# Kinetics and Mechanism of Hydantoic Ring Opening. The Alkaline Hydrolysis of 3-Arylimidazolidine-2,4-diones to 5-Arylhydantoic Acids

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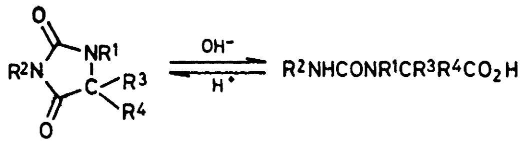
The kinetics of hydrolysis of 3-arylimidazolidine-2,4-diones to 5-arylhydantoic acids were studied in aqueous solution over the pH range 8—14 at 25°. In strongly alkaline media (pH >11.5), an ionisation equilibrium gives rise to an unreactive anion. The p$K_a$ values determined both spectrophotometrically and kinetically for the unsubstituted derivative are in good agreement. In mildly alkaline media (pH <11.5), the observed rates have a first-order dependence on hydroxide ion concentration and no general catalysis is detected. The value of the Hammett parameter ($\rho$ 0.8), the low deuterium isotope solvent effect ($k_{H_2O}/k_{D_2O}$ *ca.* 0.7), and the markedly negative values of the entropies of activation ($-30$ cal mol$^{-1}$ K$^{-1}$ $< \Delta S^{\ddagger} <$ $-20$ cal mol$^{-1}$ K$^{-1}$) are rationalized in terms of a rate-determining hydroxide ion attack which is in agreement with the p$K_a$ value of the leaving group of 3-arylhydantoins.

HYDANTOIC acids are known to cyclise to imidazolidine-2,4-diones under acidic conditions. Conversely, under mild conditions, the alkaline hydrolysis of an imidazolidinedione regenerates the corresponding hydantoic acid by ring opening. The equilibrium is completely shifted to either form, open or cyclic, according to the pH of the reaction medium (Scheme 1).[1]



SCHEME 1

Although the stability to alkaline hydrolysis of some substituted hydantoins has been investigated in some detail,[2,3] the nature of the reaction mechanism of the hydantoic ring cleavage has not yet been elucidated, in spite of the biological activity of some hydantoins.[1] Reaction mechanisms are known for barbituric acids [4,5] and 5,6-dihydrouracils,[6,7] whose six-membered rings possess structural characteristics similar to hydantoins.

Some of the hydantoins mentioned in the present study have fungicidal properties.[8,9] The investigation of the alkaline hydrolysis of 3-arylimidazolidine-2,4-diones provided quantitative data for the conversion of these hydantoins into their corresponding acids at various pH values and allowed a discussion of the dependence of the mechanism on the nature of the leaving group.

## RESULTS AND DISCUSSION

The rate constants for the alkaline hydrolysis of 3-arylimidazolidine-2,4-diones were measured in aqueous solution in the pH range 8—14 at 25°. Under the experimental conditions employed, the hydrolyses were found to follow first-order kinetics with respect to the substrate. The identity of the u.v. spectrum obtained at the completion of a kinetic experiment with that of the corresponding hydantoic acid, run at the same concentration and under the same conditions, corroborated the irreversibility of hydroxide ion attack at the carbonyl group at the 4-position.

The pH–rate profile for 3-phenylimidazolidine-2,4-dione shows two distinct regions: a straight line of slope unity in the pH range 8—12, followed by a plateau at higher pH. The shape of this profile suggests the ionisation of the substrate with formation of an unreactive anion. The lack of a plateau in the case of the hydrolysis of 1-methyl-3-phenylimidazolidine-2,4-dione, which cannot ionise (Figure 1), as well as the spectrophotometric determination of the ionisation constant of 3-phenylhydantoin (p$K_a$ 12.5; Figure 2) bear out this assumption.

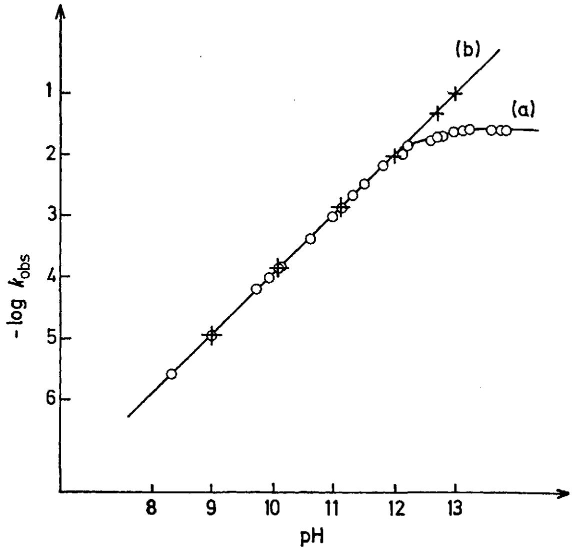


FIGURE 1 Plot of log $k_{obs.}$ against pH for the hydrolysis of (a) 3-phenylimidazolidine-2,4-dione and (b) 1-methyl-3-phenylimidazolidine-2,4-dione in water at 25° ($\mu$ 1.0, KCl)

The reaction of hydrolysis of 3-phenylimidazolidine-2,4-dione is subject to specific base catalysis by hydroxide

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[2] H. Aspelung, *Acta Acad. Aboensis*, 1962, **23**, 2.

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[6] E. G. Sander, *J. Amer. Chem. Soc.*, 1969, **91**, 3629.

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[8] A. Fujinami, N. Tottori, T. Kato, and N. Kameda, *Agric. Biol. Chem.*, 1972, **36**, 1623.

[9] (*a*) L. Lacroix, G. Bic, L. Burgaud, M. Guillot, R. Leblanc, R. Riottot, and M. Sauli, *Phytiatrie-Phytopharmacie*, 1974, **23**, 165; (*b*) M. Sault, *Ger. Offen.*, 2,149,923 (*Chem. Abs.*, 1972, **77**, 19647).

ion; for each of the buffer solutions investigated (triethylamine, carbonate, borax, tris(hydroxymethyl)aminomethane), the reaction rate is independent of the buffer concentration.

These data (first order with respect to $OH^-$, formation of an unreactive anion, lack of general base catalysis in the pH range investigated), taken together, are in agreement with Scheme 2.

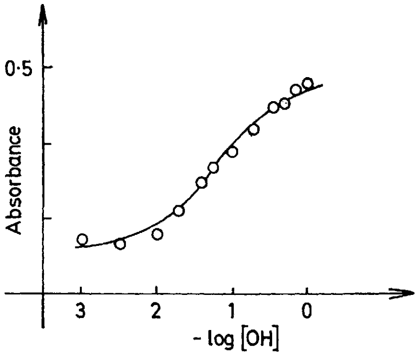
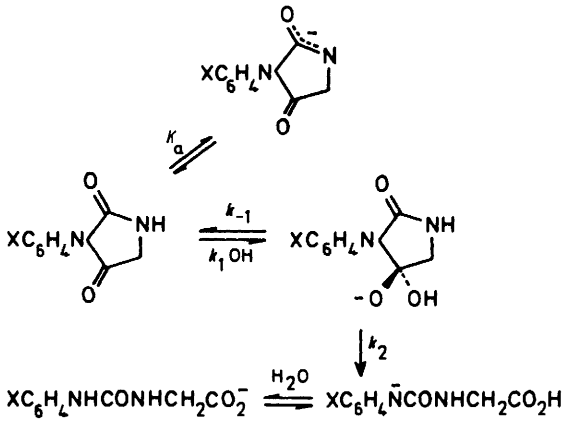


FIGURE 2 Plot of the observed optical density of 3-phenylimidazolidine-2,4-dione at 232 nm against log $[OH^-]$ at 25° ($\mu$ 1.0, KCl); p$K_a$ 12.55



SCHEME 2

This mechanism leads to the following rate equation for the hydrolysis of 3-phenylhydantoin : $k_{obs}\ (1 + K_a/a_H) = k_1k_2[OH^-]/(k_{-1} + k_2)$. Introducing the bimolecular rate constant $k_{OH} = k_1k_2/(k_{-1} + k_2)$, this equation becomes, according to the pH range: $a_H \gg K_a$, $k_{obs} = k_{OH}[OH^-]$; $a_H \ll K_a$, $k_{obs} = k_{OH}K_w/K_a$.

The p$K_a$ value of 12.4, calculated from the kinetic data, is in good agreement with that obtained spectrophotometrically (p$K_a$ 12.5). Such an acidity for a proton attached to a nitrogen atom $\alpha$ to a carbonyl group seems reasonable. It is known, for example, that the p$K_a$ of 3-methyl-5,5-pentamethylene-2-thiohydantoin is 11.21, a value which is indeed lower, owing to the higher polarisability of sulphur.[10] Few data are available in the hydantoin series; a p$K_a$ value $>11$ was reported by Siemonsen for 3-methylhydantoin.[11]

The electrophilic reactivity of the C-4 carbonyl group of the anionic species of the substrate could be considered since the delocalisation of the negative charge does not extend to that group. This point was taken into consideration for the deacylation reaction of 1-acyl-2-thiohydantoins [12] but cannot account for our kinetic data. Furthermore, the lack of a second order term with respect to hydroxide allows the involvement of the dianion $^-O-\overset{|}{\underset{|}{C}}-O^-$, which was put forward for the alkaline hydrolysis of anilides [6,13,14] and of 5,6-dihydrouracil derivatives,[4,5] to be ruled out.

If the results presented above allow the reaction scheme to be outlined unambiguously, it is, however, difficult to specify the rate-determining step. It seems to be generally agreed that, for the hydrolysis of anilides, the decomposition of the tetrahedral intermediate is subjected to general acid catalysis.[14,15] The lack of general catalysis for the hydrolysis of 3-phenylimidazolidine-2,4-dione may be considered as supporting slow addition of hydroxide ion. Nevertheless, this argument does not seem to be decisive. This is the reason why the structure–reactivity correlations, the isotope effects, and the activation entropies for the hydrolysis of a series of 3-arylimidazolidine-2,4-diones were investigated so as to determine the position of the rate-determining step along the reaction pathway.

(a) *Substituent Effects.*—Substituent effects should be sensitive to the nature of the rate-determining step. As a matter of fact, if the rate-determining step is the decomposition of the tetrahedral intermediate, then the rate equation becomes $k_{obs} = k_1k_2[OH^-]/k_{-1}$ and the observed $\rho$ value is composite representing the individual contributions of substituent effects on $k_2$ and $k_1/k_{-1}$. Such reactions are characterised by low $\rho$ values, as was observed by Bender [15] and Schowen [14] for the hydrolysis of acetanilides ($\rho$ +0.1) [15] and that of 2,2,2-trifluoro-*N*-methylacetanilides ($\rho$ +0.07).[14] On the contrary, if the rate-determining step is the addition of hydroxide ion, the observed $\rho$ value will only account for the substituent effects on the reactivity of the carbonyl group to hydroxide ion attack and will be near unity. The $\rho$ value of +0.8 [$\log k_{OH} = 0.80\sigma - 0.05$ ($r$ 0.984); Table], observed for the hydrolysis of 3-arylhydantoins, supports a slow addition of hydroxide ion. Values of $\rho$ near unity were also observed for hydroxide ion reactivity for the hydrolyses of 2,2,2-trifluoro-*N*-methylacetanilides ($\rho$ +1.18) [14] and of 1-arylazetidin-2-ones ($\rho$ +1.22),[16] when hydroxide ion addition was rate determining.

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[11] L. Siemonsen, *Annalen*, 1904, **333**, 113.

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[15] M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, 1961, **83**, 4183.

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For the hydantoin series investigated, the datum point corresponding to the $p$-nitro-substituent ($\sigma$ 0.778) falls on the correlation line of the Hammett plot of log $k_{obs}$ *versus* $\sigma$. This is in agreement with a rate-determining hydroxide ion addition, where there is no conjugation interaction by resonance between the reaction centre and the electron-withdrawing substituents. On the contrary, the $\sigma^-$ parameter should have been used if the rate-determining step was the decomposition of the tetrahedral intermediate involving cleavage of the C–N bond and formation of an amide ion, as for the alkaline methanolysis of $N$-methylbenzanilides.[17]

Substituent effects on the alkaline hydrolysis of 3-(X-phenyl)imidazolidine-2,4-diones in water at 25° ($\mu$ 1.0, KCl)

| X | p$K$ | $10^2k/_{obs}$s$^{-1}$ *a* | $10^2k/_{obs}$s$^{-1}$ *b* | $k_{OH}$/l mol$^{-1}$ s$^{-1}$ | $\Delta S^{\ddagger\,c}$/cal mol$^{-1}$ K$^{-1}$ |
|---|---|---|---|---|---|
| 4-MeO | 12.5 | 3.10 | 2.27 | 0.64 | −32.3 |
| H | 12.4 | 3.00 | 2.50 | 0.73 | −30.2 |
| 3-Cl | 12.2 | 4.50 | 3.42 | 1.62 | −29.8 |
| 3-$NO_2$ | 12.1 | 6.50 | 5.90 | 3.13 | −31.0 |
| 4-$NO_2$ | 12.2 | 8.70 | 10.50 | 4.22 | −22.2 |

[a] Measured in 1M-NaOH. [b] Measured in 1M-NaOD. [c] Measured in 0.002M-NaOH.

(b) *Deuterium Oxide Solvent Isotope Effects*.—If the rate-determining step is the addition of hydroxide ion to 3-phenylimidazolidine-2,4-dione, as suggested by the $\rho$ value, the reaction rate should be enhanced in heavy water because of the higher nucleophilicity of $OD^-$ with respect to $OH^-$.[18] As a matter of fact, the various data reported in the literature show that the rate of attack of $OD^-$ at the carbonyl group of an ester is increased by a factor of 1.3—5 with respect to that of $OH^-$ at the same concentration.[19] Moreover, the isotope effects $k_{H_2O}/k_{D_2O}$ measured for the alkaline hydrolyses of 3-methyl-5,6-dihydrouracil [6] and of 2,2,2-trifluoro-$N$-methylacetanilide [4] where, at high pH values, the rate-determining step is the formation of a tetrahedral intermediate, are 0.78 and 0.79, respectively. An isotope effect $k_{obs}(H_2O)/k_{obs}(D_2O) = 0.69$ was recently reported by Gani and Viout for the rate-determining attack of hydroxide ion on $N$-methyl-$p$-nitroacetanilide.[20]

On the contrary, when the decomposition of the tetrahedral intermediate is rate determining, Schowen showed, on a series of trifluoro-$N$-methylacetanilides, that the isotope effects $(k_1k_2/k_{-1})H_2O/(k_1k_2/k_{-1})D_2O$, lay between 2 and 3.[14] Therefore, a value smaller than unity should be obtained for $k_{obs}(H_2O)/k_{obs}(D_2O)$ so as to bear out our previous assumption.

The isotope effects for the hydrolysis of 3-phenylhydantoin were measured in sodium hydroxide solutions, at pH values lying on both sides of the p$K_a$ of the substrate, at 25° (Table). The following data were obtained for the unsubstituted substrate:

$[OH^-]$ $1.5 \times 10^{-3}$M, *i.e.*, $a_H \gg K_a$

$$k_{obs}(H_2O)/k_{obs}(D_2O) = (k_{OH})H_2O/(k_{OH})D_2O = 0.75$$

$[OH^-]$ 1.0M, *i.e.*, $a_H \ll K_a$

$$k_{obs}(H_2O)/k_{obs}(D_2O) = \frac{(k_{OH})H_2O\ (K_w/K_a)H_2O}{(k_{OH})D_2O\ (K_w/K_a)D_2O} = 1.20$$

An isotope effect $k_{OH}/k_{OD}$ of 0.72 in 1.0M-sodium hydroxide can be calculated approximately from $K_w(H_2O)/K_w(D_2O)$ 7.5 [21] and $K_a(H_2O)/K_a(D_2O)$ 4.5. This latter value, reported in the literature for trifluoroethanol, was chosen for 3-phenylhydantoin because the ionisation constants of these two compounds are identical (p$K_a$ 12.4) and their stretching vibration frequencies are close together ($\nu_{NH}$ 3 100, $\nu_{OH}$ 3 300 cm$^{-1}$).[22] Therefore, since the isotope effect $k_{OH}/k_{OD}$ is the same in the two regions of the pH profile, there is no change of rate-determining step in the pH range investigated. Moreover, the average value of 0.7 found for the whole series of derivatives bears out slow hydroxide ion attack.

(c) *Entropies of Activation*.—If the first step $k_1$ is rate determining, a highly negative entropy of activation, owing to the decrease in the degrees of freedom of hydroxide ion, can be expected. Some data reported in the literature corroborate this assumption. As a matter of fact, for the hydrolysis of esters, the addition of hydroxide ion to the carbonyl group leads to entropy values lying between −20 and −35 cal mol$^{-1}$ K$^{-1}$.[23] Moreover, Blackburn and Plackett [16] found values of −21 and −19 cal mol$^{-1}$ K$^{-1}$ for hydroxide ion attack on $N$-methyl-$p$-nitroacetanilide and on 1-$p$-nitrophenylazetidin-2-one, respectively.

If the decomposition of the tetrahedral intermediate is rate determining, the activation entropy should be less negative. It would be indeed the sum of an entropy of *ca.* −20 cal mol$^{-1}$ K$^{-1}$ for the equilibrium of addition of $OH^-$ on the carbonyl group [24] and of an entropy which is likely to be positive and near zero for $k_2$. This positive increment corresponding to $k_2$ would result from the likely decrease, in the transition state, of the ring strains existing in the tetrahedral intermediate.

The entropy of activation was derived from measures carried out in 0.002M-sodium hydroxide at three different temperatures (15, 25, and 35°). The values obtained, lying between −22 and −32 cal mol$^{-1}$ K$^{-1}$, are in agreement with slow hydroxide ion attack on the hydantoin.

The part of the hydantoic ring corresponding to the N(3)–C(4)–C(5) fragment bears a close resemblance to the framework of acetanilides. The hydrolysis of acetanilides, like the ring cleavage of hydantoins,

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[19] T. C. Bruice, T. H. Fife, J. J. Bruno, and P. Benkovic, *J. Amer. Chem. Soc.*, 1962, **84**, 3012.

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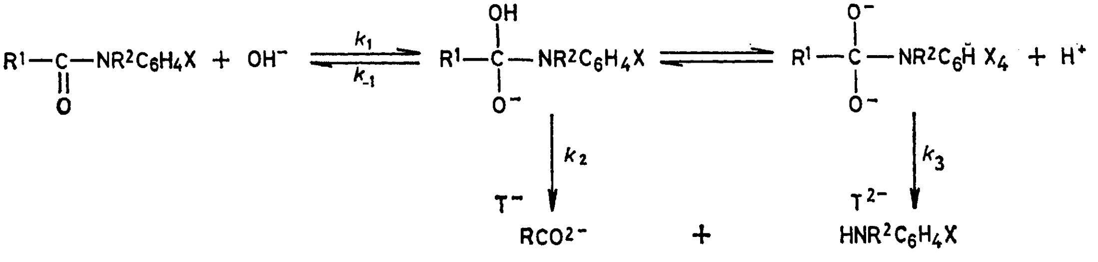
[21] P. Salomaa, *Acta Chem. Scand.*, 1971, **25**, 367.

[22] R. P. Bell, 'The Proton in Chemistry,' Cornell University Press, Ithaca, 1959, 1st edn., p. 189; Chapman and Hall, London, 1973, 2nd edn., p. 227.

[23] A. J. Kirby in 'Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1973, vol. 10, ch. 2, p. 57.

[24] J. F. Bunnett, J. H. Miles, and K. U. Nahabedian, *J. Amer. Chem. Soc.*, 1961, **83**, 2512.

involves the breaking of the amide bond. A same general mechanism, that is partly analogous to the one put forward for hydantoins, accounts for the kinetic data for the hydrolysis of anilides (Scheme 3). However, the order with respect to $OH^-$, the kind of acid–base catalysis, the position of the rate-determining step, and its possible change with pH, all depend closely on the structure of the substrate investigated. In particular, the $pK_a$ of the leaving group plays a determining role.



Scheme 3

A literature survey shows the following. (1) As the $pK_a$ of the conjugate acid of the leaving group (aniline) is greater than 20,[25] the decomposition of the dianion $T^{2-}$ is subjected to general base catalysis. It proceeds along two parallel pathways: for poor leaving groups ($X = p$-MeO, $p$-Me, H), slow protonation of the nitrogen atom by the catalyst results in the formation of an intermediate ammonium ion; for better leaving groups ($X = p$-Cl, $p$-Br, $m$-$NO_2$), C–N bond cleavage concerted with protonation of the nitrogen atom occurs.[14] Besides the tetrahedral intermediate $T^-$ leads, *via* acid catalysis, to the reaction products.[14]

(2) For the hydrolysis of anilides of the type $R^1CONR^2C_6H_4NO_2$-$p$($R^1$ = H, Me, $CF_3$; $R^2$ = H),[13,14,26] the decomposition of the dianion $T^{2-}$ does not require the involvement of a general acid catalyst. As the $p$-nitro-group is strongly electron-withdrawing, the leaving group has a better nucleofugic ability ($p$-nitroaniline, $pK_a$ 18.37).[27] However, Pollack and Dumsha observed, for the hydrolysis of $p$-nitrotrifluoroacetanilides, general acid-catalysed decomposition of the monoanion $T^-$, together with the non-catalysed decomposition of the dianion $T^{2-}$.[28] The same kinetic process, spontaneous decomposition of the dianion, holds for the alkaline hydrolysis of $N$-acetylpyrrole[29] (pyrrole, $pK_a$ 17.5) and for that of 3-methyl-5,6-dihydrouracil;[6] the $pK_a$ of the conjugate acid of the leaving group of the latter derivative (*i.e.* 6-methylureidopropionic acid) can be estimated as 18.3 by analogy with that of $N$-methylurea.[30] In such cases, the $pK_a$ of the conjugate acid of the leaving group is 2—3 units greater than that of $H_2O$ [$pK_a(H_2O)$ 15.7].

(3) Last, slow hydroxide ion addition was put forward for the hydrolysis of $N$-methyl-$p$-nitroacetanilide[20] and that of $N$-arylazetidin-2-ones[16] in the pH range 12—14.

Such a classification of the mechanisms of hydrolysis, based upon the $pK_a$ of the leaving group, is not restricted to the case of anilides; Bender[31] extended it to the nucleophilic reactions of carboxylic acid derivatives, including amides and esters. For the reactions involving substrates possessing a leaving group whose $pK_a$ is several units greater than that of water, the decomposition of the tetrahedral intermediate is rate determining, whereas its formation is slow when the $pK_a$ of the leaving group of the substrate is equal to or smaller than that of water. Therefore it is interesting to assess whether the mechanism of hydrolysis of hydantoins can be included in this classification. This is the reason why the acidity of N-5 of the hydantoate ion $PhNHCONHCH_2CO_2^-$ was determined, as the corresponding anion is formed during cleavage of the hydantoic ring. Proton abstraction can theoretically occur at either N-3 or -5. However, the 5-H is likely to be more mobile than 3-H, because the anion formed is then stabilised by conjugation between the negative charge and the aromatic nucleus. The determination of the acidity constants of 5-phenylhydantoic acid and of its 3-methyl derivative allowed this point to be cleared up.

The almost identical $pK_a$ values measured for 5-phenylhydantoic acid (16.40) and 3-methyl-5-phenylhydantoic acid (16.60) bear out that proton abstraction occurs at N-5. The $pK_a$ of the conjugate acid of the leaving group $Ph\bar{N}CONHCH_2CO_2^-$ is two units smaller than that of $p$-nitroaniline. It is therefore one of the best leaving groups encountered so far for the cleavage of an amide bond. Moreover, according to Bender's classification, as this $pK_a$ is of the same order of magnitude as that of water, the rate-determining step should be the addition of hydroxide ion to the carbonyl group. This is corroborated by our experimental data.

Apparently, for the hydrolysis of anilides, kinetic evidence for the dianion step can be given only if the $pK_a$ of the leaving group is 2—3 units greater than that of water. For substituted 3-arylhydantoins bearing

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[31] M. L. Bender in 'Mechanisms of Homogeneous Catalysis from Protons to Proteins,' Wiley, New York, 1971, p. 107.

electron-withdrawing groups, the conjugate acids of the leaving groups (5-arylhydantoates) are more acidic than the unsubstituted derivative (p$K_a$ 16.4); their acidity is likely to be of the order of magnitude of that of alcohols. The rate-determining step is again the addition of hydroxide ion, as for the hydrolysis of esters.

## EXPERIMENTAL

*Chemicals*.—All chemicals used were of analytical or reagent grade. Triethylamine hydrochloride was twice recrystallized from ether–ethanol. Aqueous solutions were prepared from deionized freshly glass distilled water.

*Substrates*.—5-Aryl- and 3-methyl-5-phenylhydantoic acids were prepared from glycine or sarcosine by treatment with aryl isocyanate; they cyclised to 3-arylimidazolidine-2,4-diones by refluxing in concentrated hydrochloric acid,

5-*Phenylhydantoic acid*. To a solution of glycine (3.75 g, 0.05 mol) and pellets of sodium hydroxide (4.5 g) dissolved in water (150 ml) ([NaOH] 0.75M) phenyl isocyanate (6 g, 0.05 mol) was added dropwise within 1/2 h. The mixture was stirred and heated to 50° for 2 h. Diphenylurea, a by-product, was filtered off, and the filtrate acidified with concentrated hydrochloric acid gave 5-phenylhydantoic acid. The solid was twice recrystallized from water–ethanol, m.p. 198° (lit.,[32] 195°).

3-*Arylimidazolidine*-2,4-*diones*. 5-Phenylhydantoic acid (2 g) in hydrochloric acid (20%, 40 ml) was refluxed for 2 h. After cooling, the precipitated 3-phenylimidazolidine-2,4-dione was recrystallized from water–ethanol, m.p. 155° (lit.,[33] 155°).

Similarly prepared were the following 3-(X-phenyl)-imidazolidine-2,4-diones: X = 4-$NO_2$, m.p. 255° (from water–ethanol) (lit.,[34] 244°); X = 3-$NO_2$, m.p. 165°; X = 3-Cl, m.p. 148°; X = 4-MeO, m.p. 206°. 1-Methyl-3-phenylimidazolidine-2,4-dione had m.p. 110—112° (from water–ethanol) (lit.,[35] 109—110°). The structures assigned to these hydantoins were confirmed by n.m.r. spectroscopy.

*Apparatus*.—A Unicam model SP 1800 recording spectrophotometer fitted with a SP 1805 program controller and a thermostatted multiple cell compartment was used for all spectroscopic measurements. The pH measurements were carried out using a Radiometer model PHM 64 pH meter equipped with a Radiometer GK 2301 C electrode.

*Kinetic Method*.—The kinetics of hydrolysis of 3-arylimidazolidine-2,4-diones were followed spectrophotometrically by recording at appropriate wavelengths the changes in optical density corresponding to the appearance of the hydantoic acids (X and λ given): 4-MeO, 244; H, 240; 3-Cl, 244; 3-$NO_2$, 250; 4-$NO_2$, 346 nm. The reverse of the hydrolysis reactions was studied under identical conditions but no visible reactions were noted suggesting that the reactions were for all practical purposes irreversible under the conditions employed. Similarly, the u.v. spectra recorded at the completion of the hydrolysis of 3-arylimidazolidine-2,4-diones at all pH values were identical with the spectra of authentic samples of the corresponding hydantoic acids, run at the same concentration and under the same conditions.

The absorbance–time plots were analysed in all cases to give the pseudo-first-order rate constants graphically, either by the method of Guggenheim, or using the experimental infinity value. Apparent second-order rate constants, $k_{OH}$, are the mean values calculated from $k_{obs}/[OH^-]$. The entropies of activation $\Delta S^{\ddagger}$ were obtained from the equation $\Delta S^{\ddagger} = 2.303R\,(\log k_{obs} - \log T - \log eK/h) + E_0/T$ and regression lines from a weighted least squares program written for the Olivetti–Underwood Programma 102.

p$K_a$ *Measurements*.—(1) 3-*Phenylimidazolidine*-2,4-*dione*. The acid dissociation constant at 25° (μ 1.0, KCl) was determined spectrophotometrically at 232 nm, the wavelength for which the absorbance difference between the neutral molecule and the anionic species is the highest. The decomposition of the substrate was sufficiently fast ($t_{1/2}$ *ca*. 30 s in 1.0M-NaOH) to require extrapolation of absorbance data back to zero time. The theoretical titration curve, obtained from the equation $O.D._{obs} - O.D._0 = O.D._{max.}K_a/(K_a + K_w/_{\gamma}[OH^-])$ was compared with the plot of the observed optical density *versus* hydroxide ion concentration to give the p$K_a$.

(2) 5-*Phenyl- and* 3-*methyl*-5-*phenylhydantoic acids* $PhNHCONRCH_2CO_2H$. The u.v. absorption of 5-phenylhydantoic acid (R = H) ($5 \times 10^{-5}$M) and of 3-methyl-5-phenylhydantoic acid (R = Me), obtained *in situ* through alkaline hydrolysis of 1-methyl-3-phenylhydantoin, was measured at 25° for various sodium hydroxide concentrations (1.0—11M). As the completely ionised form could not be reached for each of these substrates, the data obtained from spectroscopic measurements were treated by the method developed by Maroni and Calmon[36] and later adopted in the revised edition of Albert and Serjeant:[37] $1/(\varepsilon_{obs} - \varepsilon_A)$ was plotted against $h^-$ at various wavelengths. From the extrapolated value of $\varepsilon_B$, $\log_{10}(\varepsilon_{obs} - \varepsilon_A)/(\varepsilon_B - \varepsilon_{obs})$ was then plotted against $H^-$.[38] ($\varepsilon_A$, $\varepsilon_B$, and $\varepsilon_{obs}$ are the molar extinction coefficients of the free acid, of the conjugate base, and of the mixture, respectively.) The slope of the straight lines thus obtained (R = H, slope 0.99, $r$ 0.99; R = Me, slope 1.05, $r$ 1.00), is a criterion of good accuracy of the measures and of the appropriateness of the chosen acidity function.

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