Cinnamaldehyde arylhydrazones: (1, H, 0, 760), (2, NO_2, 0.78, 829), (3, CH_3, −0.17, 765), (4, Cl, 0.23, 758). Input order of equation = 2. Parameters of the regression equation: A = 150.173, B = −25.6864, C = 757.482. Total sums of squares = 3494.0000. Sums of squares due to regression : 3483.7500. Sums of squares due to deviation = 10.2500. Standard deviation of residuals = 2.263 846. Correlation coefficient = 0.998 532.

Tetracyclone arylhydrazones (major absorption): (1, NO_2, 0.78, 881), (2, H, 0, 841), (3, CH_3, −0.17, 851), (4, CH_3O, −0.27, 872). Input order of equation = 2. Parameters of the regression equation: A = 158.890, B = −69.9495, C = 838.985. Total sums of squares = 1020.7500. Sums of squares due to regression = 989.7500. Sums of squares due to deviation = 31.0000. Standard deviation of residuals = 3.937 004. Correlation coefficient = 0.984 698.

Tetracyclone arylhydrazones (minor absorption): (1, NO_2, 0.78, 805), (2, H, 0, 773), (3, CH_3, −0.17, 762), (4, CH_3O, −0.27, 765). Input order of equation = 1. Parameters of the regression equation: A = 40.9291, B = 772.771. Total sums of squares = 1166.7500. Sums of squares due to regression = 1141.2600. Sums of squares due to deviation = 25.25000. Standard deviation of residuals = 3.570 714. Correlation Coefficient = 0.989 012.

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Registry No. **2**, 121597-12-4; **3**, 121597-13-5; **4**, 121597-14-6; **5**, 4828-86-8; **6**, 121597-15-7; **7**, 121597-16-8; **8**, 15056-71-0; **9**, 1237-69-0; **10**, 121597-17-9; **11**, 1216-15-5; **12**, 5584-21-4; **13**, 88254-45-9; **14**, 121597-18-0; **15**, 88254-47-1; **16**, 121597-19-1; **17**, 88254-46-0; **19**, 32387-09-0; **23**, 121597-20-4; **24**, 121597-21-5; **25**, 121597-22-6; **26**, 121597-23-7; **27**, 116594-85-5; **28**, 121597-24-8; **29**, 121597-25-9; PhCH=CHCHO, 104-55-2; PhCH=CClCHO, 18365-42-9; Ph_2C=CHCHO, 1210-39-5; tetracyclone, 479-33-4; myrtenal, 564-94-3; phthalhydrazide, 1445-69-8; *p*-fluorobenzaldehyde, 459-57-4; (2,4-dinitrophenyl)hydrazine, 119-26-6; (4-nitrophenyl)hydrazine, 100-16-3; (2-nitrophenyl)hydrazine, 3034-19-3; phenylhydrazine hydrochloride, 59-88-1; *p*-tolylhydrazine hydrochloride, 637-60-5; (4-methoxyphenyl)hydrazine hydrochloride, 19501-58-7; 2-furanacrolein, 623-30-3; (4-chlorophenyl)hydrazine hydrochloride, 1073-70-7; *o*-nitrocinnamaldehyde, 1466-88-2; 3-phenylpropanal, 104-53-0; 2-phenylpropanal, 93-53-8; *N*-aminophthalimide, 1875-48-5.

Kinetics and Mechanisms of Cyclization in Acidic Media of *N*-[(3,5-Dichloroanilino)carbonyl]-*N*-[(isopropylamino)carbonyl]glycine to Hydantoins: Iprodione and Its Isomer

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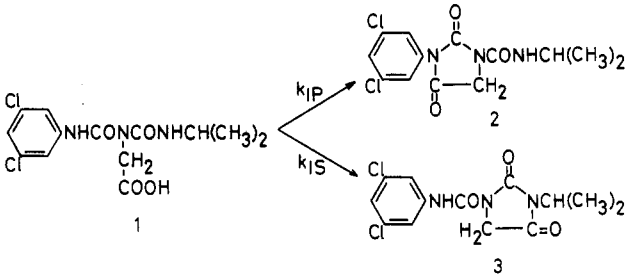
N-[(3,5-Dichloroanilino)carbonyl]-*N*-[(isopropylamino)carbonyl]glycine (**1**) cyclizes quantitatively and irreversibly at 50 °C in the pH range 0.5–6 by two parallel paths to give iprodione (**2**) and its isomer **3**. Formation of the antifungal agent **2** is characterized by a general base catalysis with carboxylate anions, water, and hydroxide ion (β = 0.38) and a solvent isotope effect of 2.90. These results are consistent with a specific base catalyzed addition of the enolate anion of the ureido group to the carboxylic function of hydantoic acid (pK_{a1} = 4.25) to give tetrahedral intermediate T^- whose general acid catalyzed decomposition is rate limiting. Formation of isomer **3** occurs by a specific base catalyzed cyclization of **1** compatible with a nucleophilic attack of the enolate anion of the ureido moiety on the carboxylic group in the pH range 2–6. Below pH 2 hydantoic acid undergoes a specific acid catalyzed and a spontaneous hydrolysis involving a nucleophilic attack of the ureido enol on the carboxylic function, protonated or not, respectively. Formation of iprodione is general base catalyzed while that of its isomer is not: this can be explained by the change in basicity of the leaving groups from the tetrahedral intermediate, i.e., the *N*-[(3,5-dichlorophenyl)ureido] (pK_{a2} = 11.7) and the *N*-isopropylureido ($pK_{a3} \simeq 18$) anions, respectively.

Iprodione [3-(3,5-dichlorophenyl)-*N*-isopropyl-2,4-dioxo-1-imidazolidinecarboxamide] (**2**) is a contact antifungal agent that is active with respect to phytopathogenic fungi.[2]

In ethanolic solution, iprodione is rearranged to its isomer [*N*-(3,5-dichlorophenyl)-3-isopropyl-2,4-dioxo-1-imidazolidinecarboxamide] (**3**), which is a much less effective fungicide.[3] This last reaction requires the intermediate formation of the 3-(isopropylcarbamoyl)-5-(3,5-dichlorophenyl)hydantoic acid (**1**). An industrial procedure of synthesis of iprodione involves the conversion in strongly alkaline media of the isomer to hydantoic acid, which is cyclized to iprodione in acidic solution.[4,5]



In this paper, we describe a kinetic study of the cyclization of the hydantoic acid **1**, undertaken in order to elucidate the mechanism of formation of iprodione and its isomer and to better understand the behavior of iprodione in its conditions of use.

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The ring closure of **1** can occur on both sides of the molecule due to the presence of two carbamoyl groups. The rate constants of these two parallel reactions leading to **2** and **3** have been determined in neutral and acidic media in aqueous dioxane. In basic media, the reaction is complicated by the hydrolysis of iprodione. This last reaction has been studied previously.[6]

Experimental Section

Materials. Iprodione (2). Rovral (a 500 g kg^{-1} w.p. from Rhône-Poulenc) was treated with dichloromethane and mixed thoroughly, and the insoluble material was filtered off. The filtrate was washed with saturated aqueous sodium chloride, the organic phase was separated and dried, and the solvent was removed under vacuum. Hexane was added to the remaining oily product and the precipitate formed was recrystallized from hexane to give iprodione, mp 135–136 °C [lit.[7] mp 135–136 °C]. ^1H NMR [$(CD_3)_2CO$]: δ 7.56 (d, 2 H, 2-H), 7.50 (s, 1 H, 4-H), 4.36 (s, 2 H, CH_2), 3.30 (m, 1 H, CH), 1.20 (d, 6 H, CH_3). Anal. Calcd for $C_{13}H_{13}Cl_2N_3O_3$: C, 47.29; H, 3.96; N, 12.72. Found: C, 47.69; H, 3.92; N, 12.71.

3-(Isopropylcarbamoyl)-5-(3,5-dichlorophenyl)hydantoic Acid (1). Iprodione (1 g) was dissolved in a 1 M NaOH aqueous solution (50 mL) at room temperature. Ice-cold concentrated HCl (10 mL) was added with stirring and the precipitate was collected by filtration. The crude product was washed with cold water and recrystallized from petroleum ether–ether (7:3, v/v) to give the hydantoic acid, mp 174 °C [lit.[8] mp 175 °C]. ^1H NMR (Me_2SO-d_6): δ 11.1 (br, 1 H, COOH), 7.8–7.7 (br, disappears on addition of D_2O, 2 H, NH), 7.60 (d, 2 H, 2-H), 7.26 (t, 1 H, 4-H), 4.50 (s, 2 H, CH_2), 3.85 (m, 1 H, CH), 1.16 (d, 6 H, CH_3). Anal. Calcd for $C_{13}H_{15}Cl_2N_3O_4$: C, 44.84; H, 4.34; N, 12.06. Found: C, 45.03; H, 4.31; N, 11.91.

***N*-(3,5-Dichlorophenyl)-3-isopropyl-2,4-dioxo-1-imidazolidinecarboxamide (3).** 3-(Isopropylcarbamoyl)-5-(3,5-dichlorophenyl)hydantoic acid (1 g) in ethanol (20 mL) was heated to reflux and stirred for 4 h. The mixture was cooled to room temperature and the white precipitate was filtered. Recrystallization from ethanol gave the pure isomer of iprodione, mp 200 °C [lit.[8] mp 200 °C]. ^1H NMR [$(CD_3)_2CO$]: δ 7.71 (d, 2 H, 2-H), 7.21 (t, 1 H, 4-H), 4.30 (s, 2 H, CH_2) superimposed on 4.2–4.6 (m, 1 H, CH), 1.42 (d, 6 H, CH_3). Anal. Calcd for $C_{13}H_{13}Cl_2N_3O_3$: C, 47.29; H, 3.96; N, 12.72. Found: C, 47.28; H, 3.94; N, 12.73.

The HPLC properties of compounds **1**, **2**, and **3** were studied to examine the purity of the samples prior to kinetic work.

Buffer components were from analytical-grade material and the aqueous solutions were prepared by using deionized water, which was then distilled over potassium permanganate and sodium hydroxide.

Reaction Products. The identification of the reaction products was made by employing a high-performance liquid chromatograph (Dupont de Nemours 850) equipped with a UV detector and a reversed-phase column (Zorbax ODS, 25 cm × 4.6 mm i.d.) that was eluted with a mobile phase consisting of a mixture of acetonitrile and 5 mM formic acid (7:3, v/v). The flow rate was 1.5 mL min^{-1} and detection was made at 221 nm.

For a run in a formate buffer at pH 4.21, the peak corresponding to the hydantoic acid **1** disappears completely with simultaneous appearance of two peaks with retention times of 4.1 min and 6.6 min, identical with that of authentic samples of **2** and **3**, respectively. Furthermore we have checked that the ultraviolet spectra of **2** and **3** are stable in acidic media and that the rate of hydrolysis of **2** is negligible at the higher limit of the pH range used.

Thus, under the experimental conditions used, the hydantoic acid is converted quantitatively and irreversibly to iprodione and its isomer and the final mixture is binary.

Kinetic Measurements. The changes in concentration were followed spectrophotometrically by recording at an appropriate wavelength (λ around 250 nm) the changes in optical density with time on a Unicam SP 1800 recording spectrophotometer, fitted with a SP 1805 program controller, or a Cary 210 machine, both equipped with thermostatted cell compartments.

Stock solutions of 5×10^{-3} M hydantoic acid were prepared in dioxane. Reactions were initiated by injecting 30 μL of stock solution into a 1.0-cm quartz cuvette equilibrated at 50.0 ± 0.2 °C and containing 3.0 mL of HCl or buffered solutions in a mixture of water–dioxane (7:3, v/v) owing to the low solubility of **3**. Reaction rates were performed at pH 0.4–6.1 and ionic strength was maintained at 0.5 M throughout by addition of KCl.

In a water–dioxane (7:3, v/v) mixture at pH 4.04 and 50 °C, the UV spectra of **1** (λ_{max}(250 nm), ϵ = 17 700) and of **3** (λ_{max}(249 nm), ϵ = 19 900) are very similar but the absorbance of **2** is very low (λ (250 nm), ϵ = 480). Since the cyclization of the hydantoic acid leads to a mixture of **2** and **3**, the change in optical density near this wavelength is large enough to permit accurate measurements.

Pseudo-first-order rate constants k_{obsd} for the cyclization of hydantoic acid **1** were calculated from plots against time of log $(A_t - A_\infty)$, where A_∞ is the final absorbance of the reaction mixture. In all cases, reactions followed excellent first-order kinetics with respect to the substrate.

The observed rate constant is equal to the sum of the first-order rate constants of formation of **2** and **3** (eq 1). The ratio of the

$$k_{obsd} = k_{IP} + k_{IS} \quad (1)$$

concentration of the products at the completion of the reaction gives

$$C_{IP}/C_{IS} = k_{IP}/k_{IS} \quad (2)$$

From eq 1 and 2 k_{IP} and k_{IS} were determined.[9] The concentrations C_{IP} and C_{IS} were determined from pairs of absorbance reading measured at six wavelengths from 242 to 252 nm by using the following equations

$$A_1 = \epsilon_{1IP}C_{IP} + \epsilon_{1IS}C_{IS} \quad (3)$$

$$A_2 = \epsilon_{2IP}C_{IP} + \epsilon_{2IS}C_{IS} \quad (4)$$

where ϵ_{1IP}, ϵ_{1IS} and ϵ_{2IP}, ϵ_{2IS} are the molar extinction coefficients of **2** and **3** determined with authentic samples at λ_1 and λ_2, respectively; A_1 and A_2 are the absorbances of the binary mixture at these wavelengths.[10] Among the 15 pairs of C_{IP} and C_{IS}, only those values whose sum was within ±5% of I_0, the initial hydantoic acid concentration, were kept to calculate k_{IP} and k_{IS}.

The rate constants for the cyclization of **1** (k_{obsd}) and that of the formation of iprodione (k_{IP}) and its isomer (k_{IS}) determined in HCl solutions (Table S1) and chloroacetic, formic, acetic, and cacodylic buffers in the range 0.05–0.5 M (Table S2) are provided as supplementary material. Standard deviations, relative standard deviations, and number of pairs corresponding to acceptable k_{IP} and k_{IS} values are also given (Tables S1 and S2). To illustrate, an example of determination of k_{IP} and k_{IS} in acetate buffer at pH 4.75 is included (Tables S3 and S4).

pK_a Measurement. The ionization constant of the carboxylic group of the hydantoic acid was determined by potentiometric titration from a 10^{-2} M solution of the acid dissolved in water–dioxane (7:3, v/v) with 2×10^{-2} M sodium hydroxide. The "pH" measurements were carried out on a Radiometer pHM 64 pH meter equipped with a Radiometer GK 2321C electrode. The pK_{a1}(app) taken as the pH at the half neutralization is equal to 4.25 ± 0.10 at 50 °C (μ = 0.5 M, KCl). Similarly, the ionization constants K_{app} of the carboxylic acid buffers used for this study were determined at the same experimental conditions.

Results

pH–Rate Profiles. For the two cyclization reactions the pH–rate profiles are shown in Figure 1. The data were obtained in aqueous hydrochloric acid solutions or in buffer

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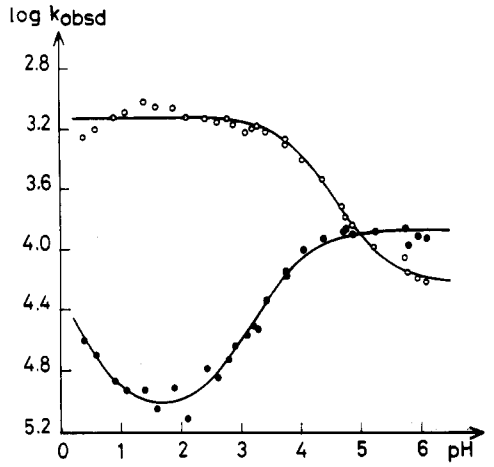


Figure 1. Plot of log k_{obsd} vs pH for formation of iprodione **2** (k_{IP}, ○) and its isomer **3** (k_{IS}, ●) at 50 °C in water–dioxane (7:3, v/v) with μ = 0.5 M (KCl). Curves are from the best-fit values of parameters of Table III obtained by a nonlinear least-squares analysis using eq 6 and 8.

Table I. Values of the Buffer Constants k_2 of Chloroacetic, Formic, Acetic, and Cacodylic Buffers for the Formation of Iprodione at 50 °C in Water–Dioxane (7:3, v/v) (μ = 0.5 M, KCl)

buffer	pH	$10^4 k_2$,[a] M^{-1} s^{-1}
chloroacetic	2.80	18.6 ± 0.2
	3.29	35.0 ± 0.8
	3.77	50.0 ± 2
formic	3.20	23.3 ± 0.2
	3.43	35.2 ± 0.9
	3.75	51.5 ± 0.2
	4.04	66.1 ± 0.6
	4.38	80.6 ± 0.2
	4.70	90.0 ± 0.1
	4.87	93.9 ± 0.1
acetic	4.75	91.9 ± 1
	5.24	172 ± 3
	5.75	259 ± 16
	5.95	308 ± 10
cacodylic	5.80	224 ± 3
	6.10	384 ± 7

[a] Uncertainties are given in terms of standard deviation from the slope of k_{obsd} vs $[B_t]$.

solutions at less acidic pHs and were extrapolated to zero buffer concentration.

In neutral media, the two reactions have approximately the same rate constant, but with decreasing pH, k_{IP} increases while k_{IS} decreases; between pH 1 and 2, the rate of formation of **2** is about 100-fold greater than that of **3**. Thus, in particular conditions of pH and temperature, **1** can act as a precursor of the fungicide iprodione.

Buffer Catalysis. The rate constant for the formation of **3** is independent of the buffer concentration in all the buffers used: chloroacetic, formic, acetic, and cacodylic acids. On the other hand, the rate of formation of iprodione is highly dependent of the buffer concentration.

$$k_{IP} = k_0^{IP} + k_2'[\text{buffer}]_{total} \quad (5)$$

The observed buffer constants k_2' based on total buffer concentration were divided by α, the fraction of carboxylic acid. This is based on the assumption that the carboxylate anion is an unreactive species. The second-order rate constants obtained, k_2, for catalysis by the buffers are given in Table I. They were plotted against the proportion of the buffer in the free base form (Figure 2). Straight lines were obtained and the intercept is zero at 0% free base and positive, equal to k_{A^-}, at 100% free base for all the

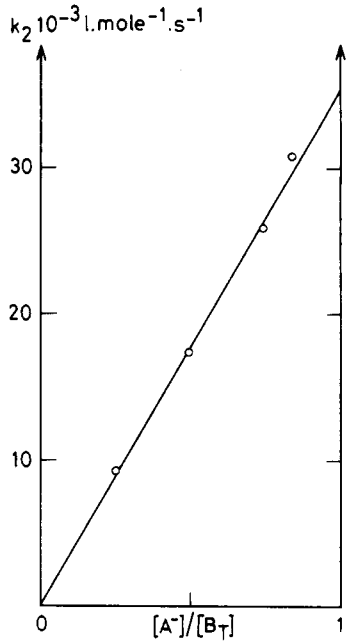


Figure 2. Dependence of the second-order rate constant k_2 for buffer catalysis of formation of iprodione (**2**) on the composition of acetate buffer in water–dioxane (7:3, v/v) at 50 °C (μ = 0.5 M, KCl). The 1 intercept is k_{A^-}.

Table II. Values of the Catalytic Constants k_{A^-} for the Formation of Iprodione and pK_{app} of the Conjugate Acid of the Catalyzing Base at 50 °C in Water–Dioxane (7:3, v/v) (μ = 0.5 M, KCl)

buffer	pK_{app}	$10^3 k_{A^-}$,[a] M^{-1} s^{-1}
chloroacetate	3.30	6.66 ± 0.2
formate	4.05	9.5 ± 0.5
acetate	5.25	36.2 ± 2
cacodylate	6.65	145.4[b]
H_2O	−1.58	(1.9 ± 0.2) × 10^{-2}
OH^-	15.97[c]	(165 ± 20) × 10^3

[a] Uncertainties are given in terms of standard deviation from the slope of k_2 vs $[B]/[B_t]$. [b] k_{A^-} was determined from two k_2 values measured at pHs 6.10 and 5.80 [c] The value of 15.97 for pK_a at 50 °C was obtained from the ratio $K_e/[H_2O]$ where K_e is equal to 4.2 × 10^{-15} extrapolated from results of Harned and Fallon.[11]

buffers examined: chloroacetic, formic, acetic, and cacodylic acids. Then, $k_2'[B_t]$ is equal to $\alpha k_{A^-}[B]$, where B is the concentration of buffer base, α is the fraction of substrate present as carboxylic acid, and k_{A^-} are the second-order rate constants for general base catalysis of the formation of iprodione. Thus we conclude that a general base catalysis of the cyclization of the unionized substrate is occuring in the formation of iprodione.

The catalytic constants k_{A^-} (Table II) plotted against the pK_a's of the corresponding acids give a β Brønsted parameter of 0.38 ± 0.02 (r = 0.991; Figure 3). The point for catalysis by water calculated from the plateau of the pH–rate profile in acidic solution and that for catalysis by hydroxide ion calculated in the less acidic and neutral media are on the Brønsted line.

Solvent Deuterium Isotope Effect. From experiments at 0.01 M HCl and DCl in a mixture of water–dioxane (7:3, v/v), solvent deuterium isotope effects were measured for the two reactions:

$$(k_{IP})_H/(k_{IP})_D = 2.9$$

$$(k_{IS})_H/(k_{IS})_D = 1.0$$

Discussion

Formation of the Iprodione. The mechanism of cyclization of the hydantoic acid to iprodione must be con-

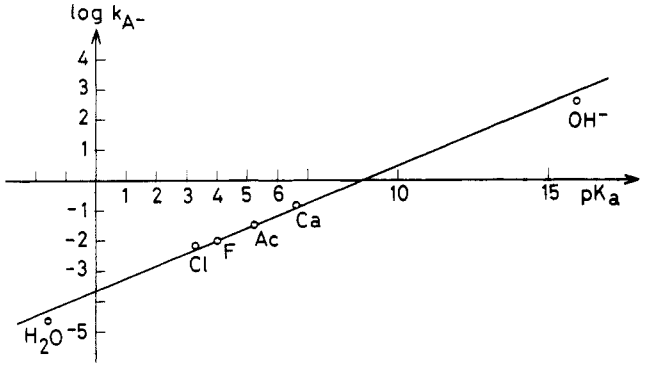
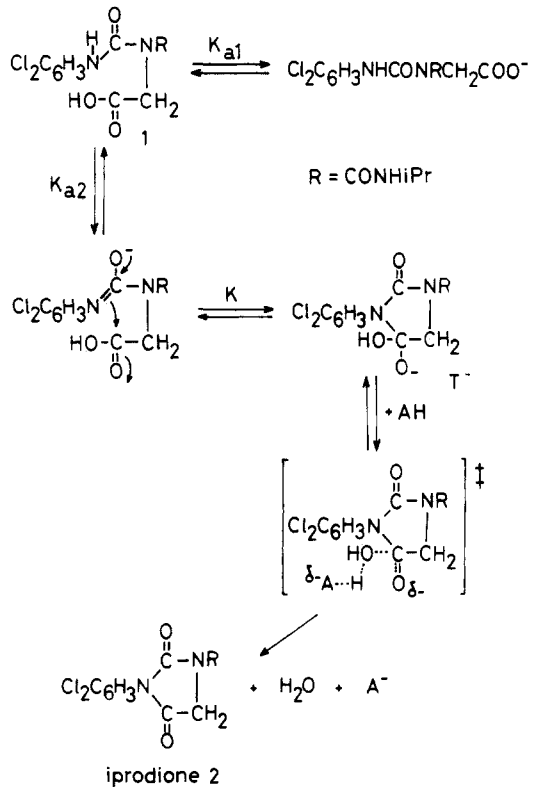


Figure 3. Plot of log k_{A^-} for general base catalyzed formation of iprodione vs the pK_{app} of the conjugate acid of the catalyzing base at 50 °C (water–dioxane, 7:3, v/v; μ = 0.5 M, KCl).

Scheme I



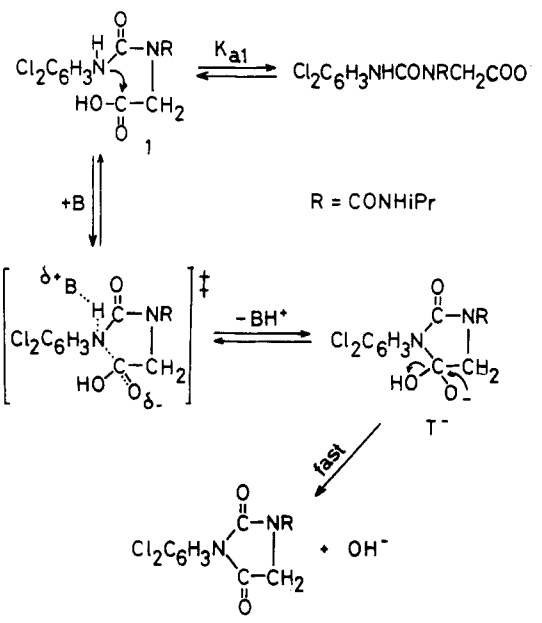
iprodione 2

sistent with the pH–rate profile, the general base catalysis for the reaction of the unionized acid, and the solvent isotope effect of 2.9 in aqueous hydrochloric acid.

A specific base–general acid catalyzed cyclization with intermediate formation of the enolate anion, the rate-determining step being the acid-catalyzed leaving of OH^- from T^-, is consistent with these results (Scheme I). It is supported by the solvent isotope effect of 2.9. It agrees with the relative basicity of the leaving groups, hydroxide and ureido: the *N*-(3,5-dichlorophenyl)ureido group (pK_a = 11.7 at 25 °C)[6] being a much better leaving group that the hydroxide group (pK_a = 15.97),[11] its return to the reactants is faster than the departure of the hydroxide group.

Another mechanism consistent with the catalysis is the base-catalyzed nucleophilic attack of the nitrogen on the carboxylic group leading to T^-, which breaks down rapidly to products as observed for lactamization of 2-(1-amino-

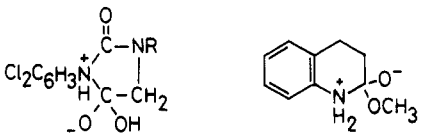
Scheme II



iprodione 2

ethyl)benzoate anion[12] (Scheme II). It would, however, be inconsistent with the mechanism of the reverse reaction, the hydrolysis of iprodione. For the latter reaction, the rate-determining step is the formation of T^- by nucleophilic attack of OH^- on the carbonyl group.[6] From the principle of microreversibility, the rate-determining step of cyclization, the reverse reaction of the alkaline hydrolysis of iprodione, must be the breaking of T^-.

The general base catalysis could have been explained by a rate-determining removal of a proton on the nitrogen of first-formed tetrahedral intermediate T^{+-} (**4a**) as has



4a 4b

been proposed for the cyclization of the methyl 3-(2-aminophenyl)propionate.[13] But the β Brønsted exponent should have been near zero since, for all the acids used, the equilibrium should be favorable in the direction of the proton removal and the rate would be diffusion controlled. The substantial Brønsted exponent of 0.38, constant over 15 pK_a units, is not consistent with a diffusion-controlled process but suggests that proton transfer is concerted with breaking or making of bonds to heavy atoms.

In the absence of buffer, Scheme I leads to the rate equation

$$k_{IP} = KK_{a2}(k_0 + k_H[H_3O^+])/([H_3O^+] + K_{a1}) \quad (6)$$

where K is the equilibrium constant between the tetrahedral intermediate T^- and the enolate anion, K_{a1} and K_{a2} are the ionization constants of the carboxylic and of the *N*-(3,5-dichlorophenyl)ureido groups of the hydantoic acid, respectively, k_0 is the rate constant for the water-catalyzed reaction, and k_H is the second-order rate constant for the apparent hydronium ion catalysis.

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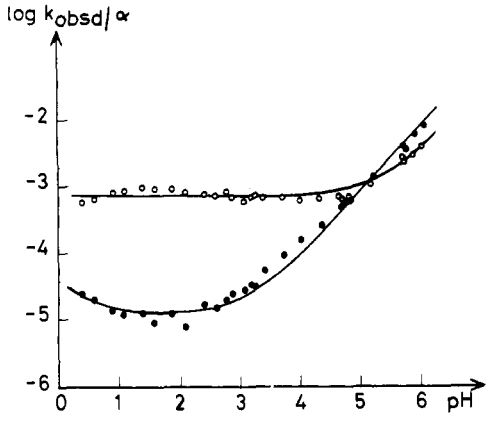


Figure 4. Plot of log k_{obsd}/α vs pH for formation of iprodione (2) (○) and its isomer 3 (●) from 1 at 50 °C in water–dioxane (7:3, v/v) with μ = 0.5 M (KCl). α is the unionized fraction of hydantoic acid 1. Curves are from the best-fit values of parameters of Table III obtained by a nonlinear least-squares analysis using eq 7 and 9.

Table III. Derived Rate Parameters for the Formation of Iprodione (2) and Isomer 3

2		3	
k_H, M^{-1} s^{-1}	2.5 ● 0.2	$10^9 k_E K_{a3}$	8.3 ± 0.6
$10^5 k_0$, M^{-1} s^{-1}	1.9 ± 0.2	$10^5 k_{EH} K_{a3}/K'_a$	1.3 ± 0.2
$10^{-8} K$, M	1.5 ● 0.1	$10^5 k_{EH_2} K_{a3}/K'_a K''_a$	4.5 ± 0.2
$10^5 K_{a1}$, M	9.6 ± 0.8	$10^4 K_{a1}$, M	1.5 ± 0.3
$10^{12} K_{a2}$, M	2.0 ● 0.4		

A nonlinear least-squares fit of eq 6 to the experimental data for **2** gave the derived rate parameters shown in Table III. The theoretical line calculated from these values is given in Figure 1. On the plateau, in more acidic media, $k_0 \ll k_H[H_3O^+]$ and $[H_3O^+] \gg K_{a1}$; eq 6 could be simplified to $k_{IP} = KK_{a2}k_H$. When the pH increases above pH 4.2, $K_{a1} \gg [H_3O^+]$, the rate decreases, and k_{IP} is given by

$$KK_{a2}(k_0 + k_H[H_3O^+])/K_{a1}$$

Above pH 6, $k_0 \gg k_H[H_3O^+]$ and a plateau rate tends to be reached with $k_{IP} = KK_{a2}k_0/K_{a1}$.

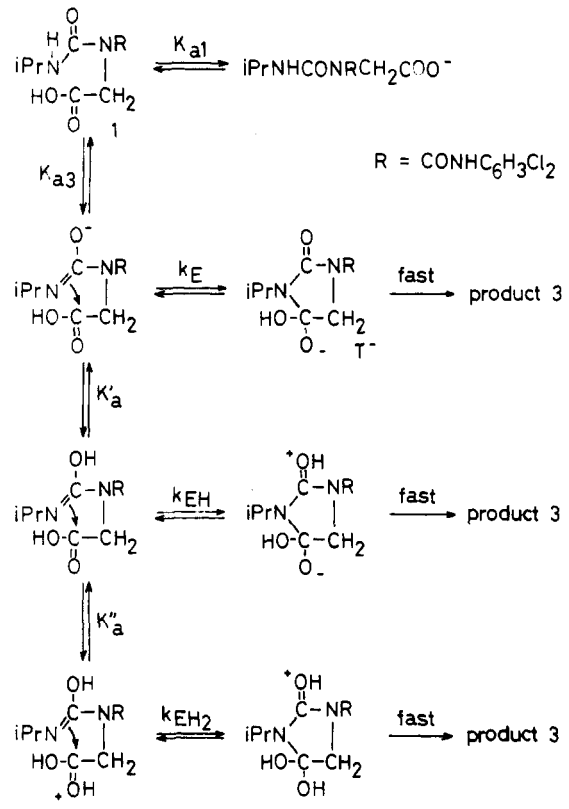
If the experimental rate constant is divided by the fraction of substrate present as carboxylic acid

$$k_{IP}/\alpha = KK_{a2}(k_0/[H_3O^+] + k_H) \quad (7)$$

and the plot of log k_{IP}/α vs pH is shown in Figure 4.

In previous papers dealing with the cyclization of hydantoic acids, the reaction of the unionized substrate was found to be specific or general acid catalyzed.[14,15] Kirby et al. found a general base catalysis for the ring closure of 2,2,3,5-tetramethylhydantoic acid in a pH range where the starting material is present as the carboxylate anion.[16] In a recent paper Blagoeva found a general base catalyzed cyclization of strained ω-phenylhydantoic acid and proposed a general base catalyzed formation of the tetrahedral intermediate T^- by a mechanism identical with Scheme II.[17] In this case the phenylureido group has a higher pK_a (16.6)[18] than the hydroxide group (pK_a = 15.97) and then the return of T^- to the reactant is slower than its breakdown. Kirby et al. found general base catalysis for a similar reaction, the cyclization of methyl 3-(2-amino-

Scheme III



phenyl)propionate, which was attributed to rate-determining removal of a proton on the nitrogen from the tetrahedral intermediate T^{+-} (**4b**) by a diffusion-controlled process because the Brønsted β value was near zero.[13]

Formation of the Isomer. A mechanism for this reaction consistent with the pH–rate profile, the lack of general acid–base catalysis, and the solvent deuterium isotope effect of 1.0 in aqueous hydrochloric acid is shown in Scheme III. The rate law governing this scheme is given as eq 8. The data corresponding to the rate law for **3** are

$$k_{IS} = \frac{k_E K_{a3}}{[H_3O^+] + K_{a1}} + \frac{k_{EH} K_{a3}[H_3O^+]}{K'_a([H_3O^+] + K_{a1})} + \frac{k_{EH_2} K_{a3}[H_3O^+]^2}{K'_a K''_a([H_3O^+] + K_{a1})} \quad (8)$$

plotted as the rate profile of Figure 1. The solid line was calculated with parameters of Table III obtained from a nonlinear least-squares fit of eq 8 to the experimental data for **3**. The plot of log k_{IS} vs pH shows three distinct regions of curvature having a negative slope at pHs < 1, a narrow plateau near pH 2, and an increase in rate with a second plateau region at pHs > pK_{a1}.

As in the formation of iprodione, we have supposed that the carboxylate anion was an unreactive species and the experimental rate constants k_{IS} have been divided by the fraction of the starting material present as carboxylic acid. In that case, eq 8 was used in a simplified form (eq 9) and

$$k_{IS}/\alpha = k_E K_{a3}/[H_3O^+] + k_{EH} K_{a3}/K'_a + k_{EH_2} K_{a3}[H_3O^+]/K'_a K''_a \quad (9)$$

the plot of log k_{IS}/α vs pH is shown in Figure 4.

For pH higher than 2.5, the specific base catalysis by hydroxide ion can be assigned to a spontaneous cyclization of the enolate form of the ureido anion, more reactive than the amide anion.

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The plateau between pH 1 and 2.5 can involve a spontaneous ring closure of the carboxylic acid. But this reaction is made difficult both by the low electrophilicity of the carboxylic group and by the poor nucleophilicity of the amidic nitrogen. However, if the base-catalyzed reaction involves the enolate anion, it may exist as a small quantity in the enolic form of the ureido group, more nucleophilic than the amide which can cyclize by a rate-determining uncatalyzed reaction.

The acid-catalyzed reaction at pHs less than 1 can involve the spontaneous ring closure of the enolic form of the acid protonated on the carboxylic group.

In the hydrochloric acid solution where the solvent deuterium isotope effect has been measured, $\alpha = 1$ and $k_{IS} = k_{EH}K_{a3}/K'_a$. The lack of significant kinetic solvent isotope effects ($k_{EH}/k_{ED} \simeq 1$) suggests that no proton transfer occurs in the cyclization of the enol. Then, the experimental kinetic isotope effect of 1.0 can be assigned to a cancelling of the equilibrium isotope effects on K_{a3} and K'_a.

The mechanism proposed here for the specific base-catalyzed reaction implies that the breaking of T^- to the products with departure of OH^- is faster than its return to the reactants with leaving of an ureido anion. This suggestion is consistent with the relative basicities of OH^- ($pK_a = 15.97$) and of the *N*-isopropylureido group ($pK_a \simeq 18$ for the *N*-methylurea).[20]

The relative basicities of the leaving groups were opposite in the formation of iprodione: the ureido anion bearing an aromatic substituent was less basic than the hydroxide anion and the rate-determining step was then the acid-catalyzed leaving of OH^-.

The nucleophilic attack of an ureido anion on a carboxylate group by a specific base-catalyzed reaction has been proposed by Hegarty and Bruice[19] for the cyclization of the 2-ureido benzoate while Kirby et al. have suggested a specific base–general acid catalyzed reaction leading to an intermediate similar to T^- for the cyclization of 2,2,3,5-tetramethylhydantoic acid.[16]

In conclusion, it appears that very different kinetic results for the formation of iprodione and that of its isomer lead to very similar mechanisms. Both involve the reaction of the enolate anion and are different only by the rate-determining step.

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Supplementary Material Available: Rate data for the cyclization of *N*-[(3,5-dichloroanilino)carbonyl]-*N*-[(isopropylamino)carbonyl]glycine and for the formation of iprodione and its isomer in HCl solutions and buffers (Tables S1 and S2) and example of determination of k_{IP} and k_{IS} in acetate buffer (Tables S3 and S4) (9 pages). Ordering information is given on any current masthead page.

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Equilibrium and Kinetic Studies of Some Reactions of 1-Anthraquinonesulfenic Acid and Its Methyl Ester[1]

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1-Anthraquinonesulfenic acid (**2**) is a stable arenesulfenic acid. Its pK_a, and the products and kinetics of its reactions, and those of its methyl ester (**3**), with both a thiol (*n*-BuSH) and *m*-chloroperoxybenzoic acid (MCPBA), have been determined. The results are compared with those for the corresponding reactions of two stable areneselenenic acids (**1a** and **1b**). The pK_a of **2** (7.51) shows it to be ~3 p*K* units *stronger* acid than *o*-$O_2NC_6H_4SeOH$ (**1a**). Reaction of **2** and **3** with *n*-BuSH occurs at comparable rates and gives *n*-butyl 1-anthraquinonyl disulfide (**5**) via a reaction that is acid catalyzed. The rate of reaction of **2** with the thiol is ~10^4 *slower* than the rate of reaction of the structurally analogous areneselenenic acid, *o*-$PhC(O)C_6H_4SeOH$ (**1b**). The probable reason for this large difference in rates is outlined. The difference in the rates of oxidation of **2** and **1b** by MCPBA is much smaller, the selenenic acid being oxidized only 6 times faster than **2**. Just as was found with selenenic acid **1a** and its methyl ester, the rate of oxidation of sulfenic acid **2** by MCPBA is much faster than the rate of oxidation of its methyl ester.

Sulfenic (RSOH) and selenenic (RSeOH) acids play important roles as reactive intermediates in organosulfur and organoselenium chemistry, respectively. Because the vast majority are too unstable to be isolated, study of their chemistry and the mechanisms of their reactions in the normal fashion is not possible, and, as Davis et al.[3] have pointed out, much of our knowledge of their reactions has been derived indirectly, via rationalization of end products.

In recent years Davis and his co-workers[3,4] have used flash vacuum pyrolysis (FVP) to generate a variety of unstable sulfenic acids. These were deposited on a cold finger at −196 °C, and their chemistry was then explored

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