2-Aminopyrrole and simple 1-substituted 2-aminopyrroles: preparation and *ab initio* study on the effect of solvent on the amino–imino tautomeric equilibrium †

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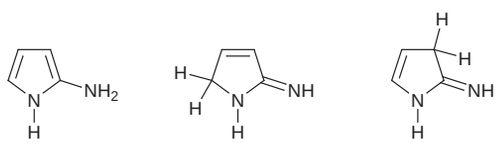
This work describes the preparation and NMR characterization of 2-aminopyrrole and simple 1-substituted-2-aminopyrroles without further substitution on the ring. The question of the effect of solvent on tautomerism in 2-aminopyrroles has been studied by using *ab initio* quantum mechanical methods. Theoretical calculations indicated that 2-aminopyrrole is the most stable form in chloroform and in water. Experimentally this is what was observed. Calculations indicated that in the case of the 1-methyl-2-aminopyrrole both amino and imino tautomers should be observable in water.

The possibility that 2- and 3-aminopyrroles can exist as either the amino or imino tautomer or as an equilibrium mixture of tautomers has been considered in the literature.[1] Theoretical calculations predict that the amino tautomer **1a** is more stable than the imino tautomers **2** and **3** (Scheme 1).[2] In 1968 it was



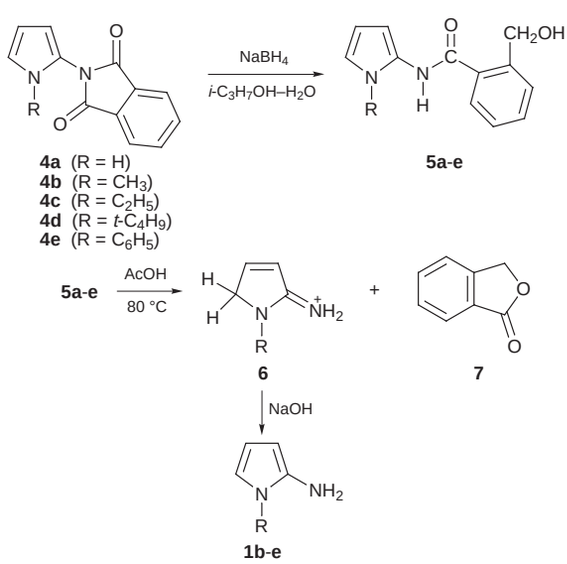
1a **2** **3**

Scheme 1

reported that, based on ^{1}H NMR evidence, 1-acetyl-2-amino-4,5-dimethylpyrrole exists as the imino tautomer.[3] Subsequent ^{1}H and ^{13}C NMR work indicated that this compound is in fact the amino tautomer.[4] Recently it was reported that 1-acetyl-2-amino-3-cyano-4-R-5-R′-pyrroles are protonated on the exocyclic nitrogen in a mixture of DMSO–trifluoroacetic acid (TFA).[4] This can be contrasted with studies that indicate that in TFA or mineral acids 2-aminopyrroles undergo ring protonation at C-5.[5] The species formed respectively in pure acid and DMSO–TFA are tautomeric conjugate acids. It has been observed that in chloroform, 1-(triphenylmethyl)-3-aminopyrrole exists exclusively as the imino tautomer.[6] These results[4,6] are contrary to theoretical predictions[2] in the gas phase and suggest the possibility that the amino–imino tautomeric equilibrium might be solvent dependent. This would be analogous to the solvent effects observed in the 3-hydroxypyrrole–1*H*-pyrrol-3(2*H*)-one system.[7]

Recently we reported the first route to 2-aminopyrrole **1a** and 1-substituted-2-aminopyrroles **1b–e** without further substitution on the pyrrole ring.[8] Prior to this work all reported examples of 2-aminopyrrole derivatives contained one or more electron-withdrawing groups or a phenyl group on the pyrrole ring.[1] Unsubstituted derivatives would allow the study of tautomerism in 2-aminopyrroles in the absence of possible complicating electronic effects. This work describes the preparation and NMR characterization of 2-aminopyrroles **1a–e** and examines the question of the effect of solvent on tautomerism in 2-aminopyrroles.

The synthetic route used to prepare 2-aminopyrroles **1** has been described in a preliminary communication.[8] It is summarized here in Scheme 2. Reaction of 1-substituted pyrroles with *N*-chlorophthalimide gave an *N*-(1-substituent-1*H*-pyrrol-2-yl)phthalimide **4** by an addition–elimination reaction.[9] This



Scheme 2

† Free energy perturbation profiles and closure thermodynamic cycles are available as supplementary data available from BLDSC (SUPPL. NO. 57555, pp. 7) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http:www.rsc.org/authors).

Table 1 ^{1}H, ^{13}C and ^{15}N Chemical shifts of conjugate acids **6**

	^{1}H[a]					J[b]	^{13}C[a]					^{15}N[c]
R	C5H[d]	C4H	C3H	NH_2	other		C5	C4	C3	C2	other	$=NH_2^+$
H	4.51 t	6.59 dt	7.51 dt	8.2 b, 8.6 b	8.9 b (NH)[e]	5.8, 1.6	54.8	121.7	150.5	167.2		69.74
CH_3	4.57 s	6.62 dt	7.43 dt	8.1 b, 8.5 b	3.34 s	6.0, 1.6	61.0	122.2	147.7	164.6	30.8	68.17
C_2H_5	4.57 t	6.63 dt	7.45 dt	8.1 b, 8.5 b	3.75 q, 1.31 t	6.0, 1.6	58.5	122.4	147.8	163.9	39.4, 11.4	68.32
t-C_4H_9	4.69 t	6.60 dt	7.39 dt	8.6 b	1.58 s	5.8, 1.5	58.7	123.9	146.8	163.4	56.6, 26.2	73.07
C_6H_5	4.98 t	6.85 dt	7.66 dt	8.0 b, 8.8 b	7.5 m	6.0, 1.6	62.3	122.4	149.0	164.6		72.31

[a] Spectra taken in glacial acetic acid and chemical shifts are in ppm relative to external TMS. [b] In Hz. [c] Spectra taken in glacial acetic acid and chemical shifts are in ppm relative to ammonium nitrate as the internal standard. [d] dt = doublet of triplets; b = broad; q = quartet; t = triplet; s = singlet. [e] Pyrrole NH may be interchangeable with one of the values of exocyclic amino protons.

Table 2 ^{1}H and ^{13}C Chemical shifts of 2-aminopyrroles (**1**)

	^{1}H[a]					J[b]			^{13}C[a]				
R	C5H[c]	C4H	C3H	NH_2	other	J_{45}	J_{34}	J_{35}	C5	C4	C3	C2	other
H									112.2	107.1	101.6	135.7	
CH_3	6.29 dd	5.94 dd	5.47 dd	3.1 b	3.47 s	3.0	3.5	2.0	116.1	105.7	94.5	135.0	31.9
C_2H_5	6.34 dd	5.96 dd	5.48 dd	3.0 b	3.82 q, 1.34 t	3.1	3.3	2.0	114.2	105.8	94.9	134.1	39.6, 16.1
t-C_4H_9	6.47 dd	5.89 t	5.53 dd	3.1 b	1.61 s	3.3	3.3	2.1	113.1	104.5	98.3	135.6	30.0, 55.4
C_6H_5	6.47 dd	6.10 t	5.53 dd	3.2 b	7.4 m	3.3	3.3	2.0					

[a] Spectra taken in $CDCl_3$ and chemical shifts are in ppm relative to TMS as the internal standard. Spectrum of R = H taken in aqueous NaOH solution (pH *ca.* 12). [b] In Hz. [c] dd = doublet of doublets; b = broad; q = quartet; t = triplet; s = singlet.

reaction did not take place with pyrrole,[9] and in order to prepare the unsubstituted 2-aminopyrrole **1a**, the reaction was carried out with 1-(trimethylsilyl)pyrrole. The trimethylsilyl group was lost during the workup process. Removal of the phthaloyl group was carried out using the method of Ganem and co-workers.[11]

Partial reduction of **4** with $NaBH_4$ gave the *o*-hydroxymethylbenzamide **5**. The benzamides **5** were isolated and characterized. A solution of **5** in glacial acetic acid at 80 °C for 2 h under a nitrogen atmosphere gave phthalide **7** and a species whose ^{1}H, ^{13}C and ^{15}N NMR spectra (Table 1) indicated was the conjugate acid **6**.

The conjugate acid was demonstrated by the presence, in the ^{1}H NMR spectra, of two broad one-proton signals at *ca.* 8.1 and 8.6 ppm attributed to the two non-equivalent hydrogens of the iminium group in **6**.[3,4,5b] In the ^{13}C NMR spectra a signal appeared at *ca.* 55–60 ppm that partially decoupled and APT spectra indicated was a methylene carbon. The ^{15}N NMR spectra were taken of glacial acetic acid reaction mixtures starting with **5** in which the exocyclic nitrogen was enriched with 90% ^{15}N.[12] A triplet (J_{N-H} = 93.0 Hz) was observed in the coupled ^{15}N NMR spectrum of the parent compound **1a** in acetic acid and was conclusive evidence for the presence of the $=NH_2^+$ group of the conjugate acid.

The 2-aminopyrroles were obtained by adding aqueous sodium hydroxide to the acetic acid solutions containing **6** and phthalide. Aminopyrroles were soluble in water and the phthalide was extracted out with chloroform. The 2-aminopyrrole was then salted out of the aqueous solution and extracted into chloroform. Pure 2-aminopyrroles **1b**–**d** were isolated in chloroform. Partial decomposition of the 1-phenyl derivative **1e** occurred during isolation and the ^{1}H NMR spectrum indicated the presence of at least two products. The parent 2-aminopyrrole **1a** was miscible in water and it was not possible to isolate it in chloroform but its ^{13}C NMR spectrum (alkaline aqueous solution) was consistent with the amino tautomer (Table 2).

As noted above the tautomeric equilibrium in the 3-hydroxypyrrole–1*H*-pyrrol-3(2*H*)-one system is solvent sensitive.[7] Water was reported to favor the keto form to the greatest extent (>80%). Analogously it might be expected that the imino tautomer **2** might be favored in water. No evidence for this species was found in the ^{13}C and ^{15}N NMR spectra taken of 2-aminopyrrole **1a** in alkaline aqueous solution as would be expected given the ΔG shown in Table 3. The 2-aminopyrrole **1a** is very unstable in alkaline aqueous solution and decomposed to give a complex mixture of products. The following section reports the theoretical results of a study of the effect of solvent on tautomerism in 2-aminopyrroles.

Gas phase calculations

In order to examine the prototropic tautomerism, the relative stability between amino and imino species of 2-aminopyrrole and its 1-methyl derivative was studied by means of *ab initio* quantum mechanical calculations performed at the QCISD(T) level of theory.

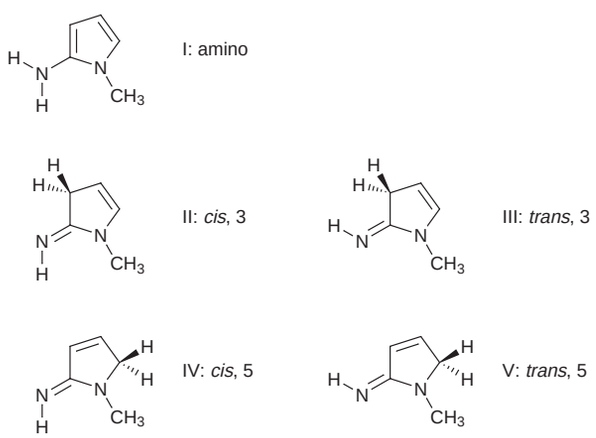
Calculations were performed using the gas phase geometries optimized at the MP2/6-31G(d,p) level. Frequency analysis was carried out to verify the minimum-energy nature of the optimized structures. Single-point calculations were performed at the HF/6-311++G(d,p) level. Correlation effects were considered from QCISD(T) calculations performed with the 6-31+G(d,p) basis. The total energy was then estimated upon addition of the correlation energy determined at this level of theory to the energy differences computed at the HF/6-311++G(d,p) level. Zero-point energies, thermal and entropic corrections (298 K) were determined from the HF/6-31G(d,p) geometries in the rigid rotor-harmonic oscillator approximation using the standard protocol in GAUSSIAN94.[13]

Comparison of the HF (data available upon request) and QCISD(T) results shows that electron correlation has a small effect (around 0.6 kcal mol^{-1}) on the relative stability of structures II and III (see Scheme 3 for nomenclature). However, a relevant influence (around 1.8 kcal mol^{-1}) is observed for structures IV and V. This behavior is probably due to differences in the resonance pattern arising upon migration of the amino hydrogen to either position 3 or 5. Inspection of the values at QCISD and QCISD(T) levels suggests that the results are reasonably converged at this level, and that any further increase in the level of theory is not expected to introduce relevant changes in the results.

Table 3 Free energy differences (kcal mol^{-1}) in the gas phase (ΔG_{gas}), water (ΔG_{son},wat) and chloroform (ΔG_{son},chl) of imino tautomers relative to the amino species of 2-aminopyrrole and 1-methyl-2-aminopyrrole[a]

Tautomer[b]	ΔG_{gas}	$\Delta\Delta G_{sol}$,wat[c]	ΔG_{son},wat	$\Delta\Delta G_{sol}$,chl[c]	ΔG_{son},chl
2-aminopyrrole					
cis,3	7.7	−2.3 (0.2)	5.4	−1.0 (<0.1)	6.7
trans,3	6.5	−0.6 (0.1)	5.9	−0.8 (<0.1)	5.7
cis,5	7.4	−1.5 (0.2)	5.9	−1.1 (<0.1)	6.3
trans,5	6.9	−2.2 (0.1)	4.7	−1.2 (<0.1)	5.7
1-methyl-2-aminopyrrole					
cis,3	5.0	−4.3 (0.2)	0.7	−0.9 (<0.1)	4.1
trans,3	3.6	−2.1 (0.1)	1.5	−0.7 (<0.1)	2.9
cis,5	5.0	−4.1 (0.1)	0.9	−1.0 (<0.1)	4.0
trans,5	3.8	−4.4 (0.1)	−0.6	−1.0 (<0.1)	2.8

[a] The ΔG_{son} values were determined upon addition of the relative free energies of solvation ($\Delta\Delta G_{sol}$) to the gas phase free energy differences. [b] The nomenclature denotes the orientation of the imino hydrogen (*cis*, *trans*) relative to the pyrrole nitrogen, and the location of the sp^3 carbon atom (Scheme 3). [c] The standard error of the MC-FEP simulations is given in parentheses.



Scheme 3

The differences in free energy relative to the amino form are given in Table 3. Results show that this latter tautomer is preferred over the imino forms for both the parent compound and the 1-methyl derivative, the preferential stability of the amino tautomer being larger than 6.5 and 3.6 kcal mol^{-1} respectively. Therefore, the amino species is expected to be the only detectable species in the gas phase.

It is worth noting that the free energy difference between the amino and imino tautomers is 2.4–3.1 kcal mol^{-1} lower for the 1-methyl compound, which can be understood mainly from the steric hindrance between methyl and amino groups in the 1-methyl-2-aminopyrrole. Indeed, the *cis*–*trans* isomerization of the imino nitrogen gives rise to a notable difference in stability, which is at least 1.2 kcal mol^{-1}. Again, this effect can be explained by the unfavorable interactions between the imino hydrogen and the methyl group for the *cis* isomer. Finally, another interesting finding is that the relative stability between imino tautomers is little influenced by the location of the sp^3 carbon. Thus, migration of the proton from the amino group to either position 3 or 5 leads to a difference in stability of less than 0.2 kcal mol^{-1} for both *cis* and *trans* species.

Calculations in solution

The differences in free energy of solvation between amino and imino tautomers in chloroform and water were determined from Monte Carlo–Free Energy Perturbation (MC-FEP) methods (see supplementary data Figs. A–D).† MC-FEP calculations were performed placing each tautomer in a cubic box containing 260 TIP4P water and 126 chloroform[14] molecules. Simulations were performed in the isothermal–isobaric (1 atm, 298 K) ensemble. Periodic boundary conditions were used in conjunction with a non-bonded cutoff of 8 Å. Long-range effects, which were small, were corrected using the Bell–Onsager model. Solute translation and rotations were adjusted to have an acceptance of around 40%. The mutation between tautomers (used to determine differences in free energy of solvation) was performed in 21 double-wide sampling windows. Each window consisted of 2 million configurations for equilibration and 3 million configurations for averaging. Each averaging window was further divided into blocks of 0.5 million configurations to determine the standard error of the average. Charges for the solute were determined by fitting to molecular electrostatic potentials[15] computed at the HF/6-31G(d) level, and solute van der Waals parameters were taken from the OPLS[14] force-field. OPLS parameters[14] were used to describe the solvent. The gas phase optimized geometries were used, since previous geometry optimization in aqueous solution at the MST/SCRF level showed no relevant change in the structural parameters upon solvation. MC-FEP calculations were performed with the BOSS 3.4 computer program.[16] Similar computational approaches allowed us to reproduce closely related tautomeric processes in other heterocyclic systems.[17]

In all cases the free energy profiles were smooth without any apparent discontinuity.† The hysteresis error (determined as half the difference between forward and reverse paths in the mutation between tautomers) and the standard error were smaller than 0.2 kcal mol^{-1} in water and 0.05 kcal mol^{-1} in chloroform. Finally, closure thermodynamic cycles were defined to further check the quality of MC-FEP simulations (see Figs. E and F in supplementary data).† These cycles were closed with no detectable error in the computed free energies. All these results support the validity of the MC-FEP simulations.

The results (see Table 3) indicate that all the imino species are better solvated than the amino tautomer, which was expected from the differences in dipole moment between amino and imino forms (in general larger than 2 Debyes). The differences between the relative free energies of solvation for the imino tautomers in water and chloroform lie in a very close range except for the tautomer III : *trans*,3, which is understandable given the smaller dipole moment of this species (around 1.3 Debye smaller than for the other imino tautomers). Another remarkable finding is that methylation of the pyrrole nitrogen has very little influence on the relative free energies of solvation of the imino tautomers in chloroform. However, methylation has an important effect on the preferential solvation of imino tautomers in aqueous solution, since the relative free energy of hydration is increased by around 2 kcal mol^{-1} upon methylation.

The differences in free energy of tautomerization in solution were determined upon addition of the tautomerization free

energy difference in the gas phase to the relative free energy of solvation (see Table 3). Inclusion of solvent effects reduces the differences in stability found in the gas phase, this effect being particularly important in water. Thus, the results indicate that in chloroform solution the amino tautomer is expected to be the main, if not exclusively the only species, since the difference in stability with regard to the imino forms is larger than 5.7 and 2.8 kcal mol^{-1} for the parent and methylated compounds. The larger preference for the amino tautomer in the parent compound, which reflects the trends found in the gas phase, can be realized from the steric hindrance between amino and methyl groups in the methylated compound. Nevertheless, the tautomeric equilibrium in aqueous solution becomes much more complex for the 1-methyl compound, since up to three imino forms and the amino species are expected to have a significant population. This finding can be realized from the better hydration of the imino tautomers, which counterbalances the gas phase preference of the amino tautomer. In fact, the results indicate that the preferred tautomer is the imino *trans*, 5 form, which is more stable than the amino tautomer by 0.6 kcal mol^{-1}. If one considers the five species involved in the prototropic tautomerism, the population of the imino species in aqueous solution can be estimated (see eqn. (1)) to be favored by 0.7 kcal mol^{-1} over the amino form for the 1-methyl compound.

$$\Delta G_{\text{imino–amino}} = -RT \ln \left(\sum_{i=1}^{4} \exp \left(-\frac{\Delta G_t^i}{RT} \right) \right) \qquad (1)$$

i refers to the four imino forms
ΔG_t^i is the free energy difference between the amino and the imino form

The theoretical calculations indicated that 2-aminopyrrole is the most stable form in chloroform and water. Experimentally this is what was observed. Calculations indicated that in the case of the 1-methyl compound both amino and imino tautomers should be observable in water. This compound was not examined in water and further study is needed to verify this prediction.

Experimental

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Pyrroles **1**–**5** and *N*-chlorophthalimide were commercially available. Pyrrole was distilled from zinc dust prior to use and 1-(trimethylsilyl)pyrrole[10] was prepared by a literature procedure.

Preparation of *N*-(1-substituent-1*H*-pyrrol-2-yl)phthalimides 4

Phthalimide derivatives **4b**,**d** and **e** have been previously reported from the reaction of the 1-substituted pyrrole and *N*-chlorophthalimide.[9] The product of the reaction of 1-(trimethylsilyl)pyrrole with *N*-chlorophthalimide lost the trimethylsilyl group after the aqueous work up and gave *N*-(1*H*-pyrrol-2-yl)phthalimide **4a**.[9] The same procedure was used to prepare the ethyl derivative **4c**.

***N*-(1*H*-Pyrrol-2-yl)phthalimide 4a.** 27% Yield; mp 183–184 °C; ^{1}H 200 MHz NMR ($CDCl_3$) δ 9.76 (br s, NH), 7.96–7.71 (m, 4H, arom), 6.71 (m, C5H), 6.64 (m, C4H), 6.25 (m, C3H) ppm. This compound was not stable.

***N*-(1-Ethyl-1*H*-pyrrol-2-yl)phthalimide 4c.** 61% Yield; mp 149–150 °C; ^{1}H 200 MHz NMR ($CDCl_3$) δ 8.00–7.27 (m, 4H, arom), 6.81 (dd, C5H, J_{54} = 3.1 Hz and J_{53} = 1.9 Hz), 6.28 (C4H, dd, J_{45} = 3.1 Hz and J_{43} = 3.7 Hz), 6.18 (dd, C3H, J_{34} = 3.7 Hz and J_{35} = 1.9 Hz), 3.78 (CH_2, q, J = 7.3 Hz), 1.35 (CH_3, t, J = 7.3 Hz). Anal. calcd. for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.03; N, 11.71. Found: C, 69.71; H, 4.98; N, 11.62%.

General method for the preparation of *N*-(1-substituent-1*H*-pyrrol-2-yl)-*o*-hydroxymethylbenzamides 5

To a solution of 76 mL of propan-2-ol and 13 mL water was added 42.8 mmol of $NaBH_4$ and 8.58 mmol of phthalimide derivative **4** and the mixture was stirred overnight at room temperature. Organic solvent was removed under reduced pressure and the water was evaporated with a stream of nitrogen and the product was separated by flash column chromatography on silica gel with chloroform–ethyl acetate 10 : 1 v/v as the solvent. Products were recrystallized from ethanol.

***N*-(1*H*-Pyrrol-2-yl)-*o*-hydroxymethylbenzamide (5a).** 77% Yield; mp 125–126.5 °C; ^{1}H 200 MHz NMR ($(CD_3)_2SO$) δ 10.73 (br s, NH), 10.60 (s, NH), 7.64–7.32 (m, 4H, arom), 6.45 (dd, C5H, J_{54} = 4.6 Hz and J_{53} = 2.1 Hz), 5.92 (dd, C4H, J_{45} = 4.6 Hz and J_{43} = 5.9 Hz), 5.78 (dd, J_{34} = 5.9 Hz and J_{35} = 2.1 Hz), 5.30 (br s, OH), 4.68 (s, CH_2) ppm; Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.66; H, 5.59; N, 12.96. Found: C, 66.69; H, 5.70; N, 12.57%.

***N*-(1-Methyl-1*H*-pyrrol-2-yl)-*o*-hydroxymethylbenzamide (5b).** 74% Yield; mp 141–143 °C; ^{1}H 200 MHz NMR ($(CD_3)_2SO$) δ 9.92 (br s, NH), 7.68–7.34 (m, 4H, arom), 6.65 (m, C5H), 5.96 (m, C3H and C4H), 5.35 (t, OH, J = 4.4 Hz), 4.71 (d, CH_2, J = 4.4), 3.49 (s, 3H) ppm; Anal. calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.86; H, 6.25; N, 12.05%.

***N*-(1-Ethyl-1*H*-pyrrol-2-yl)-*o*-hydroxymethylbenzamide (5c).** 97% Yield; mp 104–106 °C; ^{1}H 200 MHz NMR ($(CD_3)_2SO$) δ 9.81 (br s, NH) 7.60–7.34 (m, 4H, arom), 6.68 (dd, C5H, J_{54} = 3.2 Hz and J_{53} = 2.0 Hz), 5.97 (t, C4H, J_{43} = 3.3 Hz and J_{45} = 3.2 Hz), 5.90 (dd, C3H, J_{34} = 3.3 Hz and J_{35} = 2.0 Hz), 5.37 (br s, OH), 4.68 (s, CH_2), 3.81 (q, CH_2, J = 7.2 Hz), 1.26 (t, CH3, J = 7.2 Hz); Anal. calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.05; H, 6.75; N, 11.43%.

***N*-(1-*tert*-Butyl-1*H*-pyrrol-2-yl)-*o*-hydroxymethylbenzamide (5d).** 93% Yield; mp 123–124 °C; ^{1}H 200 MHz NMR ($(CD_3)_2SO$) δ 9.67 (s, NH) 7.62–7.37 (m, 4H, arom), 6.77 (dd, C5H, J_{54} = 3.3 Hz and J_{53} = 2.1 Hz), 5.94 (t, C4H, J_{43} = 3.4 Hz and J_{45} = 3.3 Hz), 5.88 (dd, C3H, J_{34} = 3.4 Hz and J_{35} = 2.1 Hz), 5.30 (t, OH, J = 5.5 Hz), 4.69 (d, CH_2, J = 5.5 Hz), 1.52 (s, 9H); Anal. calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.45; H, 7.46; N, 10.30%.

***N*-(1-Phenyl-1*H*-pyrrol-2-yl)-*o*-hydroxymethylbenzamide (5e).** 97% Yield; mp 124–126 °C; ^{1}H 200 MHz NMR ($(CD_3)_2SO$) δ 9.84 (s, NH) 7.56–7.27 (m, 9H, arom), 6.95 (dd, C5H, J_{54} = 3.3 Hz and J_{53} = 1.9 Hz), 6.21 (t, C4H, J_{43} = 3.4 Hz and J_{45} = 3.3 Hz), 6.15 (dd, C3H, J_{34} = 3.4 Hz and J_{35} = 1.9 Hz), 5.15 (br, OH), 4.46 (d, CH_2, J = 3.3 Hz). This compound was not stable.

General procedure for the preparation of 2-aminopyrroles and their conjugate acids

To 2.0 mL of glacial acetic acid there was added 100 mg of *o*-hydroxymethylbenzamides **5** and the solution was heated at 80 °C for 2 h under a static blanket of nitrogen. This produced a solution containing the conjugate acid of the 2-aminopyrrole **6** and phthalide. Table 1 summarizes the ^{1}H, ^{13}C and ^{15}N NMR data used to characterize **6**.

The 2-aminopyrroles were isolated as follows: To the acetic acid solution of **6** and phthalide there was added 2.5 mL of chloroform and 2.5 mL of water. The layers were separated and the chloroform layer was washed with 2.5 mL of water and the water layer added to the water layer obtained in the first extraction step. The combined aqueous fraction was washed with an equal volume of chloroform and 5 mL of a 40% sodium hydroxide solution saturated with NaCl was added. The resulting solution was extracted with 5 mL of chloroform and again

with 3 mL of chloroform. The chloroform extract was dried with anhydrous Na_2SO_4 and the solvent evaporated with a stream of nitrogen and as soon as all the solvent was evaporated 0.5 mL of $CDCl_3$ was added. Table 2 summarizes the ^1H and ^{13}C NMR data of the 2-aminopyrroles.

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References

1 G. Cirrincione, A. M. Almerico, E. Aiello and G. Dattolo, in *Pyrroles*, *Part Two*, *The Synthesis*, *Reactivity and Physical Properties of Substituted Pyrroles*, R. A. Jones, Ed., John Wiley & Sons Inc., New York, 1992, chap. 3.
2 N. Bodor, M. J. S. Dewar and A. J. Harget, *J. Am. Chem. Soc.*, 1970, **92**, 2929.
3 C. T. Wie, S. Sunder and C. DeWitt Blanton, Jr., *Tetrahedron Lett.*, 1968, 4605.
4 A. M. Almerico, G. Cirrincione, P. Diana, S. Grimaudo, G. Dattolo and E. Aiello, *J. Heterocycl. Chem.*, 1995, **32**, 985.
5 (*a*) H. Warmhoff and B. Wehling, *Synthesis*, 1976, 51; (*b*) J. A. S. Laks, J. Ross, S. M. Bayomi and J. W. Sowell, Sr., *Synthesis*, 1985, 291.
6 D. J. Chadwick and S. T. Hodgson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1983, 93.
7 H. MacNab and L. C. Monhain, in *Pyrroles*, *Part Two*, *The Synthesis*, *Reactivity and Physical Properties of Substituted Pyrroles*, R. A. Jones, Ed., John Wiley & Sons Inc., New York, 1992, chap. 4.
8 M. De Rosa, R. P. Issac and G. Houghton, *Tetrahedron Lett.*, 1995, **36**, 9261.
9 M. De Rosa, G. Cabrera Nieto and F. Ferrer Gago, *J. Org. Chem.*, 1989, **54**, 5347.
10 R. Fessenden and D. F. Crowe, *J. Org. Chem.*, 1960, **25**, 598.
11 J. O. Osby, M. G. Martin and B. Ganem, *Tetrahedron Lett.*, 1984, **25**, 2093.
12 Phthalic anhydride was converted to phthalimide with 90% ^{15}N labeled ammonium hydroxide (Cambridge Isotope Laboratories, Inc.). The phthalimide was *N*-chlorinated with *tert*-butyl hypochlorite and the resulting *N*-chlorophthalimide was used to prepare labeled **4.**
13 GAUSSIAN94, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Anfres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defress, J. Baker, J. J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, (Rev. A.1), GAUSSIAN Inc., Pittsburgh, PA, USA, 1995.
14 W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. Impey and M. J. Klein, *Chem. Phys.*, 1983, **79**, 926; W. L. Jorgensen, J. M. Briggs and M. L. Contreras, *J. Phys. Chem.*, 1990, **94**, 1683.
15 (*a*) F. A. Momany, *J. Phys. Chem.*, 1978, **82**, 592; (*b*) U. C. Singh and P. A. Kollman, *J. Comput. Chem.*, 1984, **5**, 129; (*c*) M. Orozco and F. J. Luque, *J. Comput.-Aided Mol. Des.*, 1990, **4**, 411.
16 Jorgensen, W. L. BOSS Version 3.4. Yale University, New Haven, CT, 1990.
17 C. Colominas, F. J. Luque and M. Orozco, *J. Am. Chem. Soc.*, 1996, **118**, 6811.

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