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SYNTHESIS AND CHEMISTRY OF AZOLENINES.* PART 19.† BASICITIES OF SOME 2*H*- AND 3*H*-PYRROLES AND THE REMARKABLY LARGE $\mathrm{p}K_a'$ OF 2,2,3,5-TETRAMETHYL-2*H*-PYRROLE

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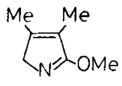
$\mathrm{p}K_a'$ Values are reported for two 2*H*-pyrroles and their 3*H*-pyrrole isomers. The latter have basicities of the same order as similarly substituted pyridines, whereas the former are 2–2·5 p*K* units more basic, 2,2,3,5-tetramethyl-2*H*-pyrrole having a $\mathrm{p}K_a'$ of 8·40, close to that for 2-aminoimidazole. Possible reasons are given.

INTRODUCTION

Few basicity measurements on 2*H*-pyrroles have been reported. With the exception of the methoxy compound **1** for which two independent determinations by electromeric titration[2,3] gave $\mathrm{p}K_a'$ values of 10 and 10·2 ± 0·2, all data have been for 1-azafulvenes.[3] No such data have been reported for 3*H*-pyrroles. The availability from our recent work[4,5] of alkyl- and aryl-substituted 3*H*-pyrroles and by rearrangement their 2*H*-isomers prompted this study.



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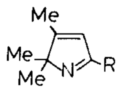

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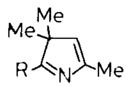
3 R=Ph



4 R=Me

5 R=Ph

RESULTS AND DISCUSSION

The $\mathrm{p}K_a'$ values for compounds **2**–**5** were recorded spectrophotometrically[6] in aqueous solution, and are given together with UV data in Table 1. The 2*H*-pyrroles **2** and **3** are stable in aqueous solution both at high and at low pH, their UV spectra showing negligible change with time. Measurements were carried out at two separate analytical wavelengths, which in turn yielded self-consistent $\mathrm{p}K_a'$ values, giving overall means for **2** and **3** of 8·40 ± 0·04 (14 measurements) and 7·42 ± 0·06 (16 measurements) respectively. In contrast, 3*H*-pyrroles are unstable in aqueous solution, particularly at low pH, first adding water across the C=N bond and subsequently hydrolysing to give a 1,4-diketone.[4,5] For solutions of the 3*H*-pyrrole **5**, the absorbance was observed to change slowly with time, but by working rapidly acceptable isosbestic points could be obtained in plots of $\lambda_{\max.}$ against pH. The UV spectrum of the tetramethyl compound **4**, however, showed rapid changes in absorbance with time, and it was not possible to obtain clean isosbestic points. The $\mathrm{p}K_a'$ value of the latter is therefore less reliable. For the 3*H*-pyrroles, measurements were carried out at only one analytical wavelength.

3*H*-Pyrroles **4** and **5** have basicities of the same order as for similarly substituted pyridines. Thus, for 2-methyl-,[7] 2,6-dimethyl-[7] and 2-phenyl-pyridines,[8] the $\mathrm{p}K_a$ values are 5·97, 6·75, and 4·48 respectively. The isomeric 2*H*-pyrroles, in contrast, are more basic by 2–2·5 p*K* units. In fact, their basicities are significantly greater than that of imidazole ($\mathrm{p}K_a' = 7\cdot13$),[9] whereas that of the tetramethyl compound **2** is similar to reported values for 2,4-dimethylimidazole ($\mathrm{p}K_a = 8\cdot36$)[10] and 2-aminoimidazole ($\mathrm{p}K_a' = 8\cdot46$)[11], making it among the most basic of the known alkyl azoles.

It is interesting to speculate on the possible reasons for the larger basicity of the 2*H*-pyrroles relative to the 3*H*-isomers, a result which is consistent with the observation that 1*H*-pyrroles protonate at C-2 in preference to C-3.[12] A structural comparison between the cations

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[*] The term 'azolenines' refers to the non-aromatic isomers of the azoles.

[†] For Part 18, see Ref. 1.

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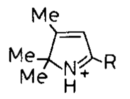
Table 1. pK_a' values at 20 °C in aqueous solution and UV data for 2*H*- and 3*H*-pyrroles

	pK_a' measurement						UV			
		$10^{-3}\varepsilon$					Base		Cation	
Compound	λ/nm[a]	Base	Cation	pK_a'	SD[b]	n[c]	$\lambda_{max.}$	$10^{-3}\varepsilon$	$\lambda_{max.}$	$10^{-3}\varepsilon$
2	235	3·52	2·42	8·41	0·03	6	234	3·54	252	4·58
	254	1·84	4·43	8·39	0·04	8				
3	244	14·80	3·44	7·41	0·06	8	244	14·80	278	22·15
	280	3·36	22·02	7·43	0·05	8				
4	255	1·47	1·10	6·4	0·2	5	253	1·47	271	1·45
5	330	5·74	10·65	5·08	0·06	7	215	9·30	258	5·31
							303	8·70	325	10·66

[a] Analytical wavelength.
[b] Standard deviation.
[c] Number of different pH values at which measurements were made.



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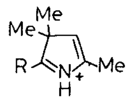

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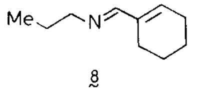
6 and **7** reveals that the former should be the more stable, in that the positive charge may be more extensively delocalized within the heterocyclic ring, and at the same time further stabilized by both the positive inductive effect of the *gem*-dimethyl group, and the greater p character of the C-2—N bond. It also seems likely, however, that steric constraints imposed by the *gem*-dimethyl group will influence solvation in the cations **6** relative to the free bases to a significantly different extent than in the case of the cations **7**, causing the ΔS term to have a different influence on K_a. A comparison with gas-phase pK_a values would be informative.

An alternative approach is to recognize that 2*H*- and 3*H*-pyrroles are Schiff's bases, the former being derived from saturated amines and unsaturated ketones, and the latter from enamines and saturated ketones. We were unable to find pK_a data for suitable open-chain analogues of 3*H*-pyrroles; benzylideneanilines, for which some data have been reported, are structurally too far removed. However, the Schiff's bases **8** and **9**



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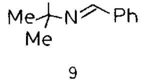

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are reasonable models for the 2*H*-pyrroles **2** and **3**, respectively, and are found to have pK_a values (25 °C in water) which are similar to their counterparts (8·34 ± 0·03[13] and 6·70,[14] respectively). 2*H*-Pyrroles thus have unusually large basicities in comparison with other azoles, but not when compared with structurally similar Schiff's bases.

Replacement of the imino *C*-methyl group by phenyl reduces the basicity of both the 2*H*- and the 3*H*-pyrroles. A similar effect has been observed with pyridines, and was explained in terms of a larger angle between the ring planes in the solvated 2-phenylpyridine cation than in the conjugate base.[8]

EXPERIMENTAL

The pK_a' values were determined spectrophotometrically[6] at 20 °C using a Shimadzu UV240 spectrophotometer and a cell with a 1-cm path length; deionized water was used as reference. Compounds **2**–**5** were prepared and purified as reported earlier.[5] Stock solutions of each were prepared by dissolving 10–50 mg in 10 ml of 95% ethanol, and standard buffer solutions were prepared according to Ref. 15.

Separate aliquots (20–50 μl) of stock solution were diluted to 2·00 ml with buffer, giving final concentrations of azole in the range 10^{-3}–10^{-4} M (a constant concentration was employed for all measurements on a given base). Measurements were carried out at (a) pH 2·2–2·8, (b) pH 10·8–11·6 and (c) at least five intermediate pH values in the range of values $pK_a' \pm 1$. Each measurement was repeated three times and the mean was used to determine pK_a' at a given pH. All pH values were checked with a Cole-Parmer Digi-Sense pH meter, which was standardized beforehand. The observed pK_a' values were not corrected to give thermodynamic (pK_a) values.

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