Constants $k_1$ through $k_4$ of Table II are substantially slower than the diffusion-limited constants for the ionization of normal or classical acids such as carboxylic, phenolic, and nitrogen acids (8, 9). The ionization kinetics generated in this work will be used to determine whether, in fact, the nonclassical phase-transport behavior of phenylbutazone (1–7) can be traced to this relatively slow ionization rate.

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# Kinetic Analysis of Penicillin Degradation in Acidic Media


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**Abstract** □ Degradation of penicillin in acidic media (pH 2.7) was monitored by high-pressure liquid chromatography and UV spectroscopy. The effects of temperature, buffer concentration, and ionic strength were examined. A degradation pathway is proposed, and the apparent first-order rate constant and energy of activation were calculated for each reaction. One or more degradation products containing a sulfhydryl group, a functional group often suggested as having a major role in eliciting allergic responses to penicillin therapy, were present throughout the degradation scheme.



**Keyphrases** ◻ Penicillin—degradation in acidic media, kinetic analysis, monitored by high-pressure liquid chromatography and UV spectroscopy, effect of temperature, buffer concentration, and ionic strength ◻ Degradation—penicillin in acidic media, kinetic analysis, monitored by high-pressure liquid chromatography and UV spectroscopy, effect of temperature, buffer concentration, and ionic strength □ High-pressure liquid chromatography—used to monitor degradation of penicillin in acidic media, kinetic analysis □ UV spectroscopy—used to monitor degradation of penicillin in acidic media, kinetic analysis □ Antibacterial agents—penicillin, degradation in acidic media, kinetic analysis


It is estimated that between 1 and 10% of the population experiences allergic response after penicillin therapy, with 300 fatalities in the United States each year (1). Research on penicillin allergy has considered four factors which may be of importance: (*a*) direct reactions of the drug with protein *in vivo*, (*b*) degradation products of penicillin that can react with protein, (*c*) impurities other than degradation products that may be in the dosage form with penicillin, and (*d*) metabolites of penicillin that can react with protein (2).

One approach to the problem of penicillin allergy would be to determine the role of specific penicillin degradation products in producing an allergic response and, through dosage form design, to minimize the formation of degradation products showing significant potential as allergenic determinants. To use this approach, the time sequence for the presence of penicillin degradation products in aqueous media needs to be established.

Several reviews (2, 3) suggested schemes for the degradation of penicillin. It was proposed that penillic and penicilloic acids are the major degradation products when penicillin is aged in acidic solutions (4). The mechanism of penicillin degradation was studied in acidic solution, and it was proposed that penicillenic acid forms from the reaction of the penicillin ion with a proton or from the spontaneous rearrangement of undissociated penicillin (5). It was suggested also that penillic acid forms from penicillenic acid and that penilloic acid is the product from the acid catalysis of

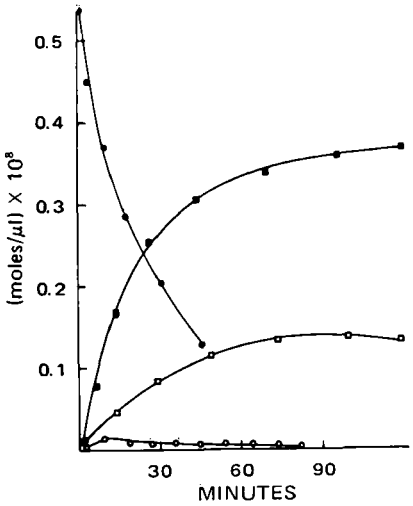



**Figure 1**—*Occurrence of penicillin G potassium degradation products at pH 2.70 (Condition I). Key: ●, penicillin G potassium; ○, benzylpenicillenic acid; □, benzylpenamaldic acid; and ■, benzylpenillic acid.*

undissociated penicillin, with penicilloic acid as the intermediate (5). Other investigators hypothesized the presence of an oxazolone–thiazolidine intermediate in the formation of penicillenic acid (6) or the formation of penicillamine and penaldic acid (7) as degradation pathways for penicillin in acidic media.

Because of its high reactivity and its suggested role in penicillin allergy, added attention has been given to the fate of benzylpenicillenic acid after it forms in aqueous solution. It was speculated that four reaction products could form from benzylpenicillenic acid, and their theoretical yields if penicillenic acid was aged at pH 0.5–14 were calculated (8). The investigators concluded that only penillic and penamaldic acids were formed at pH 2.0 and 2.9, with no indication of penicilloic acid being present in the solution.

The objective of this study was to use a combination of high-pressure liquid chromatography (HPLC) and UV spectroscopy to identify and quantify the degradation products that form during the aging of penicillin in acid media (pH 2.70). These data permitted the development of a pathway for the acidic degradation of penicillin. By using the scheme, the rate constant and the energy of activation of each degradation product were calculated. The presence of degradation products

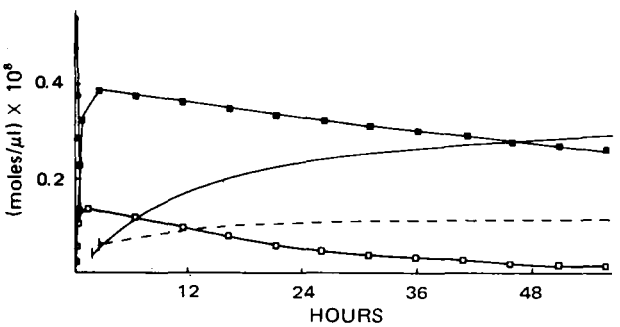



**Figure 2**—*Occurrence of penicillin G potassium degradation products at pH 2.70 (Condition I). Key: -●-, penicillin G potassium; -□-, benzylpenamaldic acid; -■-, benzylpenillic acid; —, benzylpenilloic acid; and – –, penicillamine.*

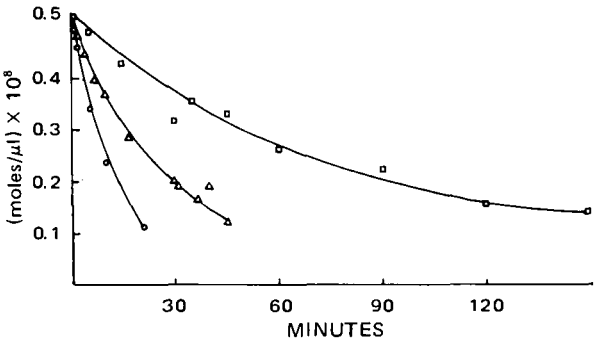



**Figure 3**—*Loss of penicillin G potassium with time at pH 2.70. Key: ○, 45°; △, 37°; and □, 25°.*

that could be responsible for eliciting an allergic response is especially noted.

## EXPERIMENTAL

**Materials**—All chemicals used were official or reagent grade. Penicillin G potassium[1], benzylpenicillenic acid, and penicillamine[2] were obtained commercially.

Benzylpenillic acid, benzylpenilloic acid, and benzylpenicilloic acid were synthesized by standard methods (9–11). Their identities were confirmed using combinations of UV spectroscopy, IR spectroscopy, mass spectrometry, NMR spectroscopy, potentiometric titration, and elemental analysis.

Benzylpenamaldic acid was obtained using HPLC. Penicillin G potassium (0.05 *M*) was dissolved in 0.03 *M* citric acid–0.0067 *M* disodium phosphate buffer, pH 2.70, and aged at 37° for 2 hr. Ten-microliter samples were withdrawn and injected onto an anion-exchange[3] column in a high-pressure liquid chromatograph[4]. The compounds were eluted with a mobile phase of 15.4 ml of 0.1 *M* citric acid and 7.0 ml of 0.2 *M* disodium phosphate diluted to 650 ml with double-distilled water. The fraction of eluant containing the compound with a retention time of 13 min was collected immediately after it had passed through a refractive index detector and was then lyophilized[5].

**Instrumentation**—The liquid chromatograph was equipped with a UV detector operating at 254 nm. The refractive index detector was double beamed, referenced against a cell filled with mobile phase.

The stationary phase was an anion-exchange resin prepacked into a pair of coupled 0.61-m stainless steel columns, 2.3 mm i.d. The mobile phase was 15.4 ml of 0.1 *M* citric acid and 7.0 ml of 0.2 *M* disodium phosphate diluted to 650 ml with double-distilled water, giving a 0.0045 *M* buffer solution at pH 3.80.

All injections were made on-stream with a 25-μl high-pressure syringe[6].

Operating parameters for the instrument were as follows: flow rate, 0.7 ml/min (pressure 1000–1200 psi); temperature, ambient; and UV attenuation, 0.04 absorbance unit full scale, except for the assay of benzylpenillic acid which was at 0.08 unit full scale.

An analog computer was used to fit the data to potential degradation schemes. A digital computer was used to confirm the scheme selected and to perform statistical analysis.

**Assay Methods**—Benzylpenicillenic acid was determined by measuring the UV absorbance[7] of the aqueous solutions at 322 nm (12). By using $\epsilon$ max of 31,500 (13) and Beer's law, the molar concentration of penicillenic acid was calculated.

Penicillin, benzylpenillic acid, benzylpenamaldic acid, benzylpenilloic acid, and penicillamine were monitored using HPLC (14). Linear calibration curves were obtained for each compound, and their equations were used to convert UV peak areas into solution concentrations.

[1] Chas. Pfizer and Co., New York, N.Y.
[2] Sigma Chemical Co., St. Louis, Mo.
[3] Bondapak AX/Corasil, Waters Associates, Framingham, Mass.
[4] Model ALC 202, Waters Associates, Framingham, Mass.
[5] Model USM-15, Virtis Co., Gardiner, N.Y.
[6] Series B-110 Pressure-LOK liquid syringe, Precision Sampling Corp., Baton Rouge, La.
[7] Cary model 17 spectrophotometer, Cary Instruments, Monrovia, Calif.

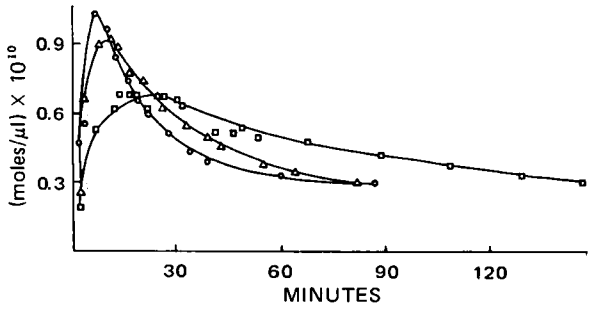



**Figure 4**—*Kinetic behavior of benzylpenicillenic acid at pH 2.70. Key:* O, *45°;* Δ, *37°; and* □, *25°.*

**Kinetic Studies**—*Condition I*—The solvent was a 0.03 *M* citric acid–0.0067 *M* disodium phosphate buffer, pH 2.70 and ionic strength 0.028. The temperature was maintained at 37 ± 0.01° in a constant-temperature water bath[8].

*Conditions II and III*—All conditions were similar to those described for I, except that the solvent temperatures were 25 and 45°, respectively.

*Condition IV*—Sodium chloride was added to the solvent described for I, 0.977 g/100 ml, to adjust the ionic strength to 0.195.

*Condition V*—The solvent was a 0.11 *M* buffer at pH 2.7, prepared from 90 ml of 0.1 *M* citric acid and 10 ml of 0.2 *M* disodium phosphate. The ionic strength was adjusted to 0.195 by adding sodium chloride, 0.649 g/100 ml. The temperature of the solvent was maintained at 37°.

Penicillin G potassium, 2 mg/ml, was added to the described solvents. Injections of the aging solutions, ranging in size from 4 to 15 μl, were made into the HPLC system. The UV absorbance of each solution at 322 nm was also monitored for the initial 2.5 hr.

## RESULTS AND DISCUSSION

**Monitoring Penicillin Solutions**—Five degradation products were detected and quantified in penicillin solutions aged at pH 2.70. The results at 37° are presented in Figs. 1 and 2. After 45 min, penicillin was no longer present in amounts detectable by the HPLC system. Benzylpenicillenic acid reached its point of maximum concentration in solution at 10 min. At 2 hr, benzylpenillic acid and benzylpenamaldic acid were the only two degradation products detected.

Benzylpenilloic acid and penicillamine were detected after 4 hr. Four degradation products, benzylpenillic acid, benzylpenamaldic acid, benzylpenilloic acid, and penicillamine, were still present after 48 hr.

Benzylpenicilloic acid (retention time of 19.5 min) was not detected in the reaction mixture, as anticipated (4). It is believed that the five degradation products detected represent the compounds that form

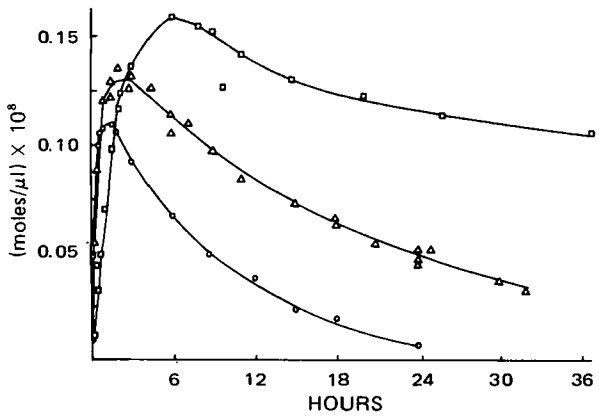



**Figure 5**—*Kinetic behavior of benzylpenamaldic acid at pH 2.70. Key:* O, *45°;* Δ, *37°; and* □, *25°.*

[8] Model ST Sargent-Welch Thermonitor, Sargent-Welch Scientific Co., Skokie, Ill.

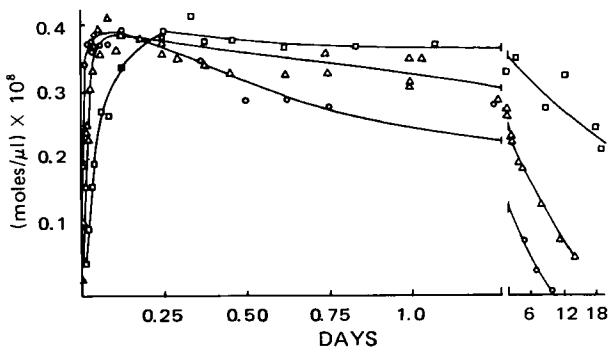



**Figure 6**—*Kinetic behavior of benzylpenillic acid at pH 2.70. Key:* O, *45°;* Δ, *37°; and* □, *25°.*

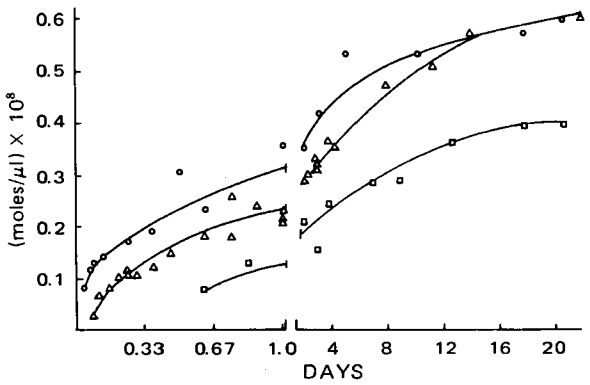



**Figure 7**—*Kinetic behavior of benzylpenilloic acid at pH 2.70. Key:* O, *45°;* Δ, *37°; and* □, *25°.*

in significant amounts, since the average mass balance during the first 12 hr was 101.8% of theory with a range of 96–108% of theory.

Increased temperature accelerated the rate of degradation of penicillin (Fig. 3). The rates of formation and loss of benzylpenicillenic acid (Fig. 4), benzylpenamaldic acid (Fig. 5), and benzylpenillic acid (Fig. 6) were also directly related to temperature. Benzylpenilloic acid appeared most rapidly in solutions aged at 45° (Fig. 7). No difference in the number or identity of the compounds formed was seen at the temperatures studied.

The rate of degradation of penicillin was directly related to buffer concentration. This relationship is seen by comparing the degradation profiles at Conditions IV (37°, 0.0367 *M* buffer, 0.195 ionic strength) and V (37°, 0.110 *M* buffer, 0.195 ionic strength). The increased buffer concentration increased the rate of penicillin degradation (Fig. 8). Figure 9 shows that there was a small increase in both the rates of formation and loss of benzylpenicillenic acid when the buffer concentration was increased. A similar effect was noted for benzylpenamaldic acid (Fig. 10) and benzylpenillic acid (Fig. 11). As with temperature, there was no change in the number or identity of degradation products due to the buffer effect.

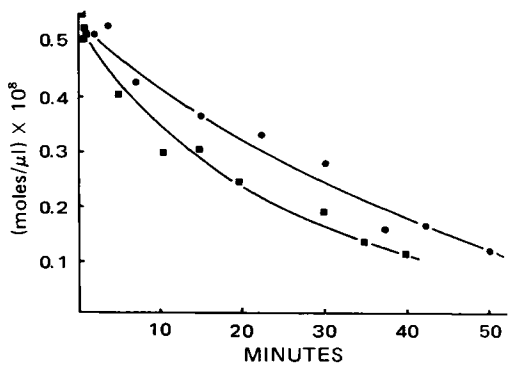



**Figure 8**—*Loss of penicillin with time at pH 2.70 and 37°. Key:* ●, *0.0367* M *buffer; and* ■, *0.11* M *buffer.*

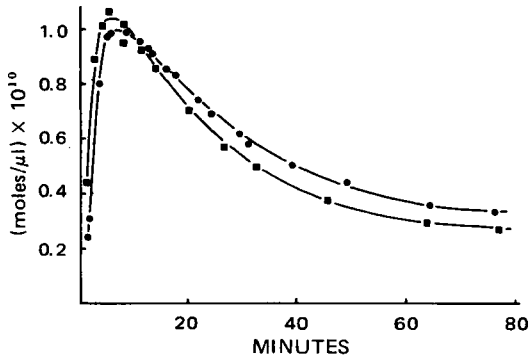



**Figure 9**—*Kinetic behavior of benzylpenicillenic acid at pH 2.70 and 37°. Key: ●, 0.0367 M buffer; and ■, 0.11 M buffer.*

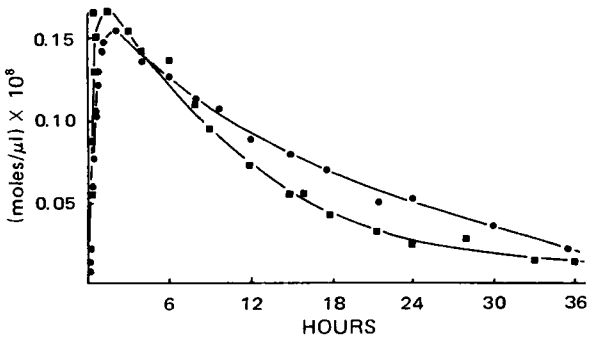



**Figure 10**—*Kinetic behavior of benzylpenamaldic acid at pH 2.70 and 37°. Key: ●, 0.0367 M buffer; and ■, 0.11 M buffer.*

The catalytic effect of the buffer was not unexpected; at pH 2.7, the citric acid in the buffer is present as dihydrogen citrate anion, which is known to have a catalytic effect on the degradation of penicillin in aqueous solution (15, 16).

The effect of ionic strength on the degradation of penicillin was examined by comparing the degradation profiles at Conditions I (37°, 0.0367 *M* buffer, 0.028 ionic strength) and IV (37°, 0.0367 *M* buffer, 0.195 ionic strength). The increase in ionic strength had no significant effect on the degradation of penicillin at pH 2.7, as illustrated by benzylpenicillenic acid (Fig. 12) and benzylpenamaldic acid (Fig. 13). There was also no change in the number or identity of the compounds formed in the 3-week aging period of the solutions.

**Proposed Degradation Scheme**—Based on the order of appearance and peak times for the degradation products (Figs. 1 and 2), it appears that benzylpenicillenic acid forms from penicillin. Benzylpenamaldic acid (peak at 1.5 hr) and benzylpenillic acid (peak at 2 hr) appear to form next. The final products are penicillamine and benzylpenilloic acid, which were still increasing after 92 hr at 37°.

To establish the role of benzylpenicillenic acid in the scheme, the decomposition of benzylpenicillenic acid in 0.0367 *M* buffer, pH 2.70, was monitored by HPLC. Ten milligrams of benzylpenicillenic acid was dissolved in 1 ml of absolute methanol and diluted to 5 ml with

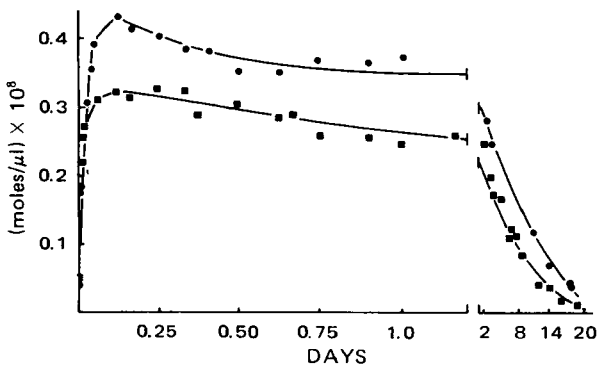
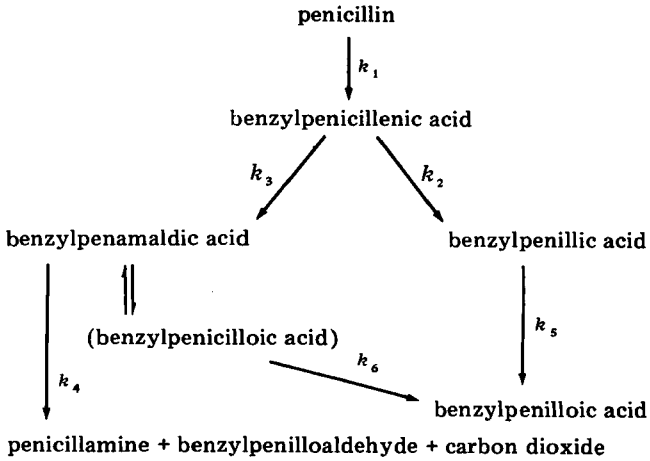



**Figure 11**—*Kinetic behavior of benzylpenillic acid at pH 2.70 and 37°. Key: ●, 0.0367 M buffer; and ■, 0.11 M buffer.*




*Scheme I—Proposed degradation pathway for penicillin in acidic media*

pH 2.7 buffer. The solution was aged at 25° and monitored by HPLC at 0, 37, 90, 130, and 200 min. A peak with a retention time corresponding to benzylpenamaldic acid was seen to increase in height from the 0- to the 37-min sample and then decrease at 90, 130, and 200 min. A peak with a retention time equal to benzylpenillic acid followed the same pattern. Peaks corresponding to penicillamine and benzylpenilloic acid steadily increased during the 190-min sampling period.

Based on this observation of the degradation of benzylpenicillenic acid and Longridge and Timms' (8) study of the hydrolysis of benzylpenicillenic acid in which they found both benzylpenamaldic acid and benzylpenillic acid in benzylpenicillenic acid solutions aged at pH 2.9, the sequence illustrated in Scheme I is proposed for the degradation of penicillin in acidic aqueous media.

Benzylpenicilloic acid was not detected in the study, but it is known to exist in equilibrium with benzylpenamaldic acid (3) and it is probably quickly decarboxylated to produce benzylpenilloic acid. Benzylpenilloaldehyde and penicillamine form upon the degradation of benzylpenamaldic acid. Benzylpenilloaldehyde was probably not

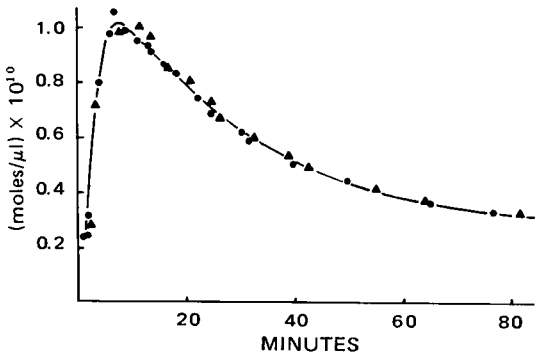



**Figure 12**—*Kinetic behavior of benzylpenicillenic acid at pH 2.70 and 37°. Key: ▲, 0.028 ionic strength; and ●, 0.195 ionic strength.*

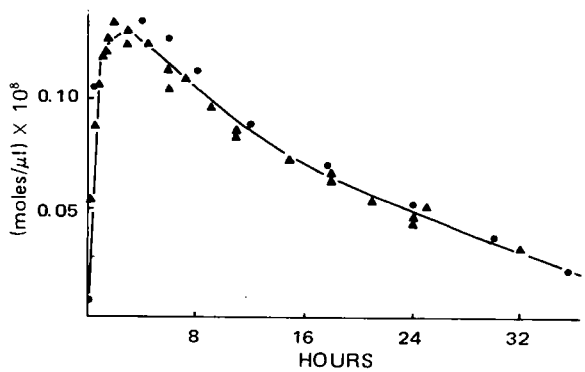



**Figure 13**—*Kinetic behavior of benzylpenamaldic acid at pH 2.70 and 37°. Key: ▲, 0.028 ionic strength; and ●, 0.195 ionic strength.*

**Table I—Apparent First-Order Rate Constants and Energy of Activation**

| Constant | 25°, 0.0367 *M* Buffer | 37°, 0.0367 *M* Buffer | 37°, 0.11 *M* Buffer | 45°, 0.0367 *M* Buffer | $E_a$, kcal mole$^{-1}$ deg$^{-1}$ | $R^2$ for $E_a$ |
|---|---|---|---|---|---|---|
| $k_1$, min$^{-1}$ | $9.0 \times 10^{-3}$ | $3.1 \times 10^{-2}$ | $3.7 \times 10^{-2}$ | $7.9 \times 10^{-2}$ | 20.3 | 0.998 |
| $k_2$, min$^{-1}$ | $2.5 \times 10^{-1}$ | $5.0 \times 10^{-1}$ | $7.0 \times 10^{-1}$ | 1.0 | 12.8 | 0.992 |
| $k_3$, min$^{-1}$ | $8.0 \times 10^{-2}$ | $2.0 \times 10^{-1}$ | $4.0 \times 10^{-1}$ | $3.3 \times 10^{-1}$ | 13.2 | 0.999 |
| $k_4$, min$^{-1}$ | $3.8 \times 10^{-5}$ | $2.3 \times 10^{-4}$ | $3.5 \times 10^{-4}$ | $6.4 \times 10^{-4}$ | 26.8 | 0.999 |
| $k_5$, min$^{-1}$ | $4.9 \times 10^{-5}$ | $1.2 \times 10^{-4}$ | $2.0 \times 10^{-4}$ | $2.1 \times 10^{-4}$ | 13.8 | 0.999 |
| $k_6$, min$^{-1}$ | $1.8 \times 10^{-4}$ | $5.0 \times 10^{-4}$ | $8.5 \times 10^{-4}$ | $8.1 \times 10^{-4}$ | 14.6 | 0.996 |

**Table II—Mean Square Relative Deviations**

| Conditions | Penicillin | Benzylpenicillenic Acid | Benzylpenillic Acid | Benzylpenamaldic Acid | Penicillamine | Benzylpenilloic Acid |
|---|---|---|---|---|---|---|
| 25°, 0.0367 *M* buffer | 0.13 (8)[a] | 0.17 (7) | 6.2 (21) | 348.7 (20) | — | 1875 (8) |
| 37°, 0.0367 *M* buffer | 0.005 (10) | 0.25 (7) | 0.68 (24) | 0.25 (24) | 2.42 (10) | 0.85 (13) |
| 37°, 0.11 *M* buffer | 0.002 (9) | 0.21 (7) | 0.43 (24) | 0.25 (23) | — | 1.59 (15) |
| 45°, 0.0367 *M* buffer | 0.011 (5) | 0.04 (6) | 6.5 (20) | 0.17 (14) | — | 0.19 (15) |

[a] Parenthetical values denote the number of experimental points.

separated from the solvent and, therefore, was not detected by the HPLC system. It is included in Scheme I.

Benzylpenicillenic acid, benzylpenamaldic acid, and penicillamine each contain a free sulfhydryl group which is the functional group often suggested as having a major role in eliciting allergic responses to penicillin therapy. One or more of these free sulfhydryl-containing compounds are present during the entire degradation scheme.

**Kinetics**—The apparent first-order rate constants $k_1$, $k_2$, and $k_3$ were initially determined by fitting the data by eye to the proposed reaction sequence using an analog computer. Figure 14 shows the fit obtained at 37° and is typical of results at other conditions.

The apparent first-order rate constant $k_5$ was determined by plotting the logarithm of benzylpenillic acid concentration *versus* time and assuming that the exponential term in $k_5$ dominated during an observed linear region of the semilogarithmic plot. This assumption was shown to be true by the analytical solution.

Similar treatment of a graph of the logarithm of benzylpenamaldic acid concentration *versus* time yielded $k_4 + k_6$. A graph of the logarithm of the concentration of benzylpenilloic acid *versus* time produced $k_5 + k_6$. Since $k_5$ was known from the direct data on the degradation of benzylpenillic acid, it was possible to determine $k_6$ and, hence, $k_4$. In all cases, the assumption that the term of interest dominated during the linear portion of the graphs was confirmed by the analytical solution.

The apparent first-order rate constants and the energy of activation for each reaction are given in Table I. The square of the correlation coefficient ($R^2$) approaches 1 for each energy of activation. Minimal literature values are available for comparison. However, the energy of activation for the hydrolysis of penicillin agrees well with Brodersen (3), and the sum of $k_2$ and $k_3$ at 25° agrees with Longridge and Timms' (8) rate constant for the hydrolysis of benzylpenicillenic acid.

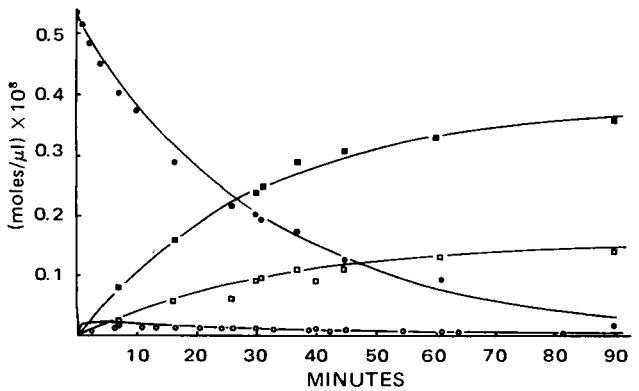



**Figure 14**—*Analog fit of penicillin degradation at pH 2.70 and 37° in 0.0367* M *buffer using Scheme I and rate constants from Table I. Key: ●, penicillin; ○, benzylpenicillenic acid; □, benzylpenamaldic acid; and ■, benzylpenillic acid.*

The system of equations describing the proposed scheme was integrated analytically, and the solution was programmed for a digital computer. No single criterion can be used to determine the best set of values for the reaction rate constants. The best set of values will depend, among other things, on the use to which the information will be put. For example, if one compound is known to cause the allergic response and normal storage is at one temperature, one would wish to fit the data to minimize deviations for that compound at the storage temperature. If two or more compounds are important, one would wish to fit each compound in a best sense. Similarly, if two or more temperatures are involved, one would fit one or more compounds over the pertinent range. Finally, one must decide whether relative or absolute deviations are more important.

Since so many possible criteria for a best fit exist, no attempt was made to optimize the fit by any of the criteria. Instead, a reasonable fit was obtained. The mean square relative deviations (relative deviation equals observed value minus predicted value divided by predicted value) are shown in Table II. Penicillamine was only monitored at 37°, 0.0367 *M* buffer. As can be noted from Table II, an appreciable mean square relative deviation only occurred for the later appearing compounds at 25°. At the lower temperature, these compounds only appeared in small concentrations, so a small absolute deviation resulted in a large relative deviation. The proposed degradation scheme and rate constants accurately describe the observed degradation of penicillin G potassium at pH 2.70.

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# Effect of Intragranular and Extragranular Disintegrating Agents on Particle Size of Disintegrated Tablets

**E. SHOTTON x and G. S. LEONARD ***

**Abstract** □ Five materials were compared for their effectiveness as disintegrating agents: maize starch, sodium calcium alginate, alginic acid, microcrystalline cellulose, and a colloidal aluminum silicate. The effect of the proportion of the agent present and the position with respect to the granule, intra- and extragranular, was examined. The extragranular formulations disintegrated much more rapidly than the intragranular ones, but the latter gave a much finer dispersion of particles. A combination of intra- and extragranular disintegrating agents gave the best compromise; of those tested, the alginates appeared to effect the breakdown to the smallest particles when placed intragranularly. A method of assessing the effectiveness of disintegrating agents for uncoated tablets is suggested, but the resulting weight mean particle size is the more important criterion for tablets complying with a pharmacopoeial disintegration test. The porosity and crushing strength of tablets are useful as guides to disintegration only when a given formulation is used.

**Keyphrases** □ Disintegrating agents—intra- and extragranular, effect on particle size of disintegrated tablets □ Particle size—disintegrated tablets, effect of intra- and extragranular disintegrating agents □ Tablets—effect of intra- and extragranular disintegrating agents on particle size □ Dosage forms—tablets, effect of intra- and extragranular disintegrating agents on particle size

The disintegration test described in the British Pharmacopoeia ensures that the tablet will break down to pass a 1.70-mm sieve aperture. This size is larger than the granule size used for most tablets and has been criticized (1). A few attempts have been made to assess the particle sizes formed on disintegration.

A nest of three sieves with apertures of 0.81, 0.54, and 0.27 mm was used in the USP disintegration test apparatus instead of the tube described (2). An automated particle counter[1] was used to determine particle-size frequencies for tablets prepared from aspirin and starch mixtures (3). Sandell (4) used a method similar to that of Sanders (2), but the sieves had apertures of 0.1, 0.5, and 2.0 mm.

Previous work on the sizing of the disintegrant has been reviewed (5). To obtain rapid dissolution, disintegration should release drug as near as possible to its original particle size.

## EXPERIMENTAL

**Materials**—Sulfadiazine BP was used as the active drug. The solubility was determined as 14.4 mg in 100 ml of water at 37°, and the density was 1.505 g/ml at 21°.

The size distribution of the sulfadiazine powder was determined using an automated particle counter[1] with 0.9% (w/v) solution of sodium chloride saturated with sulfadiazine as the electrolyte. The average mean weight diameter was approximately 9 μm (6).

The following disintegrating agents were used: maize starch BP, microcrystalline cellulose[2], sodium calcium alginate[3], alginic acid, and a synthetic colloidal aluminum silicate[4]. Povidone was used as a binder to form the granules.

**Preparation**—Wet granulation was accomplished by moistening sulfadiazine with a sufficient quantity of 10% povidone solution to give a final content of 3% (w/w) followed by additional distilled water. The moistened mass was pushed through a granulator[5], the granules were then dried, and a sieve fraction of 355–500-μm particles was used. Extragranular agents were added to the dried granules.

Intragranular disintegrating agents were mixed with the sulfadiazine powder before granulating with the povidone solution.

Granulation by precompression was used only for the sodium calcium alginate, since this method was recommended by the suppliers. One gram of the mixed powders was compressed in a 15.35-mm diameter die to form a weak tablet. Such tablets were then broken to form granules, and a 355–500-μm fraction was selected. Before precompression, povidone powder (3%) was incorporated in one batch of powder but not in a second batch. The tablets produced from these granules were thus comparable with the intragranular tablets containing sodium calcium alginate from the wet granulation method.

The proportions of these agents are shown in Table I.

[1] Coulter.
[2] Avicel PH.
[3] Alginate F417, Alginate Industries Ltd.
[4] Laponite CP, Laporte Industries Ltd.
[5] Erweka F.A.G.