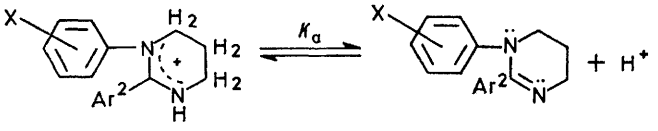
# Basicity and Alkaline Hydrolysis of 1,2-Diaryl-1,4,5,6-tetrahydropyrimidines. Application of the Hammett Equation

By **Beatriz Fernández, Isabel Perillo,** and **Samuel Lamdan,*** Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junin 956, Republica Argentina

The p$K_a$ values of nine 1,2-diaryl-1,4,5,6-tetrahydropyrimidines have been determined spectrophotometrically. The influence of substituents at N-1 and C-2 upon basicity has been studied. When the tetrahydropyrimidine ring is considered to be a substituent of the benzene ring at N-1. a good correlation with the Hammett equation is found. The stability of these compounds to hydrolysis in boiling alkaline 95% ethanol was studied. Reaction rates were enhanced by electron-releasing phenyl substituents at N-1 and reduced by electron-withdrawing groups. Agreement with the Hammett equation allowed calculation of rate constants. The observed and calculated rate constants of hydrolysis are nearly equal. An equation relating the rate constants with the ionization constants of tetrahydropyrimidinium ions is given.

In continuation of our study on the properties of cyclic amidines,[1] the basicity and stability to alkaline hydrolysis of 1,2-diaryl-1,4,5,6-tetrahydropyrimidines [2] have been studied.

*Basicity.*—The experimental p$K_a$ values in Table 1 account for the behaviour of these compounds as monoprotic bases and support N-3 protonation [1,3] (Scheme 1). It is observed from the data that the



Scheme 1

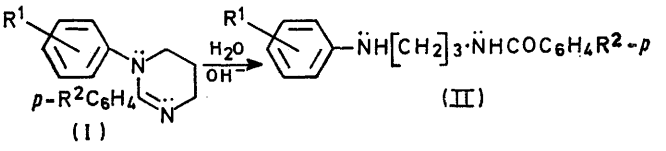
introduction of aryl groups at N-1 and C-2 in the 1,4,5,6-tetrahydropyrimidine ring (p$K_a$ 13·0),[3] reduces basicity markedly.

If 1,2-diphenyl-1,4,5,6-tetrahydropyrimidine (1) is taken as the reference, it can be seen (Table 1) that basicity is increased by electron-donating phenyl substituents at N-1 and decreased by electron-accepting substituents. This behaviour is similar to that of other cyclic [1] or acyclic amidines.[4-7] A 4-nitro-group in the benzene ring at C-2 decreases basicity by >1 p$K_a$ unit [compounds (8) and (9)].

Ionization constants in our investigation show that tetrahydropyrimidines have a basicity similar to that of acyclic amidines,[4] but the former are stronger bases (2—3 p$K_a$ units) than the homologous 1,2-diaryl-2-imidazolines.[1]

When the tetrahydropyrimidine ring is considered as a substituent of the benzene ring at N-1, the Hammett equation gives a good linear correlation. A plot of log ($K_a/K_a^0$) against $\sigma$ [8] for compounds (1)—(6) gave a straight line [$\rho$ 0·948 with standard deviation ($s$) 0·064 and correlation coefficient ($r$) 0·9941]. For the 4-nitro-group $\sigma^- = 1{\cdot}27$ was used.[8]

*Alkaline Hydrolysis.*—Kinetic studies were carried out with nine 1,2-diaryl-1,4,5,6-tetrahydropyrimidines in order to determine the influence of substituents



Scheme 2

at N-1 and C-2 upon the rates of alkaline hydrolysis (Scheme 2).

All the kinetic runs were performed in boiling alkaline 95% ethanol with a molar ratio of alkali to tetrahydropyrimidine of 350 : 1. The reactions were followed by u.v. spectrophotometry, selecting a wavelength at

Table 1

U.v. spectral data used for p$K_a$ determination of 1,2-diaryl-1,4,5,6-tetrahydropyrimidines in water at 25°

| | | | Tetrahydropyrimidine | | Tetrahydropyrimidinium ion | | | |
|---|---|---|---|---|---|---|---|---|
| Compound | *N*-Ar | *C*-Ar | $\lambda_{max.}$/nm | log $\varepsilon$ | $\lambda_{max.}$/nm | log $\varepsilon$ | p$K_a$ | $K_a$ |
| (1) | Ph | Ph | 216; 265 | 4·08; 3·89 | 203; 227 | 4·38; 4·12 | 11·67 | $2{\cdot}14 \times 10^{-12}$ |
| (2) | 4-MeO·$C_6H_4$ | Ph | 216 | 4·12 | 203; 227 | 4·43; 4·23 | 11·99 | $1{\cdot}02 \times 10^{-12}$ |
| (3) | 4-Me$C_6H_4$ | Ph | 216; 263 | 4·12; 3·90 | 203 | 4·41 | 11·87 | $1{\cdot}35 \times 10^{-12}$ |
| (4) | β-Naphthyl | Ph | 220 | 4·67 | 224 | 4·67 | 11·51 | $3{\cdot}09 \times 10^{-12}$ |
| (5) | 4-Cl$C_6H_4$ | Ph | 216; 269 | 4·19; 3·99 | 203; 230 | 4·43; 4·18 | 11·36 | $4{\cdot}36 \times 10^{-12}$ |
| (6) | 4-$NO_2C_6H_4$ | Ph | 216; 359 | 4·36; 4·11 | 203; 289 | 4·46; 4·06 | 10·51 | $3{\cdot}09 \times 10^{-11}$ |
| (7) | 2-$NO_2C_6H_4$ | Ph | 216; 258 | 4·16; 4·00 | 203; 233 | 4·35; 4·20 | 10·55 | $2{\cdot}82 \times 10^{-11}$ |
| (8) | 2-$NO_2C_6H_4$ | 4-$NO_2C_6H_4$ | 216; 258 | 4·18; 4·16 | 203; 260 | 4·39; 4·22 | 9·23 | $5{\cdot}89 \times 10^{-10}$ |
| (9) | 4-$NO_2C_6H_4$ | 4-$NO_2C_6H_4$ | 216; 359 | 4·18; 4·08 | 203; 268 | 4·36; 4·26 | 9·16 | $6{\cdot}92 \times 10^{-10}$ |

[1] B. Fernández, I. Perillo, and S. Lamdan, *J.C.S. Perkin II*, 1973, 1371.
[2] I. Perillo and S. Lamdan, *J. Heterocyclic Chem.*, 1973, **10**, 915.
[3] D. J. Brown and R. F. Evans, *J. Chem. Soc.*, 1962, 527.
[4] E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.*, 1949, **71**, 3992.
[5] D. J. Carswell, J. Zymermen, and L. E. Lyons, *J. Chem. Soc.*, 1952, 431.
[6] B. V. Passet, G. N. Kul'bitskii, N. A. Kalashnikova, and T. I. Vorobaeva, *Zhur. Org. Khim.*, 1972, **8**, 1246.
[7] J. Sevcik, *Chem. Zvesti*, 1972, **26**, 49.
[8] L. P. Hammett, 'Physical Organic Chemistry; Reaction Rates, Equilibria and Mechanisms,' McGraw-Hill, New York, 1970.

which the absorptivity of the tetrahydropyrimidine (I) and its corresponding reaction product (II) differed appreciably (0·4—0·7 absorbance units). Control experiments indicated that Beer's law was valid at the selected wavelength.

In order to establish that hydrolysis of the tetrahydropyrimidine was the only degradative pathway (Scheme 2) under the conditions employed in the runs, it was necessary to verify that (II) did not undergo subsequent hydrolysis. This was investigated by t.l.c. For compounds (1)—(7) no trace of degradation products from (II) was detected throughout the reactions. At constant pH the rates of disappearance of the tetrahydropyrimidines were found to be first-order. Plots of log (absorbance) against time were linear for at least 90% of the reaction for all the samples except for compounds (6) and (7) for which linearity held up to 60% of the reactions. Pseudo-first-order rate constants are given in Table 2.

TABLE 2

Rate constants, relative rates, and half-lives for the hydrolysis of 1-(substituted phenyl)-2-phenyl-1,4,5,6-tetrahydropyrimidines in boiling alkaline 95% ethanol

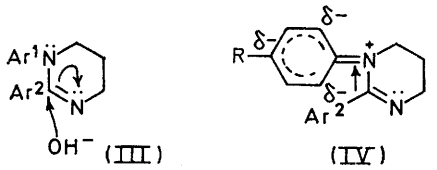
| Compound | Selected λ/nm | $10^6k$/s$^{-1}$ at 80·5 °C [a] | Rel. rate | $t_{\frac{1}{2}}$/h |
|---|---|---|---|---|
| (1) | 266 | 8·85 [b] | 1·00 | 21·7 |
| (2) | 266 | 10·63 | 1·20 | 18·1 |
| (3) | 266 | 9·97 | 1·13 | 19·3 |
| (4) | 266 | 7·89 | 0·89 | 24·4 |
| (5) | 266 | 7·43 | 0·84 | 25·9 |
| (6) | 280 | 4·53 | 0·51 | 42·5 |
| (7) | 430 | 4·57 | 0·52 | 42·2 |

[a] The degree of certainty of the rate constants obtained from duplicate experiments was ±0·09. [b] Average of four runs.

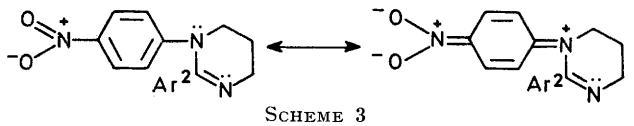
For the 2-(*p*-nitrophenyl)-derivatives [compounds (8) and (9)] earlier deviations from the first-order kinetics were observed. The decreased stability of (II), when $R^2$ = *p*-nitro, to alkaline hydrolysis [9] explains the appearance of the corresponding *N*-(*p*-nitrophenyl)trimethylenediamine before one half-life has elapsed. This fact and the formation of resinous products may account for our failure to determine rate constants for compounds (8) and (9).

From the half-life obtained for the 2-phenyl-1,4,5,6-tetrahydropyrimidine ($t_{\frac{1}{2}}$ *ca.* 7 h) * it is observed that introduction of an aryl group in N-1, independent of its nature, increases the stability of the resulting compound to the hydrolysis.

If compound (1) is again taken as a reference, relative rate (Table 2) indicate that electron-withdrawing substituents in the benzene ring at N-1 retard hydrolysis while electron-releasing groups accelerate it. These results agree with the generally accepted mechanism for this type of reaction in which initial attack (III) on C-2 is performed by hydroxide ion.[10] The electron-deficient N-1 that results from the contribution of mesomeric structures (IV),[1] decreases the possibility of activation of the C=N bond. This effect will be more important in the case of those substituents which have

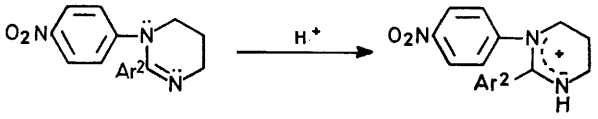



$-I$ and $-M$ effects (Scheme 3). In fact, the 2- and 4-nitro-derivatives (6) and (7) are the most stable compounds.




SCHEME 3

Contributions by mesomeric structures in Scheme 3 manifest themselves in compounds (6) and (9) (see Table 1), the u.v. absorption at 359 nm undergoing a hypsochromic effect on protonation (Scheme 4).




SCHEME 4

A quantitative evaluation of the influence of substituents upon the reaction rates of hydrolysis was made through the Hammett approach. A plot of the rates for compounds (1)—(6) against Hammett σ-constants gave good correlation with ρ −0·238 ($r$ 0·9938, $s$ = 0·019). The small value of the slope indicates that the phenyl substituents at N-1 have but low influence. The Hammett equation allowed us to obtain ' calculated ' rate constants ($k'$) which are presented in Table 3. Though $k'_{calc}$ values are close to $k_{obs}$ values, better agreement is obtained ($k''_{calc}$) when new effective substituent constants, denoted by $\sigma_{py}$ (Table 3), are used in the Hammett equation. These $\sigma_{py}$ values were calculated from the ionization of tetrahydropyrimidine hydrochlorides using the corresponding equation $\sigma_{py} = (pK_a^0 - pK_a)/0{\cdot}948$. Accordingly, a

TABLE 3

Observed and calculated rate constants for 1-(substituted phenyl)-2-phenyl-1,4,5,6-tetrahydropyrimidines

| Compound | σ [a] | $\sigma_{py}$ | $10^6k$/s$^{-1}$ (obs.) | $10^6k'$/s$^{-1}$ (calc.) | $10^6k''$/s$^{-1}$ (calc.) |
|---|---|---|---|---|---|
| (1) | 0·00 | 0·00 | 8·85 | | |
| (2) | −0·268 | −0·337 | 10·63 | 10·24 | 10·64 |
| (3) | −0·17 | −0·211 | 9·97 | 9·71 | 9·93 |
| (4) | 0·17 | 0·169 | 7·89 | 8·06 | 8·07 |
| (5) | 0·227 | 0·327 | 7·43 | 7·81 | 7·40 |
| (6) | 1·27 | 1·223 | 4·53 | 4·41 | 4·53 |

[a] Hammet substituent constants.[8]

* Titration with standard base indicates a purity of *ca.* 93%. The sample used here must be considered impure and the results only of qualitative significance.

[9] C. K. Ingold, ' Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, 1953.

[10] B. G. Harnsberger and J. L. Riebsomer, *J. Heterocyclic Chem.*, 1964, **1**, 188.

plot of the log $k/k_0$ against $\sigma_{py}$ for compounds (1)—(6) gave $\rho$ −0·237 ($r$ 0·9995, $s$ 0·005).

The fact that $k_{obs}$ and $k''_{calc}$ values are nearly equal makes evident the close linear relationship between rate and ionization constants given by the expression $\log k = 0{\cdot}25pK_a - 7{\cdot}97$.

According to our results, substituents in the benzene ring at N-1 influence the electronic density at N-1 by inductive and mesomeric effects. These changes inductively alter the electronic density at the site of nucleophillic attack (C-2), an effect which is quantitatively reflected in the tetrahydropyrimidinium ionization constants.

## EXPERIMENTAL

*Preparations.*—Analytical samples of 1,2-diaryl-1,4,5,6-tetrahydropyrimidines, prepared by cyclization of *N*-aryl-*N'*-aroyltrimethylenediamines with polyphosphoric acid ethyl ester,[2] were used. M.p.s were in accord with those reported.[2] 2-*Phenyl*-1-(p-*tolyl*)-1,4,5,6-*tetrahydropyrimidine* was obtained as an oil which solidified on standing, m.p. 84° (Found: C, 81·5; H, 7·4; N, 11·1. $C_{17}H_{18}N_2$ requires C, 81·6; H, 7·2; N, 11·2%). 2-Phenyl-1,4,5,6-tetrahydropyrimidine was synthesized by Aspinall's method.[11] Analytical samples of *N*-aryl-*N'*-aroyltrimethylenediamines [2] and benzoyltrimethylenediamine [12] were used for determining the absorbance at infinity in the kinetic studies.

$pK_a$ *Determinations.*—From the equilibrium $PH^+ \rightleftharpoons P + H^+$ for the tetrahydropyrimidine P and its conjugate acid $PH^+$ it follows $pK_a' = pH + \log [PH^+]/[P]$. The ionization ratios $[PH^+] : [P]$ were obtained from the corresponding extinction coefficients.

In every case calculations were made from five selections of pH values with two independently determined sets of data. Good isosbestic points were observed and three wavelengths were considered for calculations in each case. Corrections were made for ionic strength.

18 Values of $pK_a$ were thus obtained that usually agreed to within ±0·06 $pK$ units. U.v. spectral data used for the $pK_a$ determinations are presented in Table 1.

The procedure was the following: measured volumes of an aqueous solution of the salt of a pyrimidine were diluted accurately to known final concentrations of $10^{-5}$—$10^{-4}$M by means of a series of five buffers. The pH of each buffer solution was measured at 25° in a Beckman Zeromatic II pH meter using a standardized glass electrode. The ionic strength of each series of final solutions varied between 0·1 and 0·3. The entire spectra of the solutions were run between 190 and 390 nm using a Perkin-Elmer 202 u.v.–visible spectrophotometer. Extinction coefficients were obtained with a Beckman DB-G grating spectrophotometer. The corresponding buffer solutions were used as blanks. Solutions were thermostatted at 25 ± 0·1°.

*Kinetic Measurements.*—Ethanol was redistilled, b.p. 78·5°, and distilled water added to 95% (v/v). The stock hydrolytic solvent was 0·07M-sodium hydroxide in 95% ethanol. More concentrated solutions of alkali were not used because precipitation occurred in the reaction flask on heating and opalescent solutions were obtained after neutralization.

The ' apparent ' pH values of all the reaction mixtures were measured before and after each run and were constant. This value was always above the pH value given by the end-point in the neutralization of the tetrahydropyrimidine hydrochlorides with 0·1N-NaOH in 95% ethanol.

All ' apparent ' pH values, entire spectra, and absorbances of the acid solutions at 20° were determined with the same apparatus used for the $pK_a$ determinations.

*General Kinetic Procedure.*—$2 \times 10^{-4}$M Solutions of the tetrahydropyrimidines were prepared in the basic hydrolytic solvent. This solution was refluxed (80·5°) in a three-necked flask fitted with a condenser, a thermometer, and a port for the insertion of a pipette. No evaporation loss occurred. At known intervals the contents of the flask were suddenly cooled to 20° and samples (10 ml) were transferred to a volumetric flask (50 ml) containing concentrated hydrochloric acid (0·2 ml). The acidified solution was made up to 50 ml with 95% ethanol at 20°, and the absorbance at time zero was estimated by extrapolation. The same procedure was followed with the solvent without tetrahydropyrimidine to prepare the blank solution.

The long times required for the hydrolysis of all the compounds under our conditions allow errors due to the reaction mixture being at temperatures different from 80·5° to be neglected.

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[12] H. Mikolajewska, S. Grudzinski, and A. Kotelko, *Acta Polonica Pharm.*, 1965, **22**, 401.