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Stability of Pharmaceuticals

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CONTENTS

Many in-depth articles and seminar proceedings have appeared in the past 2 decades on various aspects of stability (1–10), but no single report has treated the overall subject in an integrated fashion. Investigations into the stability of pharmaceuticals have ranged from fundamental studies on the rates and mechanisms of reactions of the active substance, through evaluation of the influence of the formulation and production processes on the drug and drug product, to, finally, the role of the container and the effect of storage and distribution of the finished packaged article on the integrity of the product.

The objectives of this article are to review the many facets of stability and to outline what a present-day stability program does and should include. We hope to interrelate scientific considerations with regulatory requirements.

It has been recognized that there are legal, moral, economic, and competitive reasons, as well as those of safety and efficacy, to monitor, predict, and evaluate drug product stability (7). However, stability can and does mean different things to different people or to the same people at different times, even those in pharmaceutical science and industry. Although unified nomenclature has been proposed, various terminology is still employed to encompass the what and the how and the why of stability: stability study, kinetic study, compatibility study, stability evaluation, stability-indicating assay, expiration dating, outdating, shelflife, storage legend, preformulation studies, failures of a batch to meet specifications, microbiological stability, stability of the active ingredient, stability of the formulation, stability in the marketed package, stability in sample packages, stability in the dispensing package, and stability in the hands of the consumer. All of these areas have been referred to as stability.

In the pharmaceutical industry, the disciplines primarily involved with stability are pharmaceutical analysis and product development. However, physical and organic chemistry, mathematics, physics, microbiology, toxicology, production, packaging, engineering, quality control, and distribution are all included. Basic subjects for consideration are physical organic chemistry—the evaluation of rates and mechanisms of reactions, kinetics and thermodynamics, and, importantly, organic analysis.

One cannot monitor stability, determine the reaction rate, or investigate any mechanism without an analytical measurement. Hence, the pharmaceutical analyst is pri-

marily involved in stability, because he or she must develop a method that will quantitatively determine the drug in the presence of, or separate from, the transformation product(s). This determination is required to assure that the drug has not undergone change. To select the appropriate method(s), the analyst should have a thorough knowledge of the physicochemical properties of the drug, including an understanding of the routes by which a drug can be degraded or transformed.

The knowledge of the physicochemical properties of the drug is equally important to the development pharmacist in efforts to achieve the optimum drug formulation. Likewise, this knowledge is needed by the package development group so that an appropriate container can be provided.

The stability of this resultant product in various channels of commerce is of concern to the marketing and distribution departments and to the physician, pharmacist, and patient. This concern is manifested by the use of storage legends, expiration dates, protective packaging, and dispensing directions. Furthermore, from a regulatory viewpoint, one should assure that the product is of the "quality, strength, purity, and identity" that it is purported to be throughout the time it is held or offered for sale.

An in-depth discussion on all aspects of this topic is beyond the scope of this review. We intend, however, to highlight the areas involved, with particular attention to recent literature, and to present an integrated overview of a total stability program.

RATES, MECHANISMS, AND PATHWAYS OF DEGRADATION

Kinetics—Two of the main contributors to an understanding of kinetic principles as applied to drug development are T. Higuchi and Garrett (7, 11–13); they brought the principles of chemical kinetics to the evaluation of drug stability. Although the theory was well understood and groundwork in chemical reaction kinetics was underway, only a few papers on drugs appeared in the literature through the 1940's. Detailed studies on drugs were not undertaken until the 1950's. The classical concepts brought to bear were the consideration of factors influencing reactions in solution (14–19), as summarized below.

Most degradation reactions of pharmaceuticals occur at finite rates and are chemical in nature. These reactions are affected by conditions such as solvent, concentration of reactants, temperature, pH of the medium, radiation energy, and presence of catalysts. The manner in which the reaction rate depends on the concentration of reactants describes the order of the reaction. The degradation of most pharmaceuticals can be classified as zero order, first order, or pseudo-first order, even though they may degrade by complicated mechanisms and the true expression may be of higher order or be complex and noninteger.

The quantitative relationship of the specific reaction rate and temperature is the Arrhenius expression:

$$k = Ae^{-\Delta H_a/RT} \qquad \text{(Eq. 1)}$$

where k is the specific rate constant; T is temperature in degrees Kelvin; R is the gas constant; A, the preexponential factor, is a constant associated with the entropy of the reaction and/or collision factors; and ΔH_a is defined as the heat of activation. The equation is usually employed in its logarithmic form:

$$\log k = -(\Delta H_a/2.303RT) + \log A \qquad \text{(Eq. 2)}$$

The slope of a plot of log k against $1/T$ yields the activation energy. This equation provides the underlying basis which allows prediction of stability of pharmaceuticals by extrapolation of rate data obtained at higher temperatures.

An understanding of the limitations of the experimentally obtained heat of activation values is critical in stability prediction; the pitfalls of extrapolation of kinetic data were described (20–22). For example, the apparent heat of activation at a pH value where two or more mechanisms of degradation are involved is not necessarily constant with temperature. Also, the ion product of water, pKw, is temperature dependent, and $-\Delta H_a$ is approximately 12 kcal, a frequently overlooked factor that must be considered when calculating the hydroxide-ion concentration. Therefore, it is necessary to obtain the heats of activation for all bimolecular rate constants involved in a rate–pH profile to predict degradation rates at all pH values for various temperatures.

If photolysis is the rate-determining step of the reaction, most often no predictive advantage is gained by higher temperature studies because the ΔH_a is small and, hence, the effect of temperature is small. Conversely, the heat of activation may be high for pyrolytic reactions, but the degradation rates obtained at elevated temperatures may be of little practical value when extrapolated to room temperature.

Complex reactions, including reversible reactions, consecutive reactions, and parallel reactions, are occasionally encountered in the decomposition of pharmaceuticals. Some of these reactions are discussed under *Physical Organic Chemistry*. A recent review (23) dealt with the kinetics of the most frequently encountered complex drug degradation reactions.

Many drugs are derivatives of carboxylic acids or contain the functional group based on this moiety, *e.g.*, esters, amides, lactones, lactams, imides, and carbamates. The members of this class include many important drugs such as aspirin, penicillin, ascorbic acid, procaine, meperidine, and atropine. This class can illustrate the basic factors affecting the rates of all reactions (24).

The study of hydrolytic reactions as a function of pH yields a rate–pH profile. For an ester, the overall hydrolysis rate of a drug, D, may be expressed as follows:

$$-\frac{dD}{dt} = K_U + K_{H^+}[H^+] + K_{OH^-}[OH^-] + K_N[N] + K_{GB}[GB] + K_{GA}[GA] \qquad \text{(Eq. 3)}$$

where K_U is the rate constant for the uncatalyzed or water-catalyzed reaction, K_{H^+} is the rate constant for the hydrogen-ion-catalyzed hydrolysis, K_{OH^-} is the rate constant for the hydroxide-ion-catalyzed hydrolysis, K_N is the rate constant for nucleophilic catalysis, K_{GB} is the rate constant for general base catalysis, and K_{GA} is the rate constant for general acid catalysis.

The hydrolysis of a compound may be subject to some or all of these terms; however, at any given pH, only one or two terms are significant. The simplest profile is observed when a compound is subjected to only hydrogen-ion

or hydroxide-ion catalysis. The effects of other nucleophiles or general acids or bases are usually studied by varying their concentrations while maintaining the pH constant.

Solvent has a significant effect on the reaction rate. A simplified treatment of solvent effects is presented here. When both reactants are ions in a solvent medium or a continuous dielectric, absolute rate theory gives the following equation:

$$\ln k = \ln k_0 - \frac{N}{RT}\frac{Z_A Z_B e^2}{\epsilon\gamma} \qquad \text{(Eq. 4)}$$

where $\ln k$ is the rate constant at the dielectric constant ϵ, $\ln k_0$ is the rate constant in the medium of infinite dielectric constant, N is Avogadro's number, Z_A is the charge on ion A, Z_B is the charge on ion B, e is the electronic charge, T is absolute temperature, R is the gas constant, ϵ is the dielectric constant, and γ is proportional to the interatomic distance in the activated complex.

This equation predicts a linear relationship between $\ln k$ and $1/\epsilon$. No effect of the dielectric constant would be noted if one of the molecules were neutral because Z_A or Z_B would be zero. The effect of the dielectric constant on the reaction rate between an ion and a neutral molecule is expressed as:

$$\ln k = \ln k_0 + \frac{NZ^2e^2}{2\epsilon RT}\left(\frac{1}{\gamma_1} - \frac{1}{\gamma_2}\right) \qquad \text{(Eq. 5)}$$

where γ is the radius of the reactant ions and the other symbols are as defined in Eq. 4.

Equation 5 predicts that the logarithm of the rate constant will vary linearly with the reciprocal of the dielectric constant. However, many drugs are quite complex and often do not appear to follow theory; *e.g.*, the solvolysis rate of the aspirin anion increases with an increasing ethanol content, but the rates are relatively constant with an increasing dioxane content. Both of these solvents should have produced a decrease in the overall rate. However, based on this type of information, it was concluded that a possible rate-determining step was the attack of water or ethanol on an uncharged cyclic intermediate (25, 26).

For reactions involving two ionic species, the rate constant is dependent on the ionic strength, μ. For aqueous solutions at 25°, Eq. 6 expresses the variation of the rate constant with ionic strength:

$$\log k = \log k_0 + 1.02 Z_A Z_B \sqrt{\mu} \qquad \text{(Eq. 6)}$$

A straight line with a slope equal to $1.02Z_AZ_B$ is obtained when one plots $\log k$ *versus* $\sqrt{\mu}$. Equation 6 would predict no effect on a reaction when one reactant is neutral; but the activity coefficient of a neutral molecule is affected by ionic strength, and one can observe a linear relationship between the logarithm of the rate constant and ionic strength:

$$\ln k = \ln k_0 + b\mu \qquad \text{(Eq. 7)}$$

where b is an empirical constant.

These two ionic effects are commonly called the primary salt effect. In addition, one observes what is called the secondary salt effect, which is the effect of ionic strength on the dissociation constant of a buffer species.

Many pharmaceuticals are subject to general acid, general base, or nucleophilic catalysis in addition to hydrogen-ion or hydroxide-ion catalysis. Several linear free energy relationships quantitate the catalytic rate constant with a property of the species and relate the rate constant for a series of reactions. For acid–base catalysis, this free energy relationship is the Brönsted catalysis law and can be expressed as:

$$k_{GA} = G_A K_A^{\alpha} \qquad \text{(Eq. 8)}$$

and:

$$k_{GB} = G_B K_B^{\beta} \qquad \text{(Eq. 9)}$$

where K_A and K_B are acid and base dissociation constants, respectively; and G_A, G_B, α, and β are constants characteristic of the solvent, temperature, and reaction.

Many drugs have ionizable groups, and the reactions may proceed differently for the ionized and unionized forms. However, analytically one usually measures the total drug concentration, D_T. For a weak base, the contribution of the ionized, D_{H^+}, and unionized, D, drug are related through the pKa of the drug and the pH of the medium; thus:

$$D_T = D + D_{H^+} \qquad \text{(Eq. 10)}$$

The overall reaction rate observed is the sum of both reactions. Two examples, aspirin and barbiturates, that demonstrate the effect of ionization on the rate constant and the mode of degradation are provided in the next section.

The basic kinetic effects are important to an understanding of the reaction and of possible adverse, practical effects. For example, addition of an inert salt such as sodium chloride to adjust isotonicity can affect the reaction rate as a primary salt effect. Buffers used to control pH are also ionic species and can exert a primary salt effect. In addition, they exert a secondary salt effect and also act as catalysts. Sulfite salts are frequently added as antioxidants, but they can form addition products with the active ingredient or act as catalysts.

Organic solvents such as alcohol are generally used for solubilization; the concentration of the organic solvent can affect the dielectric constant of the solvent and thus influence the degradation rate of the active ingredients. The preservatives used to inhibit bacterial growth or other pharmaceutical aids may decompose and their decomposition products may, in turn, influence the decomposition rate of the active ingredients by one or more of the means discussed previously.

Physical Organic Chemistry—The basic kinetic principles outlined are applicable to all chemical systems. However, relatively simple molecules have been used to elucidate a principle or to establish fundamental relationships. A generation ago, physical chemistry and organic chemistry were considered to be two separate nonrelated disciplines. But a number of standard textbooks in the field, ranging from Hammett's (27), through classic works by Bell (28) and Ingold (29), to more recent treatises, relate reaction mechanisms and catalysis to biochemical systems. Most modern textbooks in organic chemistry now integrate physicochemical principles (16–19, 30–36).

Since most modern pharmaceuticals are complex organic molecules, a firm understanding of mechanistic organic chemistry is vital to any detailed study of drug degradation; conversely, degradation studies of many classic drugs have added to an understanding of the mechanism

of many organic reactions. Most widely used drugs have been studied and provide good models for future studies. It is not within the scope of this article to review the myriad studies that have been conducted, but we shall illustrate the complexity and depth through review of two classic examples—aspirin and barbiturates—and highlight the types of reactions that drugs can undergo by a review primarily of the literature of the last few years.

Aspirin is an excellent example of a pharmaceutical compound on which in-depth kinetic studies have been performed and for which reaction mechanisms have been proposed (37–39). The first detailed studies on aspirin hydrolysis were published in 1950 by Edwards (40, 41), 42 years after the first study was reported (42). His work clearly demonstrated specific acid–base catalysis and pH-independent solvolysis of aspirin to salicylic acid. The rate constants for hydrogen-ion and hydroxide-ion catalyses were found to differ with the charge of the molecule. Edwards explained the relationship between the observed rate constant and pH on the assumption that aspirin hydrolysis occurs according to the six simultaneous reactions shown in Scheme I.

$$CH_3COO{\cdot}C_6H_4COOH + H_3O^+ \xrightarrow{k_1} HOC_6H_4COOH + CH_3COOH + H^+$$

$$CH_3COO{\cdot}C_6H_4COOH + H_2O \xrightarrow{k_2} HOC_6H_4COOH + CH_3COOH$$

$$CH_3COO{\cdot}C_6H_4COOH + OH^- \xrightarrow{k_3} HOC_6H_4COOH + CH_3COO^- \text{ or } HOC_6H_4COO^- + CH_3COOH$$

$$CH_3COO{\cdot}C_6H_4COO^- + H_3O^+ \xrightarrow{k_4} HOC_6H_4COOH + CH_3COOH$$

$$CH_3COO{\cdot}C_6H_4COO^- + H_2O \xrightarrow{k_5} HOC_6H_4COOH + CH_3COO^- \text{ or } HOC_6H_4COO^- + CH_3COOH$$

$$CH_3COO{\cdot}C_6H_4COO^- + OH^- \xrightarrow{k_6} HOC_6H_4COO^- + CH_3COO^-$$

Scheme I

The observed overall first-order rate constant, k, can be expressed as a function of the six second-order rate constants and the acid dissociation constant, K, of aspirin:

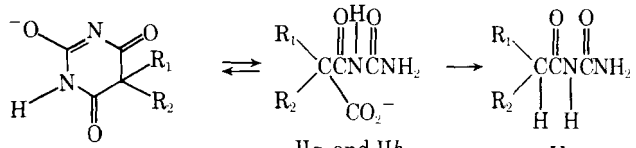
$$k = \frac{k_1[C_{H^+}] + k_2[C_{H_2O}] + k_3[C_{OH^-}]}{1 + K/[C_{H^+}]} + \frac{k_4[C_{H^+}] + k_5[C_{H_2O}] + k_6[C_{OH^-}]}{1 + [C_{H^+}]/K} \quad \text{(Eq. 11)}$$

Garrett (25, 26) also investigated the pH–rate profile for aspirin hydrolysis, particularly in the pH 4–8 range. Garrett's work pointed to intramolecular nucleophilic catalysis by the ionized carboxyl group. When the carboxylate ion is intramolecular, it catalyzes a number of ester reactions, although it is not a particularly strong nucleophile. As mentioned, the addition of alcohol increases the solvolysis rate, thus strongly suggesting the involvement of a solvent molecule in the transition state. On the basis of the kinetic and isotopic studies, aspirin hydrolysis was shown to be an intramolecular nucleophilic catalyzed hydrolysis involving an anhydride intermediate. It was assumed that the transition state of the reaction involved addition of the carboxylate ion to the carbonyl group of the ester, forming a tetrahedral addition intermediate.

Fersht and Kirby (43, 44) studied the reactivity of a series of substituted aspirins toward hydrolysis. The results show that the most likely mechanism for aspirin hydrolysis was one in which the carboxylate group acted not as a nucleophile but as a general base. The pH–rate profile for aspirin hydrolysis, as determined by Edwards (40, 41), showed that the transition state for hydrolysis in the pH-independent region involved the aspirin anion, either alone in a unimolecular reaction or together with one or more molecules of solvent.

Three mechanisms have been proposed on the basis of the kinetic results for the intramolecular catalytic hydrolysis of aspirin by the carboxyl group: (*a*) a unimolecular process in which the carboxylate group acts as a nucleophile, (*b*) a general acid catalysis in which the undissociated carboxylic acid group reacts with hydroxide ion, and (*c*) a general base catalysis in which the carboxylate anion reacts with a water molecule.

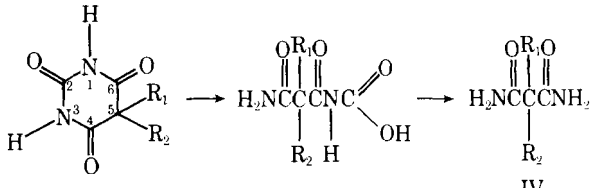
The barbiturates provide another excellent example of the complex mechanisms by which drugs degrade (Scheme II). Early workers (45, 46) assumed that the hydrolysis of barbiturates I*a* and I*b* to the corresponding malonuric acids was irreversible, and various degradation schemes were predicted on that assumption. Garrett *et al.* (47), in the process of further elucidating the hydrolysis kinetics of several important barbiturates, discovered that diethylmalonuric acid (II*a*) in basic solution may cyclize to form barbital (I*a*). Gardner and Goyan (48) confirmed the reversibility of hydrolysis of the barbituric acid nucleus and noted that it may have interesting biological ramifications. Furthermore, they rationalized previous findings (46) in the light of a similar reaction involved in the cyclization of 2-ureidobenzoic acid (49). Thus, the unionized barbiturate (III) could be cleaved at the 1,2-position, leading to production of the bisamide (IV), or at the 1,6- (3,4-) position, leading to the ureide (V); the ionized barbiturate would cleave only at the 1,6- (3,4-) position, leading to the ureide (or malonic acid) exclusively.



I*a*: $R_1 = R_2 = C_2H_5$
I*b*: $R_1 = C_2H_5$, $R_2 = C_6H_5$

II*a* and II*b*

V



III

IV

Scheme II

Recently, Khan and Khan (50) observed that earlier workers did not kinetically detect the existence of di- and trianionic tetrahedral addition intermediates in the base-catalyzed hydrolysis of barbituric acid because their alkali concentration range was low. At pH values higher than the pKa_2 of barbituric acid, the equilibrium concentration of undissociated barbituric acid was negligible compared to the concentration of mono- and dianionic

barbituric acids. The equations were developed for $k_{1,obs}$ and $k_{2,obs}$ for the following consecutive irreversible first-order reaction path: barbituric acid $\xrightarrow{k_{1,obs}}$ malonuric acid $\xrightarrow{k_{2,obs}}$ ammonia. The rate constants showed three regions of hydroxide-ion dependence:

1. The reciprocals of the rate constants were linearly related to the reciprocal of the hydroxide concentration at low concentration.
2. The rate constants were independent of the hydroxide-ion concentration at higher concentrations of hydroxide ion.
3. The rate constants observed the following relationships at even higher concentrations of hydroxide ion:

$$k_{obs} = a + b[OH^-] + c[OH^-]^2 \qquad \text{(Eq. 12)}$$

The empirical parameters a, b, and c were evaluated using the method of least squares. A trianionic tetrahedral intermediate was proposed to account for the second power of the hydroxide ion in Eq. 12.

Hydrolysis—One common pathway by which drugs degrade is hydrolysis; the two reactions already discussed exemplify this route. Several other examples of drug hydrolysis are included in Table I. Also included in this table are drugs containing other functional groups that can undergo various elimination or addition reactions in an aqueous medium frequently classified as hydrolysis, although the elements of water are not necessarily involved. This list was drawn primarily from the literature of the 1970's; the references listed earlier (1–19) give numerous other examples.

Oxidation—After hydrolysis, the next most common pathway for drug breakdown is oxidation. Many major drugs, such as narcotics, vitamins, antibiotics, and steroids, are prone to undergo this reaction, but there is a dearth of detailed studies on oxidation reactions.

The most common form of oxidative decomposition occurring in pharmaceuticals is autoxidation through a free radical chain process. The free radicals are produced by homolytic bond fission of a covalent bond: $A{:}B \rightarrow A\cdot + B\cdot$. The radicals readily remove electrons from other molecules, and this process is oxidation. The autoxidation of the free radical chain process can be described by the reactions in Scheme III.

$$RH \xrightarrow[\text{catalysis}]{\text{heat, light}} R\cdot + H\cdot$$

$$R\cdot + O_2 \rightarrow RO_2\cdot$$

$$RO_2\cdot + RH \rightarrow ROOH + R\cdot$$

$$ROOH \rightarrow RO\cdot + \cdot OH$$

$$RO_2\cdot + X \rightarrow \text{products}$$

$$RO_2\cdot + RO_2\cdot \rightarrow \text{products}$$

Scheme III

The heavy metals (copper, iron, cobalt, and nickel) catalyze oxidation by shortening the induction period and also affect the oxidation rate by promoting free radical formation.

Oxidations in solution are also subject to specific acid–base catalysis and generally follow first- or second-order kinetics. For example, the oxidative degradation of prednisolone is base catalyzed and exhibits first-order dependency (82). Other solvents may have a catalytic effect on reactions when used alone or in combination with water.

Table I—Hydrolytic Reactions

Compound	Reaction	Reference
Salicylamide	Amide hydrolysis	51
N-Haloacetylphthalimides	Substituted amide hydrolysis	52
1-Acyl-3,5-dimethylpyrazoles	Substituted amide hydrolysis	53
N-Acylphthalimides	Imide hydrolysis	52
Meperidine	Ester hydrolysis	24
Pyridoxine monooctanoate	Ester hydrolysis	54, 55
Trantelinium bromide	Ester hydrolysis	56
Salicylanilide *N*-methylcarbamate	Carbamate hydrolysis	57
4-Biphenyl-*N*-methylcarbamate	Carbamate hydrolysis	57
17α-Acetoxy-6α-methyl-4-pregnen-3,20-dione 3-oximino ester	Hydrolysis of oximino ester	58
Penicillins	Hydrolysis of β-lactam	59–61
Cephalosporins	Hydrolysis of β-lactam Intramolecular aminolysis	62, 63
Clindamycin	Dethiomethylation	64
5-Aminodibenzo[*a*,*d*]cycloheptane derivatives	Deamination	65
Cytarabine (arabinosylcytosine)	Deamination	66
Cytosine	Deamination	67
Cytidine	Deamination	67
5-Azacytidine	Deamination Scission of N–C bond	68
Chlordiazepoxide	Deamination Scission of C=N linkage	69
N-Chlorosuccinimide	Dechlorination	70
N-Chloroquinuclidinium ion	Dechlorination	70
N-Chloro-*N*-methylbenzenesulfonamide	Dechlorination	70
N-Chlorinated piperidines	Dechlorination	71
Iodocytosine	Deiodination Deamination	72
Δ^9-Tetrahydrocannabinol	Hydration and ether solvolysis	73
Antimycin A_1	Hydrolytic ring cleavage Loss of CHO group	74
Dexoxadrol	Hydrolysis of ketal group	75
Hydrochlorothiazide	Ring opening through hydration of free or cationic imine	76, 77
Mazindol	Scission of C=N linkage	78
Methaqualone	Ring cleavage	79
Coumarinic acid	Lactonization	80
Canrenone	Scission of C–S bond Lactonization	81

Ketones, aldehydes, and ethers may also influence free radical reactions, either directly or through trace impurities such as peroxides.

Many drugs are complex molecules and contain multiple functional groups subject to both hydrolysis and oxidation, *e.g.*, ascorbic acid, penicillins, and phenylbutazone. The studies conducted on the latter are summarized here.

The rates and degradation mechanisms of phenylbutazone were studied extensively (83–89). Phenylbutazone can undergo both hydrolysis and oxidation; the initial hydrolytic or oxidative products can be decarboxylated and/or further hydrolyzed or oxidized. On the basis of a detailed study, it was concluded that the equilibrium between phenylbutazone and the carboxylic acid resulting from hydrolysis of the pyrazolidine ring was dependent on solvent but practically independent of pH (86). Slingsby and Zuck (87) noted that oxidation at the C-4 position to produce 4-hydroxyphenylbutazone was the major decomposition route in the solvents they investigated. Awang *et al.* (89) proposed the hydroperoxide at C-4 as an intermediate en route to its formation. They also proposed a mechanism for formation of several other compounds on hydrolysis, decarboxylation, and oxidation of 4-hydroxyphenylbutazone.

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