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ACID-BASE EQUILIBRIA OF ISOMERIC STYRYLPYRIDINES AND SOME OF THEIR DERIVATIVES

SPECTROPHOTOMETRIC STUDY

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Abstract—Acid-base equilibria of the six isomeric styrylpyridines (2-, 3- and 4-, both in *cis* and *trans* forms) have been studied spectrophotometrically using 15% ethanol in water.

The effect of geometrical isomerism and substitution in the benzene and pyridine rings on the basicity are reported and briefly discussed in terms of electronic and steric influences.

The Hammett relationship is used to calculate σ_m values for *p*-substituted styryl groups and to compare the transmission effect of 4′-substituents in the case of 3-styrylpyridines with the known behaviour of the corresponding 4-isomers.

INTRODUCTION

THE styrylpyridines (stilbazoles) have been the object of considerable interest in the last few years, both from the point of view of some recent critical reviews of their preparation[1] and of the study of their physico-chemical properties.[2–6]

The literature data on the latter point are particularly incomplete as they refer to some particular isomer and almost always to the *trans* form.

The study of the full series was of interest, as part of a programme of kinetic and photochemical studies on the geometrical isomerism of ethylenic derivatives.[7] A systematic investigation of the six isomers (2-, 3- and 4-styrylpyridine in both the *trans* and *cis* forms) and some derivatives was undertaken hoping that a general view of the spectroscopic and acid-base properties might clarify the structural effects in the isomerization process.

The influence on the basicity of geometrical and nitrogen-positional isomerism, as well as of simple substituents in different positions on the aromatic rings has been investigated; and, it was hoped to reveal the effects on the electron density at the nitrogen atom, and to separate the steric and mesomeric effects from the inductive ones and to examine the transmission of the effects of the substituents from the benzene ring through the ethylenic double bond.

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[1] See inter alia G. Galiazzo, to be published in *Gazz. Chim. Ital.*; there will be reported a brief review of the preparative methods and related literature references.

[2] A. R. Katritzky and P. Simmons, *J. Chem. Soc.* 1511 (1960); A. R. Katritzky, D. J. Short and A. J. Boulton, *Ibid.* 1516 (1960); A. R. Katritzky, A. J. Boulton and D. J. Short, *Ibid.* 1519 (1960).

[3] J. L. R. Williams, *J. Org. Chem.*, **25**, 1839 (1960); J. L. R. Williams, S. K. Webster and J. A. Van Allan, *Ibid.* **26**, 4893 (1961); J. L. R. Williams, J. M. Carlson, G. A. Reynolds and R. E. Adel, *Ibid.* **28**, 1317 (1963); J. L. R. Williams, *J. Amer. Chem. Soc.* **84**, 1323 (1962).

[4] T. Katsumoto, *Bull. Chem. Soc. Japan* **33**, 242 (1960).

[5] L. Pentimalli, *Gazz. Chim. Ital.* **91**, 991 (1961); *Tetrahedron* **14**, 151 (1961).

[6] G. Favini, *Gazz. Chim. Ital.* **93**, 635 (1963).

[7] P. Bortolus, G. Cauzzo and U. Mazzucato, manuscript in preparation; see also G. Aloisi, G. Cauzzo, G. Giacometti and U. Mazzucato, *Trans. Farad. Soc.* **61**, 1406 (1965).

RESULTS AND DISCUSSION

(a) trans *and* cis *Styrylpyridines.* No important relationship is apparent between the pK_a and the electron density at the nitrogen atom calculated by the S.C.F. method,[8] but this was not unexpected as it is probable that all the principal factors influencing the pK[9] change from 4- to 3- and 2-styrylpyridines and the variation of the solvation energy due to the protonation must also be taken into account.

TABLE 1. pK_a AT 25° FOR THE SIX ISOMERIC *trans* AND *cis* STYRYLPYRIDINES AND SOME OF THEIR DERIVATIVES IN WATER–EtOH AT 15% VOL. OF ALCOHOL

	Stilbazole		
Substituent	2	3	4
H (*trans*)	4·98	4·78	5·73
H (*cis*)	5·01	4·82	5·46
3CH_3 (*trans*)	5·40		5·94
3CH_3 (*cis*)	5·47		5·70
4CH_3 (*trans*)	5·72		
5CH_3 (*trans*)	5·34		
6CH_3 (*trans*)	5·75		
3,6$(CH_3)_2$ (*trans*)	6·11		
4,6$(CH_3)_2$ (*trans*)	6·18		
2′CH_3 (*trans*)			5·71
3′CH_3 (*trans*)			5·75
4′CH_3 (*trans*)	5·16	4·81	5·85
3,2′$(CH_3)_2$ (*trans*)			5·95
3,4′$(CH_3)_2$ (*trans*)			6·09
4′I (*trans*)		4·73	
4′NO_2 (*trans*)		4·44	5·24

For a qualitative explanation of our results, Table 1 shows that the pK_a's are in the order $3 < 2 < 4$ (which is the same order as the methyl-pyridines, although in these the 2- and 4-derivatives have almost the same value[10]) both in the *cis* and *trans* forms. This can be expected on the basis of the stabilization of the protonated 2- and 4-stilbazoles through quinonoid forms. The *p*-styryl group is known to behave as an electron donor for a combination of $-$I and $+$M effects with a prevalence of the mesomeric one.[2,6] The $+$M effect should not be very different in the *o*-styryl compounds.[11] The much lower value of the pK_a of the *o*-isomer (see the analogy with the case of azophenylpyridines[12]), must hence be attributed to a strong $-$I effect and possibly to some steric hindrance also. This is confirmed by the value for the 3-isomer, where only the $-$I effect is present and the pK_a is significantly lower than that of pyridine (5·06).

Steric hindrance to protonation should be of no great importance even in the 2-isomer, since the reaction center is within the ring. It should be noted in this regard

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[8] G. Rigatti, private communication.

[9] O. Chalvet, R. Daudel and F. Peradejordi, in *Molecular Orbitals in Chemistry, Physics and Biology* (Edited by P. Löwdin and B. Pullman) pp. 475–484. Acad. Press, N.Y. (1964).

[10] H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.* **77**, 1723 (1955).

[11] See also J. P. Cartier and C. Sandorfy, *Canad. J. Chem.* **41**, 2759 (1963).

[12] A. Foffani and M. R. Foffani, *Rend. Accad. Nazl. Lincei* **23**, 60 (1957).

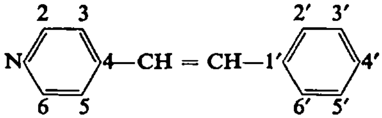
that the ΔH of dissociation of the methyl derivatives of pyridinium cations follows the behaviour of ΔG, suggesting that the electronic effects are predominant.[13]

The aforementioned results are in agreement with the Hammett σ constants for the styryl group reported by Kochi and Hammond ($\sigma_p = -0{\cdot}05$; $\sigma_m = +0{\cdot}025$).[14] The application of the Hammett relationship has been found valuable in the case of simple hetero-aromatic monocyclic compounds also. By using $\rho = 5{\cdot}71$, reported for pyridine derivatives,[15] we have obtained $\sigma_p = -0{\cdot}12$ and $\sigma_m = +0{\cdot}05$ (by the same method Katritzky has obtained $\sigma_p = -0{\cdot}11$[2]).

If our results are compared with the basic behaviour of phenylpyridines and vinylpyridines[6] it is apparent that pK_a's for styrylpyridines follow approximately the same trend. The ΔpK_a of 2- and 4-derivatives with respect to pyridine are however larger in the present series as the electron donating power of the styryl group includes both vinyl and phenyl contributions. The steric effect, important in the phenyl derivatives, is weaker here leading to a further decrease in the acid strength of styrylpyridinium ions.

Cis stilbazoles have pK_a's not much different from the *trans* compounds. The 4-derivative, where resonance effects are more important (see also the UV spectra, which show a maximum difference $\varepsilon_{\max}$ (*trans*) — $\varepsilon_{\max}$ (*cis*) for the 4-stilbazole) and where deviation from planarity may cause a serious lack of conjugation, exhibits a maximum difference of basicity between the two geometrical isomers; in the other cases, the difference is within the limits of experimental error.

(b) *Substitution on the pyridine nucleus.* The pK_a's of the methyl derivatives of stilbazoles are listed in Table 1. The notation used in this paper is as shown for the 4-stilbazole.



The CH_3-group, weakly +I and +M, increases the basicity, as expected. The effect on 2-stilbazole is higher in the 4 and 6 positions (*para* and *ortho* respectively to the N atom). Methylation in positions 3 and 5 (*meta*) show a smaller effect on the basicity, but the pK_a for the 3-derivative is slightly higher possibly because of the proximity of the styryl group.

The effects on 4-stilbazole, where measured, are similar.

The pK_a's of the two available *cis* derivatives (3-methyl-substituted 2- and 4-stilbazoles) follow the same trend as the parent stilbazoles. The decrease of pK_a with respect to the *trans* isomer is important only in the case of the 4-compound for the above reasons.

The dimethyl substitution shows an almost additive relationship for the effects of the substituents, corresponding to the values obtained for the monomethyl compounds, as in the case of dialkylpyridines.[16,10]

[13] C. T. Mortimer and K. J. Laidler, *Trans. Farad. Soc.* **55**, 1731 (1959).

[14] J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.* **75**, 3452 (1953).

[15] H. H. Jaffe and G. O. Doak, *J. Amer. Chem. Soc.* **77**, 4441 (1955); A. Bryson, *Ibid.* **82**, 4871 (1960).

[16] R. J. L. Andon, J. D. Cox and E. F. G. Herington, *Trans. Farad. Soc.* **50**, 918 (1954).

(c) *Substitution on the benzene nucleus.* IR absorption intensity measurements on the stretching $\nu_{C=C}$ of *trans* styrylpyridines, made by Katritzky,[2] indicated that the heteroatom and the 4′-substituent influence the electron distribution almost independently. The interaction between the *para* substituents on the benzene ring and the basic centre of 4-stilbazoles has been found to be stronger relative to other cases although small in comparison with the effect of direct substitution on the pyridine ring.[2]

This is confirmed by our data (Table 1) which are extended to 2- and 3-stilbazoles and also to 4-isomer substituted in *ortho* and *meta* positions. The methyl substitution has little influence on the basicity, particularly in position 2′, where the steric effects compensate the electronic ones. The effects of 4′-methyl-substitution are also small, especially in the 3-isomer as expected.

If the pK_a's of 4′-CH_3 and 4′-NO_2 derivatives of 3- and 4-stilbazoles are compared, it is apparent that the transmission of the electronic effect from the benzene ring through the ethylenic bond is much more marked when the basic centre can conjugate with the double bond. σ_m for 3-(*p*-substituted styryl)pyridines, positive for every type of 4′-substitution, has values of +0·04 and +0·11 for the groups *p*-CH_3 styryl and *p*-NO_2 styryl respectively (calculated from the experimental data using $\rho = 5{\cdot}71$). A sensibly higher $\Delta\sigma$ is found between the CH_3- to the NO_2- derivative of 4-styrylpyridines (see also [2]).

To obtain an idea of the different transmission of the effects of 4′-substituents to the basic centre in the 3- and 4-stilbazoles the Hammett ρ values can be calculated by plotting the pK_a against the normal σ_p values for the 4′-substituents.[17] For 4-stilbazoles Katritzky gives $\rho = 0{\cdot}85$. From our results, we can estimate a sensibly lower value for 3-stilbazoles, $\rho \simeq 0{\cdot}4$.

The data obtained for the disubstituted compounds show that the additivity of effects is satisfactorily verified—considering the small effect and the limits of error—also in the case of substitution on the two aromatic rings (mono-alkyl-substitution at both pyridine and benzene rings).

EXPERIMENTAL

Materials. The styrylpyridines cited in this paper were prepared by methods described elsewhere.[1] The *cis* isomers were purified before use by alumina chromatography.

UV spectra. The UV absorption data were obtained from both single and double beam grating Optica CF_4 spectrophotometers with thermostatic equipment. The maxima of the absorption spectra of the six parent isomeric styrylpyridines are reported in Table 2 for both the acid and basic forms. The data for the ring-substituted compounds are very similar.

TABLE 2. λ_{max}(mμ) AND LOG ε_{max} (IN PARENTHESIS) FOR THE ABSORPTION SPECTRA OF THE ACIDIC AND BASIC FORMS OF THE SIX ISOMERIC STYRYLPYRIDINES IN WATER-ETHANOL AT 15% VOL. OF ALCOHOL (SH = SHOULDER)

Stilbazole	Acid (pH ≃ 2)			Base (pH ≃ 8)		
2 trans	236 (3·85)	279 (3·92)	336 (4·45)	275 sh (4·12)		310 (4·42)
2 cis	~250 (3·81)		317 (3·91)	~260 sh (3·86)		289 (3·92)
3 trans	237 (3·97)		297 (4·33)		292 (4·38)	305 (4·39)
3 cis	247 (4·00)		283 (3·92)			276 (4·00)
4 trans	238 (3·96)		339 (4·50)	227 (4·13)		305 (4·47)
4 cis	235 (4·03)		326 (3·78)			279 (3·83)

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[17] The use of σ_p values for 4′-substituents in the case of 3-stilbazoles will be considered in detail in a next paper.

The spectra of styrylpyridinium ions were taken in 0·01N HCl and those of the neutral forms in buffer solutions of pH near 8. At this pH caution was necessary because of the instability of the solutions and in some cases it was necessary to follow the changes of absorption with time and to extrapolate these values to zero time. For the pK_a measurements, we used the longest wave length bands (presumed π–π[6]) at 300 mμ.

The contribution of the quinonoid forms in the protonated 2- and 4-isomers causes a noticeable bathochromic shift of the spectrum in acidic media. The shift is almost absent for the 3-isomers since a slight modification of the absorption due to the protonation is noted. This fact makes the pK_a measurements more difficult (see [6]). The hypsochromic displacement of the spectra of the *cis* isomers and the decrease in the extinction coefficient of their maxima can be accounted for by a deviation from planarity because of steric hindrance between the hydrogen atoms of the ethylenic group and the rings.[18] As in the case of stilbene, the difference between the absorption maxima of the *trans* and *cis* isomers is dependent on the ring substituents as the electron-donating and electron withdrawing groups can modify the resonance structures and the bond order between the aromatic rings.

IR spectra. For the IR data in CCl_4 solutions a Perkin–Elmer mod. 21 instrument with NaCl optics was used.

cis and *trans* Configurations were checked in most cases on the basis of IR analysis.[2,4,19] The vibrational spectra were observed both in the region of the $\nu_{C=C}$ stretching at 1642 ± 3 cm^{-1} and of the C—H deformation vibrations at 965 cm^{-1}. Very clear evidence for differentiation comes from the second region where strong absorptions are present in the *trans* compound due to out of plane in-phase vibrations of the olefinic hydrogen atoms (970 cm^{-1} for the 2-, 963 cm^{-1} for 3- and 4-isomer, respectively).

Some difficulties were encountered in obtaining the *cis* compounds entirely free from the *trans* isomer. The absence of the 965 cm^{-1} band was used as a test of good purity.

The corresponding in-plane vibration is less valuable because of the low intensity of the absorption in the 1300 cm^{-1} region (1306 for 2-, 1303 for 3- and 4-*trans* isomer); this band was often accompanied by a second weak band at 1326 ± 4 cm^{-1} in our compounds. Conversely, the *cis* compounds showed a medium intensity band at 1408 ± 4 cm^{-1} whose assignment is uncertain but can be tentatively attributed to an in-plane deformation mode.[19a]

Dissociation constants. All measurements were made at 25° in water–EtOH at 15% vol. EtOH. Solutions were freshly prepared and kept in the dark before use to avoid *trans-cis* photoisomerization. The buffers for the spectrophotometric measurements of pK_a (K_a = "apparent" dissociation constant of the conjugate acid) were Britton type of low constant ionic strength, $\mu = 0{\cdot}02$; under these experimental conditions the thermodynamic values can be obtained approximately (see inter alia[20]), by adding a ΔpK of $-0{\cdot}05$. The pH values of hydroalcoholic solutions were measured by a Radiometer instrument type TTT 1c with a Radiometer glass electrode G202C UH standardized by aqueous buffers.

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Our thanks also are due to Prof. A. R. Katritzky for his interest in this paper.

[18] see inter alia G. Riezebos and E. Havinga, *Rec. Trav. Chim.* **80**, 446 (1961).

[19] [a] N. Sheppard and D. M. Simpson, *Quart. Rev.* **6**, 1 (1952); L. J. Bellamy *The infrared spectra of complex molecules* pp. 34–53. Methuen, London (1958); [b] F. H. Clarke, G. A. Felock, G. B. Silverman and C. M. Watnick, *J. Org. Chem.* **27**, 533 (1962).

[20] U. Mazzucato, G. Cauzzo and G. Favaro, *Ric. Sci.* **33**(II-A) 309 (1963).