# 1*H*-4,5,6,7-Tetrahydro-1,3-diazepines. Part II: Basicity and Hydrolysis of 1,2-Diaryl Derivatives



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Basicity and alkaline hydrolysis of 1,2-diaryl-1*H*-4,5,6,7-tetrahydro-1,3-diazepines **1** are studied. Results are analyzed on the basis of Hammett and Swain-Lupton constants, finding good structure-basicity correlation when both, inductive and mesomeric effects, are considered together. Regioselectivity is observed in the alkaline hydrolysis of compounds **1**, and it is analyzed in light of the stereoelectronic control theory. Results are compared with those previously obtained for five and six membered ring homologues: 1*H*-4,5-dihydroimidazoles and 1,4,5,6-tetrahydropyirimidines respectively.

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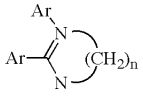
## Introduction.

1,2-Diaryl-4,5,6,7-tetrahydro-1*H*-1,3-diazepines **1** had not been extensively studied. The only investigation related to such compounds was reported by Perillo *et al.* [1] who described the synthesis of a series of 1,2-diaryl-4,5,6,7-tetrahydro-1*H*-1,3-diazepines having a nitrophenyl substituent on N1, and studied their basic character and alkaline hydrolysis.




| Compound | n |
|---|---|
| **1** | 4 |
| **2** | 3 |
| **3** | 2 |

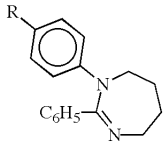
Recently, the synthesis of a series of 1-aryl-2-phenyl-4,5,6,7-tetrahydro-1*H*-1,3-diazepines **1a-d** (Table I), where the N1-substituent is a phenyl or a substituted phenyl group having releasing or weakly withdrawing substituents has been published [2], as well as their reduction and nucleophilic character.

In order to enlarge the knowledge about this type of nitrogen heterocycles, we explore in this work other properties of compounds **1a-d** such as basicity and stability under alkaline and acid conditions. Kinetic studies of alkaline hydrolysis were carried out, and the regioselectivity observed in these reactions was discussed. Results were compared with their six and five-membered homologues: 1,2-diaryl-1,4,5,6-tetrahydropyrimidines **2** and 1,2-diaryl-1*H*-4,5-dihydroimidazoles **3** respectively. These properties were also compared with those of compound **1e**, synthesized and studied by Perillo *et al.* [1].

The amidine system of compounds **1**, which lacks hydrogen on the amine nitrogen (N1), is an adequate model to observe the influence of an aryl substituent on that nitrogen. Such an amidine system is not widely described in the literature for acyclic compounds, due to the tautomeric equilibria which, when it is possible, favors the structure having the aryl group on the imine nitrogen [3,4].

Table I

1,2-Diaryl-4,5,6,7-tetrahydro-1*H*-1,3-diazepines **1**




| Compound | R |
|---|---|
| **1a** | H |
| **1b** | $CH_3$ |
| **1c** | $OCH_3$ |
| **1d** | Cl |
| **1e** [a] | $NO_2$ |

[a] Compound described by Perillo *et al.* [1].

## Results and Discussion.

### Basicity.

1*H*-4,5,6,7-Tetrahydro-1,3-diazepines **1a-d** are monobases which, upon protonation at N3, lead to a cyclic amidinium ion (**1H**$^+$) strongly stabilized by mesomeric effects (Table II).

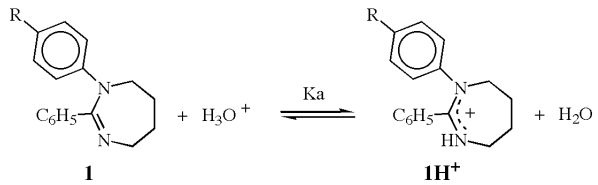
Attempts to determine *p*Ka values of compounds **1a-d** by spectrophotometry failed, due to the lack of good isosbestic points in their UV spectra. Instead, the potentiometric method was suitable for determining the basicity of compounds **1a-d**. Corrected *p*Ka values are presented in Table II. Good agreement was observed between graphical and analytically calculated values.

Compounds **1** showed a stronger basicity than the corresponding arylamines (Table II), as it was previously observed for 1*H*-4,5-dihydroimidazoles **3** [5] and 1,4,5,6-tetrahydropyrimidines **2** [6]. These results confirmed protonation at N3 to give the resonance stabilized amidinium cation (**1H**$^+$), since if N1-protonation occurred, basicity should be similar or lower than that of the corresponding arylamines.

Electron releasing groups on N1 aryl increase basicity of compounds **1**, by favouring N1 lone pair delocalization on

Table II

Basicity Constants for Compounds **1a-e**, the Homologues **2a-e** and **3a-e**, and the Corresponding Arylamines, and Hammett and Swain-Lupton Parameters [a]




**1** **1H+**

| Compound | R=H | R=$CH_3$ | R=$OCH_3$ | R=Cl | R=$NO_2$ |
|---|---|---|---|---|---|
| Ka (corr) | $2.57x10^{-10}$ | $2.09x10^{-10}$ | $8.32x10^{-11}$ | $2.63x10^{-9}$ | $3.71x10^{-9}$ |
| **1a-d** | (**1a**) | (**1b**) | (**1c**) | (**1d**) | (**1e**) [b] |
| *p*Ka (corr) | 9.59 | 9.68 | 10.08 | 8.58 | 8.43 |
| **1a-d** | (**1a**) | (**1b**) | (**1c**) | (**1d**) | (**1e**) [b] |
| $\sigma_p$ | 0.00 | -0.17 | -0.27 | 0.230 | 0.78 |
| $\mathcal{F}$ | 0.03 | 0.01 | 0.29 | 0.42 | 0.65 |
| $\mathcal{R}$ | 0.00 | -0.18 | -0.56 | -0.19 | 0.13 |
| *p*Ka **2a-d** [c] [d] | 11.67 | 11.87 | 11.99 | 11.36 | 10.51 |
| *p*Ka **3a-d**] [c] [e] | 9.26 | 9.48 | 9.64 | 8.98 | 7.65 |
| *p*Ka *p*-$RC_6H_4NH_2$ | 4.61 | 5.08 | 5.33 | 4.00 | 0.98 |

[a] Values extracted from Taft *et al.* [10]. [b] Reported by Perillo *et al.* [1]. [c] Ar = *p*-$RC_6H_4$, Ar´=$C_6H_5$. [d] Data reported by Lamdan *et al.* [6]. [e] Data reported by Lamdan *et al.* [5].

the amidine system (structure **B**, Figure 1), while electron withdrawing groups decrease it by delocalization on the aryl group (structure **A**). This behaviour was observed for other cyclic [5,6] and acyclic [7] amidines.

In order to quantify these effects, the Hammett relationship [8] (Equation 1) was applied [9],

$$\log K_a/K_0 = \rho.\sigma \quad (1)$$

rendering a slope value $\rho$=1.50 (r=0.9898, s=0.63). This is consistent with the action of both inductive and mesomeric effects exerted by the R group of the 1-aryl substituent upon the reaction site (N3) [11]. Instead, if both electronic effects are considered separately by means of the Swain and Lupton [12] equation (2),

$$\log K_a/K_0 = \rho.\mathcal{F} + \rho.\mathcal{R} \quad (2)$$

and plots of log Ka *vs.* the field inductive factor $\mathcal{F}$ or *vs.* the mesomeric factor $\mathcal{R}$ are performed independently, bad correlation coefficients r are obtained (r=0.7542 and 0.6125 respectively).

*p*Ka values of compounds **1** fall between those of analogous dihydroimidazoles **3** and tetrahydropyrimidines **2** (Table II), being the decreasing order in basicity **2** > **1** > **3**. A similar behavior for the homologous series having nitrophenyl substituents [1], was rationalized by the authors considering the planarity of the N-C=N system in five, six and seven-membered amidines, which is necessary for the delocalization of the positive charge of the resulting amidinium ion. However, the most basic homologue should be that which gains the highest resonance energy, so stability of both, the amidine and the cyclic amidinium ion, should be taken into account.

Acid Hydrolysis.

When compounds **1a-d** were treated with sulphuric acid solutions in concentrations between 0.25 *M* and 3.80 *M* at 120 °C, no hydrolytic reaction was observed. After heating for thirteen days, tetrahydrodiazepines **1** were recovered unchanged.

Considering that, at the employed acid concentrations, compounds **1** exist as their protonated form, the observed resistance to acid hydrolysis may be attributed to the high stability of the resulting tetrahydrodiazepinium cations **1H+**. The lack of reactivity of tetrahydrodiazepines **1** in acid media turned out to be more pronounced than that previously observed for the analogous dihydroimidazoles, which are stable in slightly acid solutions but undergo hydrolysis in strong acid solutions [13].

Alkaline Hydrolysis.

The alkaline hydrolysis of compounds **1a-d** leads exclusively to *N*-aryl-*N'*-benzoyltetramethylenediamines **4a-d** (Figure 2). Plots of absorbance at 272-277 nm *vs.* time for [$HO^-$]=1 *M*, resulted in the curves shown in Figure 3. Pseudo first-order reactions were observed in every case.

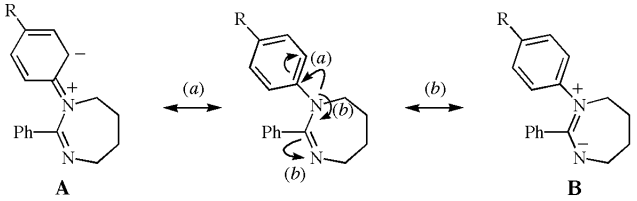
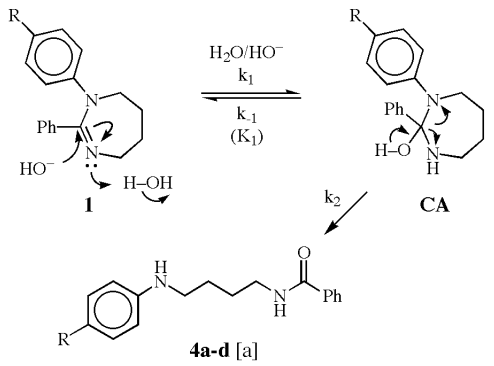



Figure 1

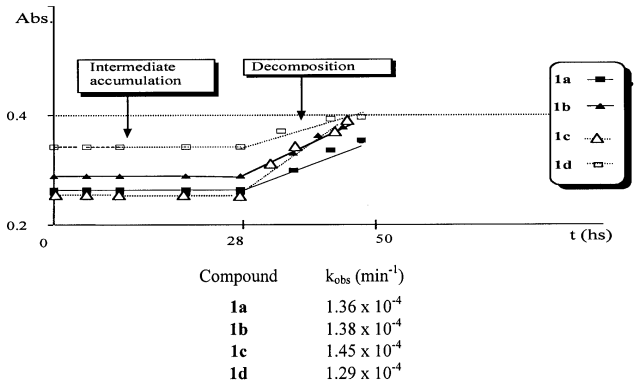
As seen in the figure, absorbance remains almost constant at a minimum value for each compound, until it begins to increase, revealing the appearance of compounds **4**. Such interval where absorbance remains constant diminishes on increasing [$HO^-$], as shown in Figure 4 for compound **1a**.

Our experimental results are consistent with a fast formation and accumulation of a cyclic carbinolamine (**CA**, Figure 2), showing that times of accumulation decrease on increasing the alkali concentration. This tetrahedral intermediate then decomposes ($k_2$, Figure 2) during the slow step of the reaction. The appearance of this type of tetrahedral intermediates in the course of hydrolysis of cyclic amidines and amidinium salts had been previously demonstrated in some cases [14-19]. Their formation arises from nucleophilic attack on C2, and probably requires a simultaneous proton transfer to a nitrogen atom (N3 in compounds **1**).




[a] Letters correspond to those employed for compounds **1**.

Figure 2




| Compound | $k_{obs}$ ($min^{-1}$) |
|---|---|
| **1a** | $1.36 \times 10^{-4}$ |
| **1b** | $1.38 \times 10^{-4}$ |
| **1c** | $1.45 \times 10^{-4}$ |
| **1d** | $1.29 \times 10^{-4}$ |

Figure 3

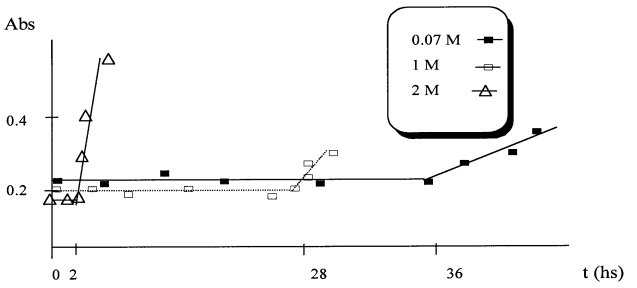



Figure 4

The plot of log $k_{obs}$ *vs.* Hammett $\sigma$ values, showed that the influence of the R substituent upon reaction rate is negligible ($\rho$=-0.08). These results differ from those previously obtained for homologues **2** and **3**, and also from those reported for other related reactions, such as hydrolysis of esters and amides [20].

Besides, when the Swain and Lupton equation (2) was applied, plots of log $k_{obs}$ *vs.* the inductive field parameter $\mathcal{F}$ and *vs.* the resonance parameter $\mathcal{R}$ individually, showed a poor linear correlation (r=0.7713 and 0.6342 respectively).

However, the *p*-nitrophenyl derivative **1e**, empirically shows an excessive decrease in hydrolysis rate [1]. This atypical behaviour of nitrophenyl derivatives was also previously observed for homologous imidazolines [18], and justified by the authors by means of a change in reaction mechanism. Taking into account those observations, it can be inferred that, when electron releasing or moderate withdrawing substituents are present on N1-aryl groups (R=4-$CH_3O$, 4-$CH_3$, 4-Cl), these electronic effects are not transmitted to N3, and the rate limiting step is the decomposition of the carbinolamine at [$HO^-$]≥0.5 *M*. However, when the substituent is a strong electron withdrawing group (4-$NO_2$) it will necessarily affect the electron density at N3, so a proton transfer to the latter to form the intermediate **CA** is difficult, and the first step of the reaction is delayed (Figure 2). Consequently, a change in the hydrolysis mechanism may occur, where formation of the tetrahedral intermediate **CA** is the rate determining step of the reaction.

Finally, when the hydrolytic behaviour of *1H*-4,5,6,7-tetrahydro-1,3-diazepines **1** is compared with that observed for the inferior homologues 1,4,5,6-tetrahydropyrimidines **2** [6] and *1H*-4,5-dihydroimidazoles **3** [18], no relevant differences among the three series of compounds are observed, being all rate constants in the order of $10^{-4}$ $min^{-1}$, although reaction rates follow the order: **2** > **3** > **1**.

Finally, as it arises from our results, the effect of N1-substituents on the rate of hydrolysis of compounds **1** is negligible in relation to the effect of those substituents on basicity, differing from what has been previously observed for the inferior homologues **2** and **3**.

## Regioselectivity in Hydrolysis of Tetrahydrodiazepines **1**.

Unsymmetric substitution of compounds **1** may lead to the formation of two different compounds in the hydrolysis reaction (Figure 5): compound **4**, arising from cleavage of the N1-C2 bond, and **5** from cleavage of the C2-N3 bond. The regioselective N1-C2 cleavage observed in hydrolysis of tetrahydrodiazepines **1a-d** may be analyzed in terms of relative basicities of N1 and N3. Expulsion of nitrogen in the hydrolysis of amidines *via* tetrahedral intermediates almost always requires a proton transfer, so that the leaving group is the free amine rather than the amide ion [21-25]. If the transition state leading to tetrahedral intermediate decomposition resembles the carbinolamine **CA** rather than the product [25], the difference between basicities of the two nitrogens in the intermediate will govern the cleavage. Then, N3 (secondary aliphatic amine) would be more basic than N1 (tertiary aromatic amine), and proton transfer should occur to N3, with cleavage of the C2-N3 bond leading to kinetic product **5**. On the other hand, if basicities of the two nitrogens in both isomers govern product distribution with expulsion of the most basic amine (as it was concluded by Perrin *et al.* [25]), products **5** (more basic than **4**) should also be achieved. Results obtained for other unsymmetrical amidines have indicated in general, that cleavage of the tetrahedral intermediate **CA** proceeds with initial formation of transient kinetic products, *i.e.* preferential expulsion of the most basic amine,

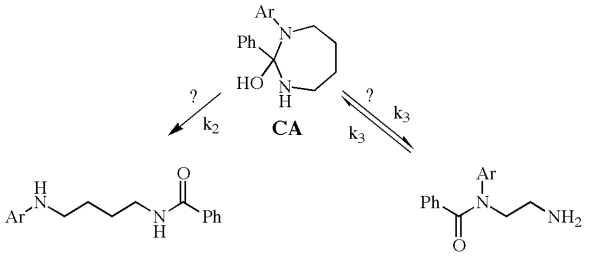



Figure 5

and further isomerization to the thermodynamically favoured one through the same intermediate carbinolamine [19,24,26,27]. However, attempts to detect a kinetic product in the hydrolysis of compounds **1a-d** proved to be unsuccessful. This fact may be interpreted in two ways: *(i)* Hydrolysis of **1** proceeds directly to the thermodynamic isomer **4** through regioselective cleavage of the C2-N3 bond, being an example of a product-development controlled reaction, such as it was postulated for the cleavage of cyclic hemiorthoesters [27]. *(ii)* A rapid isomerization of kinetic product **5** to the thermodynamically favoured **4** through an intramolecular aminolysis reaction, avoids its detection.

The last hypothesis results are of low reliability, because such rearrangements proved to be slow in alkaline medium for analogous compounds (*N*-aryl-*N*-benzoyl-*N'*-methylethylene and trimethylenediamines [28]) and the rates of the reaction diminish on increasing the polymethylene chain length. Moreover, Burdick *et al.* [24] found that cyclization of kinetic products to form intermediate carbinolamine in hydrolysis of unsymmetrical amidines, disfavours formation of the seven membered cyclic intermediate *vs.* six membered carbinolamine by a factor of $10^2$. This allows us to consider that rearrangement rates of *N*-aryl-*N*-benzoyltetramethylenediamines would be lower. Since the kinetic product **5** was not detected it is very improbable that it is formed.

The observed regioselectivity could also be explained in light of Deslonghamps´ stereoelectronic control theory, which proved to be important in directing the decomposition of tetrahedral intermediates [29,30]. Bearing this principle in mind, cleavage of carbinolamine **CA** should occur when there are two lone pairs antiperiplanar to the breaking bond. Thus, as a result of microscopic reversibility, initial hydroxide attack on tetrahydrodiazepines **1** should lead to conformer **A** (Figure 6) with $\Delta H_f$=30.88 Kcal/mol calculated by the AM1 semiempirical method. Two processes are possible for this initial conformer: nitrogen inversion and ring reversal. Nitrogen inversion of N3, N1 or both, would lead to conformations **B** ($\Delta H_f$=28.21 Kcal/mol), **C** ($\Delta H_f$=33.78 Kcal/mol) and **D** ($\Delta H_f$=30.95 Kcal/mol) respectively. In conformer **B**, N1-C2 cleavage is assisted by oxygen and the N3 lone pairs, leading to the thermodynamic isomer **4**. In **C**, instead, C2-N3 cleavage would be assisted by two antiperiplanar lone pairs leading to **5**, and in conformer **D** both cleavages are equally assisted and both isomers **4** and **5** should be obtained, which is not observed experimentally.

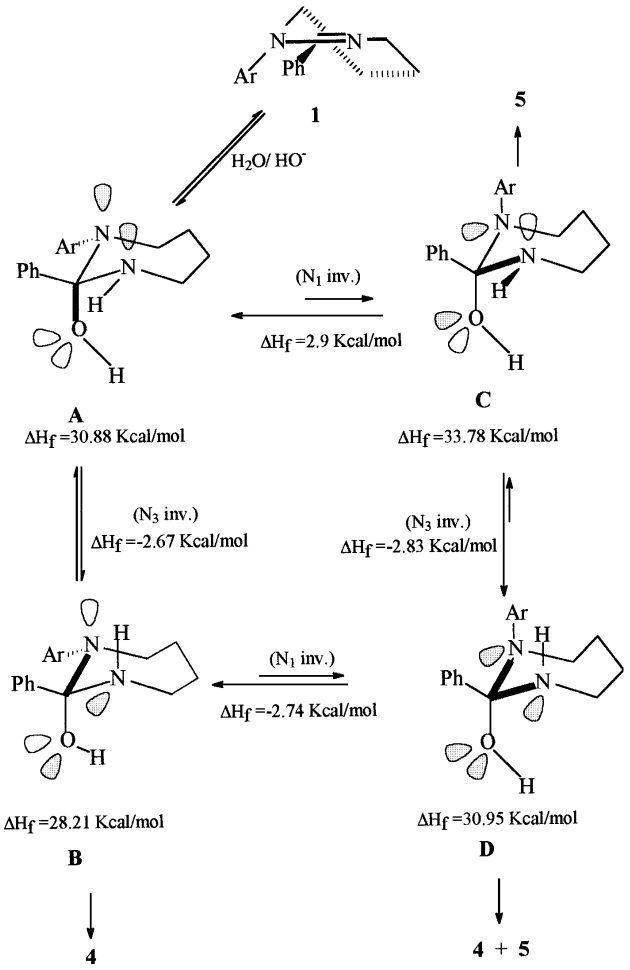



Figure 6

On the other hand, ring reversal of **A** would lead to conformer **E** ($\Delta H_f$=33.10 Kcal/mol) (Figure 7) where both cleavages are assisted and a mixture of both isomers should be obtained. Nitrogen inversions of **E** or ring reversal of **B** or **C** would lead to conformers **F** ($\Delta H_f$=31.25 Kcal/mol) and **G** ($\Delta H_f$=31.72 Kcal/mol) respectively. Nitrogen inversions of **F** or **G** would lead to conformer **H** ($\Delta H_f$=32.94 Kcal/mol). In **H** no cleavage is assisted by stereoelectronic control, while **F** should give rise to isomer **5** and **G** to **4**.

The above analysis indicates that an energy criterion would favour conformer **B** by almost 3-5 Kcal/mol over the others. Then, as an additional requirement for the application of the stereoelectronic control theory, N3 inversion should be faster than decomposition of the tetrahedral intermediate **CA**. The presence of an exchangeable hydrogen atom on N3 would favour this process by catalyzed deprotonation-reprotonation mechanisms [32].

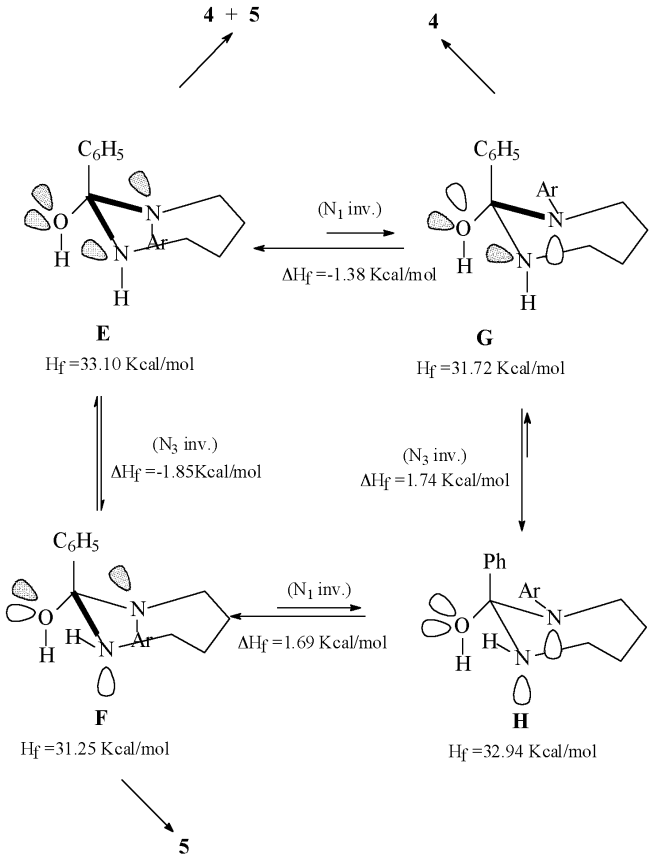



Figure 7

Thus, transformation of initial conformation **A** of the intermediate carbinolamine to a more stable conformation **B** through a rapid N3 inversion, where C2-N1 cleavage is assisted by stereoelectronic control, would be a plausible explanation for the observed regioselectivity in alkaline hydrolysis of tetrahydrodiazepines **1**.

## EXPERIMENTAL

Compounds **1a-d** were synthesized following the procedure described by Perillo *et al.* [2]. Tlc experiments were performed on Silica Gel F254 aluminium plates. Values of absorbance were read in a JASCO 7850 Uv/Vis spectrophotometer. *p*H values were measured with a Metrohm E632 *p*Hmeter.

### Basicity.

### Uv Spectrophotometric Method.

Solutions $10^{-5}$ *M* of compounds **1** were prepared in buffers of *p*H 2, 7, 8, 10, 12 and 13. Absorbance was read at 200-400 nm.

### Potentiometric Method.

Aqueous solutions of **1** were prepared weighing 0.1032 g **1a**, 0.1080 g **1b**, 0.1030 g **1c** and 0.0980 g **1d**, and dissolving in 20 mL of distilled water. These solutions were titrated with hydrochloric acid 0.0495 *N* at 20 °C.

### Acid Hydrolysis.

Solutions $10^{-3}$ *M* of compounds **1a-d** in sulfuric acid solutions 0.25 *M*, 0.95 *M*, 1.65 *M*, 2.35 *M*, 3.05 *M* and 3.80 *M* were prepared. Solutions were heated under reflux at 120 °C.

Kinetics were followed by UV spectrophotometry at 272-277 nm. "Apparent" *p*H values of the solutions were determined before and afterwards the kinetic experiment, remaining constant.

### Kinetic Procedure.

At known intervals, samples (1.25 mL) were cooled at 25 °C, transferred to a volumetric flask (25 mL) and made up to volume with distilled water to give final solutions 5 x $10^{-3}$ *M*. The same procedure was followed with the hydrolytic solvent without the tetrahydrodiazepine, to prepare the blank solution. Absorbance of each solution was read at a different wavelength between 272 and 277 nm, looking for that $\lambda_{max}$ at which only the product absorbed. Spectra remained unchanged up to thirteen days.

### Chromatographic Experiments.

Simultaneously with uv kinetic procedures, reactions were followed by tlc. An aliquote of 0.5 mL (taken at the same time as those for uv kinetic procedures) were cooled at 25 °C. Solutions were made alkaline with sodium carbonate and extracted with methylene chloride. Organic layers were washed with water, dried with anhydrous sodium sulfate, filtered and evaporated. The residue was taken up with methylene chloride, and tlc experiments performed employing benzene/methanol 9:1 as eluent.

### Alkaline Hydrolysis.

Sodium hydroxide solutions in 95% (v/v) ethanol 0.07, 1 and 2 *M* were prepared. Final concentrations 2 x $10^{-4}$ *M* in the basic hydrolytic solvents were attained. Solutions were heated at a constant temperature of 100 °C. Kinetics were followed by uv spectrophotometry at 272-277 nm. "Apparent" *p*H values of the solutions were determined before and after the kinetic experiment, remained constant.

### Kinetic Procedure.

At known intervals samples (10 mL) were cooled at 25 °C and diluted with ethanol 95% to 50 mL. Absorbances at t=∞ were spectrophotometrically achieved after several half-lives, and absorbance at time zero was estimated by extrapolation. The same procedure was followed with the hydrolytic solvent in the absence of tetrahydrodiazepine, to prepare the blank solution. Tlc experiments of the reaction mixture performed at different times, showed exclusively those spots corresponding to diazepines **1** and products **4**.

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