictions concerning the products of the solid-state reactions can be made. In particular, the crystal packing was investigated to see if the formation of a single acyl or benzoyl transfer product could be predicted.

The O···C=O intramolecular contacts are listed in Table II. No intramolecular O···C=O contacts of <4.0 Å were observed. The intramolecular contacts are within the normal range of O···C=O interactions (11) but are not unusually short since the shortest intramolecular interaction reported by Burgi *et al.* was 2.58 Å (11). In addition, the conversion of the yellow form of phenylazotribenzoylmethane (III) to α-phenylazo-β-benzoyloxybenzolacetophenone (IV) involves a benzoyl migration in a case where the O···C=O distance is 2.757 Å (12). In aspirin anhydride, the shortest O···C=O distance is 2.772 Å; however, rearrangement involving this contact regenerates aspirin anhydride. Acyl transfer involving the next closest contact (3.084 Å) leads to V and VI (or the equivalent radicals; Scheme II), which degrades to VII and VIII. If VI and VII recombine, aspirin anhydride is regenerated; if VIII and VI combine, IX is formed. Thus, a true solid-state reaction with cage recombination would be expected to yield IX.

Indeed, IX was synthesized and found to give the same degradation products as aspirin anhydride (4). Thus, the decomposition products of aspirin anhydride are completely consistent with crystal packing. However, a true solid-state reaction is expected to yield only IX. The fact that other products are isolated indicates that other reactions also occur. This finding is reasonable since liquefication of aspirin anhydride crystals occurs even at 50°. Careful study of the initial stages of aspirin anhydride degradation is in order, perhaps using high-pressure liquid chromatography, to see if IX is an initial product in aspirin anhydride degradation.

In summary, this paper illustrates the predictions and insight into the degradation of solid pharmaceuticals that can be gained by a combined X-ray crystallographic and photomicrographic study. Future studies of the degradation of solid pharmaceuticals will involve application of these techniques and should lead to both a better understanding of the solid-state degradation of pharmaceuticals and to improved methods of stabilization of pharmaceuticals.

REFERENCES

(1) S. R. Byrn, *J. Pharm. Sci.*, **65**, 1 (1976).

(2) D. Y. Curtin and I. C. Paul, *Science*, **187**, 19 (1975).

(3) M. D. Cohen and B. S. Green, *Chem. Br.*, **490**, (1973).

(4) E. R. Garrett, E. L. Schumann, and M. F. Grostic, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 684 (1959).

(5) A. Einhour and R. Seuffert, *Chem. Ber.*, **43**, 2990 (1910).

(6) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

(7) G. Germain, P. Main, and M. M. Wolfson, *ibid.*, **B26**, 274 (1970).

(8) C. S. McCammon and J. Trotter, *ibid.*, **17**, 1333 (1964).

(9) P. J. Wheatley, *J. Chem. Soc.*, **1964**, 6036.

(10) M. Sundaralingam and L. H. Jensen, *Acta Crystallogr.*, 18 1053 (1965).

(11) H. G. Burgi, J. D. Dunitz, and E. Shefter, *ibid.*, **B30**, 1517 (1974).

(12) D. B. Pendergrass, D. Y. Curtin, and I. C. Paul, *J. Am. Chem. Soc.*, **94**, 8722 (1972).

ACKNOWLEDGMENTS

Supported by National Institute of Health Grant GM-21174.