AM1 Study of a β-Carboline Set. Part III: Substituent Effects†

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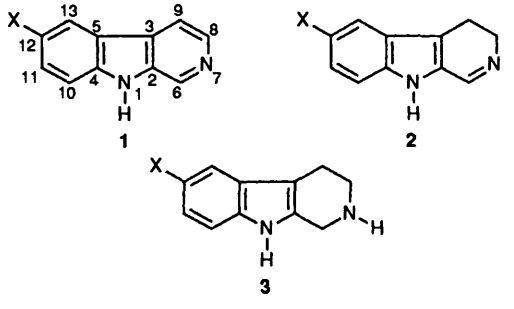
Substituent effects on the protonation and deprotonation processes of the β-carboline ring possessing different degrees of aromaticity have been studied from both an experimental and a theoretical point of view. NO_2, Cl, MeO and NH_2 groups have been selected. N-7 protonation and N-1 deprotonation enthalpies have been calculated theoretically using the AM1 semiempirical method. Some of the methoxy and nitro derivatives have been synthesized and their acidity constants for the processes mentioned earlier have been determined in aqueous media. From the p*K* values and the theoretical gas-phase free energy, ΔG°_{gp}, the solvation contribution has been calculated. Substituent effects on the β-carboline system are quite independent of the aromaticity of the ring and the general trends observed in other aromatic systems (such as benzoic acids and phenoxides) for each particular substituent are also found in the β-carboline rings. Some experimental facts on the reactivity of these molecules are discussed in connection with the reactivity indices arising from the wavefunctions.

For several years we have been interested in the analysis of the physicochemical properties and reactivity[1–4] of a set of β-carboline rings, [9*H*-pyrido(3,4-*b*)indole] and some of its derivatives, which are of biological and pharmacological interest.[5,6]

Theoretical studies have proved to be a useful tool in the description of the structural properties of some model β-carbolines.[7–10] Recently, and in connection with our investigation, we have carried out theoretical studies on this subject.[11,12] These studies have been mainly focused on the analysis of structural properties and the potential reactivity of some neutral, protonated and deprotonated derivatives. Thus, in the previous papers, the influence of the aromaticity of the ring and of the nitrogen methylation was analysed, AM1 being able in all cases to rationalize the properties of these molecules. However, as is well known, many of the β-carboline derivatives with biochemical interest possess a substituent group on the benzenic ring.[13] Moreover, the nature and position of this substituent can change the biochemical properties of these molecules.[14]



X = H, NO_2, MeO, Cl, NH_2

Scheme 1

For this reason, in the present paper we report a theoretical and experimental study on the influence of the nature of benzenic ring substituents on the structural properties and potential reactivity of neutral, protonated and deprotonated molecules. Four representative groups were selected for this study: NH_2, Cl, NO_2 and MeO. The molecules studied are shown in Scheme 1, which also gives the numbering system employed in the previous papers.[11,12] Because C-12 of the β-carboline ring should be one of the most effective substitution positions, studies have been focused on the aromatic, dehydro and tetrahydro derivatives with the four substituents in this position.

The N-1 deprotonation enthalpies and the N-7 proton affinities of the substituted derivatives have been calculated. Likewise, experimental data on the acid and base properties of some molecules in solution have been obtained. The combination of theoretical and experimental data allowed the separation of observed values into contributions due to the intrinsic acid and base properties and to the solvation phenomena.

Unfortunately, the low experimental yield for the synthesis of some derivatives (Cl and NH_2 aromatic and dehydro compounds) precluded the study of their acid or base properties in solution. However, a comparative analysis between the data obtained in this work and similar data reported for the deprotonation of substituted benzoic acids has allowed the estimation of their acid properties in aqueous media.

Finally, reactivity indices obtained from AM1 wavefunctions have been used to test the degree of confidence supplied by them in predicting the most reactive position for electrophilic substitution in solution.

Computational Method.—Semiempirical calculations at the AM1[15] level have been carried out. The geometries of the fully aromatic rings were optimized assuming C_s symmetry. AM1 geometries of **1** and the 6-methylated derivative of **1** give average errors similar to those obtained by STO-3G calculations.[9,10] In the case of compounds **2** and **3** the dihedral angles of the pyridinic ring were optimized. For the substituted derivatives of **2**, the ring remained almost planar. In contrast, the N-7 and C-8 atoms of compound **3** were twisted out of the molecular plane by *ca.* 15° and 25°, respectively, upon substitution.

Experimental

Chemicals and Solutions.—6-Methyl-β-carboline (harmane), 11-methoxy-6-methyl-β-carboline (harmine) and 11-methoxy-

† Part II is ref. 12.

Table 1 AM1 gas phase deprotonation enthalpies, ΔH°_{acid}/kJ mol^{-1} for some β-carboline derivatives

	1		2		3	
Substituent	ΔH°_{acid}	$\delta\Delta H^\circ_{acid}$[a]	ΔH°_{acid}	$\delta\Delta H^\circ_{acid}$	ΔH°_{acid}	$\delta\Delta H^\circ_{acid}$
H	1408.0	0.0	1413.6	0.0	1431.2	0.0
12-NH_2	1422.0	14.0	1425.2	11.6	1442.3	11.1
12-MeO	1404.1	−3.9	1407.9	−5.7	1425.0	−6.2
12-Cl	1388.1	−19.9	1392.7	−20.9	1409.6	−21.6
12-NO_2	1338.3	−69.7	1346.0	−67.6	1361.7	−69.5

[a] $\delta\Delta H^\circ_{acid} = \Delta H^\circ_{acid}$(substituted) − ΔH°_{acid}(unsubstituted).

6-methyldehydro-β-carboline (harmaline)* were commercial products of the best available quality (≥98% Aldrich Quimica) and were used as received. All the other β-carbolines were prepared from literature methods. The 11-methoxy, 12-methoxy and 12-chloro derivatives of 1-methyltetrahydro-β-carboline were obtained by cyclization of their corresponding tryptamines with pyruvic acid followed by further decarboxylation.[16] Derivatives of 6-methyldehydro-β-carbolines were obtained by oxidation of their tetrahydro derivatives with $KMnO_4$ in THF.[17] The 12-nitro-substituted derivarives of 6-methyl-β-carboline and 6-methyltetrahydro-β-carboline were prepared by nitration in acid media of the parent compounds[18] and of 12-amino-6-methyltetrahydro-β-carboline by reduction with Zn/acetic acid of the corresponding nitro derivative.[19]

Stock solutions of the various β-carbolines were prepared in methanol and stored in the dark to avoid photodecomposition. Final solutions obtained by dilution of the stocks did not contain more than 5% (v/v) methanol. Buffer solutions (0.010 mol dm^{-3}) for UV–VIS spectrophotometry were prepared as described in the literature[20] and pH values were measured on a Radiometer pH Model PHM82. All reagents used for buffer preparations were high purity chemicals employed as received. Sulphuric acid solutions were prepared by dilution with distilled water of Merck sulphuric acid R.A. (96% w/w) and KOH solutions from Merck R.A. potassium hydroxide as described by Yagil.[21]

pK_a *Determinations.*—The ionization ratios, I = [acid]/[base], necessary for determining the pK_a values, were obtained spectrophotometrically as in previous work.[1,2] Absorbance measurements were carried out on a Perkin-Elmer Lambda 5 with a thermostatted cell holder maintained at 25 ± 0.1 °C. Ionization constants in the pH range were determined from the Hendersson–Hasselbach equation. Outside this pH range pK_a values were obtained using eqn. (1) derived from the excess

$$pK_w + \log C_{OH^-} - \log a_w + \log I = m^*x + pK_a \quad (1)$$

acidity method[22,23] for deprotonation equilibria, where the water activity, a_w, and x functions were calculated as elsewhere.[3,24] The excess acidity method has proved to be very useful for the determination of pK_a values in non-ideal media, which are referred to infinite dilution as the standard state. A second parameter, m^*, which is related with the solvation requirements of the acid base conjugated pair, is also obtained.[25]

Results and Discussion

Deprotonation Process.—The theoretical deprotonation enthalpies for the N-1 deprotonation process in the gas phase are presented in Table 1 for the different compounds. The ΔH°_{acid} sequence obtained: aromatic > dehydro > tetrahydro does not change upon substitution on the benzenic ring. However, for a given degree of aromaticity the substituent induces different changes in the acidity. The NH_2 group decreases slightly the acidity of the pyrrolic nitrogen whereas the opposite effect is observed for the other substituents, the sequence being MeO < Cl < NO_2.

The electronic redistribution induced by the different groups in the β-carboline ring has been examined by means of the Mulliken population analysis of the wavefunctions. The total charge on the substituent group and on the deprotonation site (N_1–H or N_1^- for neutral and anionic species, respectively) has been separated into the π- and σ-contributions. The net charge, q_t, and the donated or accepted π (Δq_π), and σ (Δq_σ), charges have been included in Table 2. The data in Table 2 show that the changes in the σ and π charges on the substituents are expected on the basis of their accepting or donating character.[26] Moreover, the values of Δq_π(X) and Δq_σ(X) for a given substituent are nearly the same for the three different β-carboline rings. This behaviour runs close to that of $\delta\Delta H^\circ_{acid}$ values, which have an approximately constant value for each substituent (see Table 1).

As regards the charge borne by the pyrrolic nitrogen, the negative charge exhibited in the anion ($q_{N_1^-} = -0.253$ for **1**) is quite small compared with the charges on the oxygens in the benzoate[27] ($\Sigma q_{O^-} = -1.138$) and phenoxide anion[26] ($q_{O^-} = -0.473$). This is because the nitrogen atom is within the aromatic frame and is less electronegative than the oxygen atom. Therefore, the charge delocalization between the deprotonation site and the aromatic ring is more effective for the β-carbolines than for the benzoate and phenoxide anions. Thus, the linear relation between the gas phase acidity and the net charge on the oxygen of the substituted benzoate anions[27] is not observed along the β-carboline set.

The influence of the substituents in the deprotonation enthalpy of the β-carbolines can be compared with that derived from the experimental gas phase acidity of the benzoic acids.[28] Experimental data reported for the substituted benzoic acids are $\Delta G^\circ_{acid,gp}$. Thus, in order to obtain the experimental ΔH°_{acid} values, the entropic term has been assumed to be constant along the series and equal to the experimental value reported for the unsubstituted benzoic acid (298.15 $\Delta S^\circ_{acid,gp}$ = 29.7 kJ mol^{-1}).[29] This comparison is shown in Fig. 1. The linear correlation obtained indicates that the differential effect of the substituent group is independent of the nature of the ring and the deprotonated group. Because the slopes of the three plots are almost the same, the influence of the substituted groups is not modified by the aromaticity degree of the β-carboline ring.

The experimental and theoretical study of the deprotonation processes in the gas phase is interesting in order to understand the intrinsic properties of these equilibria. However, the biological and pharmacological processes involving β-carboline derivatives take place in solution. Thus, the primary parameters to be used in the quantification of their acidic properties is the pK_a value. In Table 3, the available pK_a values for the three 6-methyl-β-carboline rings are presented. Also, for comparison,

* *Systematic nomenclature:* harmane, 1-methyl-9*H*-pyrido[3,4-*b*]indole; harmine, 7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole; harmaline, 4,9-dihydro-7-methoxy-1-methyl-3*H*-pyrido[3,4-*b*]indole.

Table 2 Mulliken population analysis of the neutral (N) and N-deprotonated (A) molecules; net (q_t) and donated (+) or accepted (−) σ (Δq_σ) and π (Δq_π) charges

Substituent	q_t(Y)[a]	Δq_π(Y)	Δq_σ(Y)	q_t(X)[b]	Δq_π(X)	Δq_σ(X)
Compound **1**						
H (N)	0.022	0.300	−0.278			
H (A)	−0.253	0.673	0.074			
12-NH_2 (N)	0.022	0.296	−0.274	0.031	0.151	−0.120
12-NH_2 (A)	−0.250	0.675	0.075	−0.048	0.100	−0.148
12-NO_2 (N)	0.043	0.319	−0.276	−0.153	−0.041	−0.113
12-NO_2 (A)	−0.226	0.702	0.072	−0.270	−0.103	−0.166
12-MeO (N)	0.027	0.303	−0.275	−0.038	0.099	−0.137
12-MeO (A)	−0.246	0.680	0.075	−0.108	0.087	−0.195
12-Cl (N)	0.029	0.305	−0.276	−0.017	0.034	−0.051
12-Cl (A)	−0.246	0.679	0.075	−0.105	0.021	−0.127
Compound **2**						
H (N)	0.062	0.352	−0.290			
H (A)	−0.200	0.747	0.053			
12-NH_2 (N)	0.060	0.346	−0.287	0.025	0.148	−0.123
12-NH_2 (A)	−0.195	0.754	0.052	−0.054	0.101	−0.155
12-NO_2 (N)	0.080	0.367	−0.288	−0.158	−0.040	−0.118
12-NO_2 (A)	−0.189	0.754	0.057	−0.269	−0.093	−0.176
12-MeO (N)	0.067	0.355	−0.288	−0.042	0.100	−0.142
12-MeO (A)	−0.192	0.755	0.053	−0.114	0.090	−0.204
12-Cl (N)	0.068	0.356	−0.288	−0.023	0.034	−0.057
12-Cl (A)	−0.195	0.751	0.055	−0.115	0.022	−0.137
Compound **3**						
H (N)	0.048	0.346	−0.298			
H (A)	−0.273	0.722	0.054			
12-NH_2 (N)	0.046	0.341	−0.295	0.022	0.147	−0.125
12-NH_2 (A)	−0.222	0.728	0.050	−0.058	0.100	−0.158
12-NO_2 (N)	0.066	0.363	−0.297	−0.163	−0.041	−0.122
12-NO_2 (A)	−0.213	0.733	0.055	−0.276	−0.096	−0.180
12-MeO (N)	0.053	0.349	−0.296	−0.045	0.100	−0.145
12-MeO (A)	−0.219	0.729	0.051	−0.119	0.090	−0.209
12-Cl (N)	0.054	0.350	−0.297	−0.033	0.023	−0.061
12-Cl (A)	−0.222	0.725	0.053	−0.122	0.022	−0.144

[a] Y = N_1–H or N_1^-. [b] X = substituent.

Table 3 pK_a values for the deprotonation process in aqueous solution and the difference between the solvation free energy (kJ mol^{-1}) of the deprotonated and neutral molecules, $\delta\Delta G_s^\circ$[a]

	Benzoic acid		6-Methyl-β-carbolines 1		2		3	
Substituent[b]	pK_a[c]	$\delta\Delta G_s^\circ$	pK_a	$\delta\Delta G_s^\circ$	pK_a	$\delta\Delta G_s^\circ$	pK_a	$\delta\Delta G_s^\circ$
H	4.20	−272.6	14.50	−208.9	14.90	−215.3	16.00	−227.5
m-MeO	4.09	−271.2	14.43	−208.2	15.34	−211.7	15.60	−228.4
p-MeO	4.47	−274.0	14.56	−204.9	14.54	−211.4	15.60	−225.3
p-NO_2	3.44	−227.1	12.06	−153.3	12.55	−161.1	14.10	−169.4
p-NH_2	4.41[d]	−280.7	(15.2)[e]	(−219.1)	(15.2)	(−225.1)	≃16.0	≃−239.1
p-Cl	3.97	−257.0	(14.0)	(−191.0)	(14.4)	(−197.0)	≃15.2	≃−211.0

[a] $\Delta G_s^\circ(A^-) - \Delta G_s^\circ(AH) = \delta\Delta G_s^\circ = 5.71pK - \Delta G^\circ_{acid.gp} - \Delta G_s^\circ(H^+) = 5.71pK - \Delta G^\circ_{acid.gp} + 1089.9$ (kJ mol^{-1}). [b] *m* and *p* are positions 11 and 12, respectively, on the β-carboline ring. [c] Taken from reference 30. [d] Estimated from the linear correlation between gas phase and aqueous acidities of substituted benzoic acids (see ref. 28). [e] Values in parenthesis are estimated (see text).

the corresponding data for the substituted benzoic acids have been included.[30] Data in Table 3 show that the acidity sequence aromatic > dehydro > tetrahydro obtained from the theoretical gas phase deprotonation enthalpies holds up in solution. The substituent effects on the pK_a values are expected in the case of the aromatic β-carbolines (see sequence of the benzoic acid derivatives), whereas for the other two rings a change is obtained for the methoxy derivatives.

As expected, the benzoic acid pK_a values are 9–12 pK units smaller than the values of the β-carboline derivatives. This pK gap corresponds to a free energy difference of 51–68 kJ mol^{-1}. To compare this value with the corresponding value in the gas phase, the experimental gas phase acidities of the β-carboline derivatives are necessary. However, no experimental information in the gas phase is available and it does not seem likely that it would be easily obtained, given the molecular weight of these structures. Therefore, the theoretical deprotonation enthalpies are the sole source of information for predicting their gas phase acidities. In order to estimate the $\Delta G^\circ_{acid.gp}$ values, a constant value of 298.15 ΔS°_{acid} has been added to the ΔH°_{acid} in

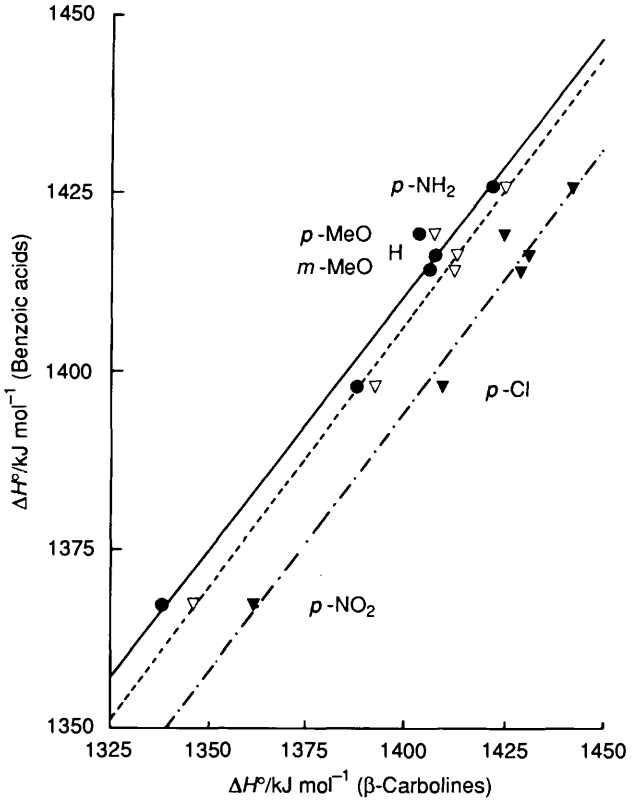


Fig. 1 Plot of the experimental gas phase deprotonation enthalpies of some substituted benzoic acids *vs.* the AM1 ΔH°_{acid} values for the corresponding substituted β-carbolines; ●, 1; ▽, 2; ▼, 3

Table 4 AM1 N-7 proton affinities, PA/kJ mol^{-1}, for some β-carboline derivatives

	1		2		1	
Substituent	PA	δPA[a]	PA	δPA	PA	δPA
H	931.2	0.0	938.0	0.0	896.2	0.0
12-NH_2	945.1	13.9	951.0	13.0	907.2	11.0
12-MeO	932.3	1.1	939.1	1.1	896.3	0.1
12-Cl	921.1	−10.1	927.2	−10.8	887.7	−8.5
12-NO_2	893.0	−38.2	898.6	−39.4	864.9	−31.3

[a] δPA = PA(substituted) − PA(unsubstituted).

Table 1. This term was estimated for the three unsubstituted β-carboline rings in a previous paper [29.3 kJ mol^{-1} (aromatic); 26.8 kJ mol^{-1} (dehydro); and 29.1 kJ mol^{-1} (tetrahydro)].[12]

At this point, an interesting fact emerges: while in solution the benzoic derivatives are stronger acids than the β-carbolines, in the gas phase they have similar acidities and in some cases *e.g.* for compounds **1**, the sequence is even reversed.

This fact has compelled us to examine the solvation contribution to the deprotonation processes. Thus, the deprotonation free energy in the aqueous media $\Delta G^{\circ}_{acid,s}$ can be divided into two terms: the gas-phase deprotonation free energy, $\Delta G^{\circ}_{acid,gp}$, and the solvation free-energy contribution, ΔG°_{s} [eqn. (2)].

$$\Delta G^{\circ}_{acid,s} = \Delta G^{\circ}_{acid,gp} + \Delta G^{\circ}_{s} = \Delta G^{\circ}_{acid,gp} + [\Delta G^{\circ}_{s}(A^-) + \Delta G^{\circ}_{s}(H^+) - \Delta G^{\circ}_{s}(AH)] \quad (2)$$

In order to examine the differential solvation contribution between benzoic acid and the β-carboline rings the term $\delta\Delta G^{\circ}_{s} = \Delta G^{\circ}_{s}(A^-) - \Delta G^{\circ}_{s}(AH)$ has been calculated. These values are included in Table 3. Data in this Table show that $\delta\Delta G^{\circ}_{s}$ values remain similar within the three series of β-carbolines. However, there is a clear difference between the benzoic acid and β-carboline sets, the solvation contribution favouring the deprotonation of the former. Thus, the unsubstituted 6-methyl derivative of **1** is more acid than benzoic acid in the gas phase, but the $\delta\Delta G^{\circ}_{s}$ difference of *ca.* −64 kJ mol^{-1} accounts for the inversion of the relative acidity in solution. As a primary indication of the differential behaviour of $\delta\Delta G^{\circ}_{s}$ for both kind of molecules, it could be inferred that the Born term, associated with the solvation of the ionized species, will be more important for small molecules such as benzoic acid. However, this term is not enough to account for the $\delta\Delta G^{\circ}_{s}$ values, because neither multipole moment contribution nor specific interactions are considered by this term.[10,31]

Taking into account the similarities between the substituent effects on the experimental acidity of benzoic and β-carboline derivatives, the pK_a values for 12-NH_2 and 12-Cl aromatic β-carbolines have been estimated. Two different approaches have been used. In the first, these pK_a values were obtained from the linear correlation between the available pK_a of benzoic acids and aromatic β-carbolines. For the second approach eqn. (2) has been used and $\delta\Delta G^{\circ}_{s}$ has been estimated from its change along the three series of β-carbolines in Table 3. Although the calculation methods are completely independent, the results arising from both approaches differ by no more than 0.3 pK units. This seems to indicate that the average estimated values included in parentheses in Table 3 might be reliable to within a reasonable degree.

Protonation Process.—The calculated proton affinities of the different compounds are presented in Table 4. Only the N-7 protonation process has been considered, since independently of the degree of aromaticity, the protonation of the β-carbolines on the N-7 atom is always favoured over the N-1 protonation.

The proton affinity sequence, dehydro > aromatic > tetrahydro, observed for the unsubstituted molecules, is retained upon substitution. In fact, the δPA data in Table 4 show the constancy of the substituent effect on the basicity of the three different β-carboline rings. As expected, the effect of the substituents on the protonation enthalpy (PA = $-\Delta H^{\circ}_{basic}$) is just the opposite of that previously observed for the deprotonation process. The influence of the NO_2 and Cl substituents is greater for the N-1 deprotonation than for the N-7 protonation processes, as should be predicted from their electron-withdrawing character. In contrast, the electron-donating nature of the NH_2 group justifies the values of δPA being similar to those of $\delta\Delta H^{\circ}_{acid}$. The mild character of the MeO group gives rise to small $\delta\Delta H^{\circ}_{acid}$ and δPA values although it is worth pointing out that these small changes are always in the sense of favouring the processes with respect to the unsubstituted molecule.

The net charge on each substituent and the σ and π charges accepted or donated by it to the aromatic β-carboline ring have been collected in Table 5. A comparison of the data in Table 5 with those in Table 2 shows how the charge transfer from the NH_2 group to the ring is enhanced in the protonation process. In this process, the π-donor nature of the substituent group dominates over its σ-acceptor character, whereas the opposite behaviour is obtained for the deprotonation process. In the case of nitro derivatives, the σ and π electron-withdrawing effect is, as expected, strongly reduced in the protonation process.

The pK_b values for the N-7 protonation process in aqueous solution of some β-carboline derivatives are collected in Table 6. Data in Table 6 show that the nitro group disfavours the protonation process of the aromatic and dehydro β-carbolines with respect to the unsubstituted molecules. The methoxy group in position 11 favours the protonation process independently of the aromaticity of the ring. However, when this group is in position 12 the acidity of the aromatic derivative and the

Table 5 Mulliken population analysis of the neutral (N) and N_7-protonated (C) molecules; net (q_t) and donated (+) or accepted (−) σ (Δq_σ) and π (Δq_π) charges

Substituent	$q_t(Y)^a$	$q_t(X)^b$	$\Delta q_\pi(X)$	$\Delta q_\sigma(X)$
Compound **1**				
12-NH_2 (N)	−0.115			
12-NH_2 (C)	−0.223	0.098	0.201	−0.103
12-NO_2 (N)	−0.113			
12-NO_2 (C)	0.227	−0.083	−0.024	−0.059
12-MeO (N)	−0.115			
12-MeO (C)	0.220	0.018	0.118	−0.100
12-Cl (N)	−0.115			
12-Cl (C)	0.222	0.046	0.046	0.001
Compound **2**				
12-NH_2 (N)	−0.164			
12-NH_2 (C)	0.071	0.094	0.197	−0.102
12-NO_2 (N)	−0.150			
12-NO_2 (C)	0.098	−0.086	−0.025	−0.062
12-MeO (N)	−0.161			
12-MeO (C)	0.075	0.016	0.117	−0.101
12-Cl (N)	−0.158			
12-Cl (C)	0.083	0.045	0.046	−0.001
Compound **3**				
12-NH_2 (N)	−0.120			
12-NH_2 (C)	0.467	0.075	0.185	−0.110
12-NO_2 (N)	−0.116			
12-NO_2 (C)	0.475	−0.107	−0.027	−0.080
12-MeO (N)	−0.119			
12-MeO (C)	0.469	−0.002	0.115	−0.117
12-Cl (N)	−0.118			
12-Cl (C)	0.471	0.024	0.042	−0.018

[a] Y = N_7 or N_7H^+. [b] X = substituent.

Table 6 pK_b Values for the N_7 protonation process in aqueous solution

	6-Methyl-β-carbolines	
Substituent	1	2
H	6.55	5.01
11-MeO	6.16	4.35
12-MeO	7.09	4.79
12-NO_2	7.76	6.37

basicity of the dehydro molecule are increased. The absence of experimental data on comparable molecules precludes an analysis similar to that performed for the deprotonation process. However, an empirical correlation between the pK_b values of the aromatic and dehydro β-carbolines and their corresponding AM1 proton affinities has been attempted. Whereas this correlation is quite satisfactory for the dehydro compounds, in the case of the aromatic derivatives a scattering of the points is observed. In any case, the small amount of data forces a careful look at these correlations.

Reactivity.—The reactivity of the β-carboline ring is quite versatile. The most characteristic reaction of these molecules is electrophilic substitution but, depending on the aromaticity of the ring and on its ionization state, different mechanisms must be proposed.

Although it is known that the static reactivity indices are only a first approach to the reactivity problem, the potential capacity of these indices is worth examining in order to predict the orientation of the electrophilic attack. If a soft electrophile, such as the peroxodisulphate anion, is considered, orbital-controlled reactivity will be expected. Therefore, in the first stage of the reaction the atom bearing the highest coefficient on the HOMO of the β-carboline can be taken as the most favourable position for the electrophilic attack. In the case of the unsubstituted aromatic derivative, this index indicates that N-1 is the most favourable position for the attack on neutral and anionic species and is kept upon substitution. However, for the protonated molecules, electrophilic substitution always occurs on the benzenic ring except for the nitro derivative which still directs the attack on the N-1 atom.

An examination of the coefficients on the HOMO of the tetrahydro derivatives indicates C-3 to be the preferred site of interaction for all the neutral and anionic species, but for the protonated derivatives attack is directed on the benzenic ring. Finally, AM1 wavefunction analysis of the cationic and anionic dehydro molecules leads to the prediction of the orientation of attack on the benzenic ring and on C-3, respectively. In the case of the neutral compounds, the electrophilic substitution position is C-3 for MeO, Cl and NO_2 derivatives but N-1 for the unsubstituted molecule. The NH_2 group directs the attack on the benzenic ring.

Although there are unfortunately no extensive and systematic studies concerning the electrophilic substitution reactions of the three β-carbolines, some experimental data can be collated with the theoretical predictions. Thus, in sulphuric acid solutions sulphonation of the protonated, unsubstituted and 11-MeO aromatic β-carbolines is known to occur on the benzenic ring.[4] On the other hand, the anions of 11-MeO, 12-MeO, 12-NO_2 and unsubstituted aromatic derivatives react with peroxodisulphate anion, the N-1 deprotonated atom being the attack [32] position. In neutral media, the peroxodisulphate substitution on the tetrahydro derivatives (11-MeO, 12-MeO, 12-NO_2 and H) occurs at C-3.[32] This experimental evidence is in close agreement with the theoretical predictions. Nevertheless, in the case of the dehydro derivatives there is accordance between theoretical and experimental data in acid media but not in basic media. The protonated 11-MeO dehydro compound is sulphonated on the benzenic ring.[4] However, although the coefficients on the HOMO of the deprotonated molecules predict the electrophilic substitution on C-3, the anions of 11-MeO, 12-MeO, 12-NO_2 and unsubstituted derivatives react with peroxodisulphate in the same way as the aromatic compounds, *i.e.* the position of attack is the deprotonated N-1 atom.[32]

This controversy suggests that other factors besides the simple electronic one, represented by the orbital index, play a significant role in determining the key points for the reactivity of the dehydro derivatives. In fact, the nuclear and electron distributions of these molecules are a delicate compromise between a fully aromatic molecular system of three fused rings and one of two fused aromatic rings joined to a saturated piperidinic ring. Thus, in the latter cases, the HOMO is a π-orbital quite similar to that of the indole molecule and as in these compounds the soft electrophilic attack is directed towards C-3. In contrast, the fully aromatic β-carboline has a π-HOMO similar to that of anthracene, where the charge is redistributed along most of the atoms of the three rings thus favouring the N-1 position.

For the dehydro compounds, the breakdown in the aromaticity of the pyridine ring leads to a HOMO like that of the indole molecules. Nevertheless, the double bond located on C(6)–N(7) maintains a nearly complete planarity of the partially unsaturated pyridinic ring, as opposed to the non-planar conformation exhibited by the piperidinic ring in the tetrahydro derivatives (see the section on Computational Methods). This introduces a differential behaviour in the attack on C-3 for these two kinds of molecules, because geometrical deformation associated with the approach of the electrophile will be much more important in the case of the dehydro than the tetrahydro derivatives. This could partially explain the N-1 substitution shown by the dehydro derivative, since, although

this position is not favoured by controlled-orbital reasons, the energy deformation contribution to the barrier height will be smaller than for attack on C-3.

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References

1 M. Balón, C. Carmona and D. González, *Tetrahedron*, 1985, **41**, 4706.
2 M. A. Muñoz, C. Carmona, J. Hidalgo and M. Balón, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1573.
3 M. Balón, M. A. Muñoz, C. Carmona and J. Hidalgo, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1165.
4 C. Carmona, M. Balón, J. Hidalgo, M. A. Muñoz and M. López, *Can. J. Chem.*, 1989, **67**, 720.
5 V. Sniecks, in *The Alkaloids*, ed. R. H. F. Manske, Academic Press, New York, 1968, vol. 1.
6 F. Bloom and R. Alan, in *β-Carbolines and Tetrahydroisoquinolines*, Liss, New York, 1982.
7 M. Martin, F. Sanz, M. Campillo, L. Pardo, J. Pérez, J. Turmo and J. M. Aulló, *Int. J. Quantum Chem.*, 1983, **23**, 1643.
8 J. Sánchez-Marín, E. Orti and F. Tomas, *J. Comput. Chem.*, 1985, **6**, 441.
9 H. Konschin, H. Tylli, J. Gynther and H. Rouvinen, *J. Mol. Struct. (Theochem.)*, 1987, **153**, 307.
10 J. Aihara, H. Ichikawa, H. Tokiwa and Y. Okamura, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2498.
11 J. Hidalgo, M. Balón, C. Carmona, M. A. Muñoz, R. R. Pappalardo and E. Sánchez Marcos, *J. Chem. Soc., Perkin Trans. 2*, 1990, 65.
12 C. Carmona, J. Hidalgo, E. Sánchez Marcos, R. R. Pappalardo, M. A. Muñoz and M. Balón, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1881.
13 E. Schilitter and H. J. Bein, in *Medicinal Chemistry*, ed. E. Schilitter, Academic Press New York, 1967, vol. 7, ch. 5.
14 R. A. Abramovitch and I. D. Spenser, *Adv. Heterocycl. Chem.*, 1964, **3**, 79.
15 M. J. S. Dewar, E. G. Zoebisch, E. F. Heady and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
16 I. D. Spencer, *Can. J. Chem.*, 1959, **37**, 1851.
17 S. Misztal and M. Cegla, *Synthesis*, 1985, 1134.
18 B. T. Ho, K. Li, K. E. Walker, L. W. Tansey, P. M. Kralih and W. M. McIsaac, *J. Pharm. Sci.*, 1970, **59**, 1445.
19 S. Siddiqui and S. I. Hammed, *Pak. J. Sci. Ind. Res.*, 1975, **78**, 243.
20 D. D. Perrin and B. Dempsey, in *Buffers for pH and Metal Ion Control*, Chapman and Hall, 1974.
21 G. Yagil, *J. Phys. Chem.*, 1967, **71**, 1034.
22 R. A. Cox and K. Yates, *J. Am. Chem. Soc.*, 1978, **100**, 3861.
23 R. A. Cox and R. Stewart, *J. Am. Chem. Soc.*, 1976, **98**, 488.
24 T. J. Hannigan and W. J. Spillane, *J. Chem. Soc., Perkin Trans. 2*, 1982, 851.
25 A. Bagno, G. Scorrano and R. A. More O'Ferral, *Rev. Chem. Intermed.*, 1987, **7**, 313.
26 A. Pross, L. Radom and R. W. Taft, *J. Org. Chem.*, 1980, **45**, 818.
27 T. Sotomatsu, T. Murata and T. Fujita, *J. Comput. Chem.*, 1989, **10**, 94.
28 T. B. McMahon and P. Kebarle, *J. Am. Chem. Soc.*, 1977, **99**, 2222.
29 J. B. Cumming and P. Kebarle, *Can. J. Chem.*, 1978, **56**, 1.
30 *CRC Handbook of Tables for Organic Compound Identifications*, 3rd edn., compiled by Z. Rappoport, CRC Press, 1974.
31 R. R. Pappalardo and E. Sánchez Marcos, *J. Chem. Soc., Faraday Trans.*, 1991, **87**, 1719.
32 Unpublished results.

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