Substituent Effects in Tautomerism. Part II.[1] *para*-Substitution in *N*-Phenylamidines

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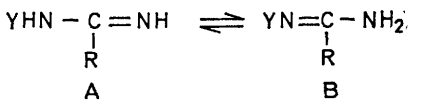
U.v. spectroscopy shows that the tautomeric equilibria in *N*-phenylacetamidine and its *p*-methoxy- and *p*-nitro-derivatives favour the imino *N*-aryl tautomers. Basicity measurements indicate pK_T 2.4 for *N*-phenylacetamidine. The basicities of *N'*-aryl-*NN*-dimethylacetamidines correlate with σ substituent constants with ρ −3.60.

RELATIVE to the numerous studies on tautomeric heteroaromatic compounds,[2] quantitative investigations of tautomeric equilibria in acyclic systems are few. In Part I [1] we initiated a study aimed, in part, to help remedy this situation, and we reported data for acyl- (1) and arylsulphonyl-amidines (2). Both series exist predominantly as tautomer B, the former having K_T, the tautomeric equilibrium constant, *ca.* 30 and the latter a K_T of 10^7. The present paper reports an extension of this study to certain *N*-arylamidines (3).



(1) Y = COR
(2) Y = SO_2R
(3) Y = aryl

In early work, Pyman [3] concluded that *N*-arylamidines (3) also exist predominantly as tautomer B, and this conclusion was later confirmed by reactivity studies [4] and i.r. [5] and u.v.[6] spectroscopy. However no systematic studies leading to quantitative estimates of K_T appear to have been made although certain basicity data, appropriate for such estimates are, in fact, available in the literature (see later). We now report u.v. spectral data and basicity data for (5a—c), (6a—g), and (7) and use the data to estimate K_T for *N*-phenylacetamidine and to assess electronic effects within the series (6a—g).

Preparation of Compounds.—The potentially tautomeric *N*-arylacetamidines (5) were prepared (Table 1) as shown in Scheme 1, using conditions simpler than procedures employing sealed tubes.[7] A series of model compounds (6a—g) was prepared using a modification of the method of ref. 8 (Table 2). Compound (7) was prepared by the pathway indicated.

EXPERIMENTAL

U.v. spectra were recorded using a Unicam SP 800 spectrophotometer and pK_a values were calculated [9] from spectrophotometric data obtained with a Unicam SP 500 series 2 spectrophotometer. Aqueous solutions for various pH ranges were prepared using hydrochloric acid (pH 0.6—3.3), acetic acid–sodium hydroxide (3.6—5.6), potassium dihydrogen phosphate–sodium hydroxide (5.2—7.8), boric acid–

[1] Part I, S.-O. Chua, M. J. Cook, and A. R. Katritzky, *J.C.S. Perkin II*, 1974, 546.

[2] For reviews see (*a*) A. R. Katritzky and J. M. Lagowski in *Adv. Heterocyclic Chem.*, 1963, **1**, 311, 339; 1963, **2**, 1, 27; (*b*) A. R. Katritzky, *Chimia (Switz.)*, 1970, **24**, 134, 236; (*c*) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, ' The Tautomerism of Heterocycles,' Academic Press, New York, 1975,

[3] F. L. Pyman, *J. Chem. Soc.*, 1923, **123**, 367, 3359; C. Chew and F. L. Pyman, *ibid.*, 1927, 2318.

[4] J.-A. Gautier, M. Miocque, C. Fauran, and A.-Y. le Cloarec, *Bull. Soc. chim. France*, 1971, 478.

[5] D. Prevorsek, *J. Phys. Chem.*, 1962, **66**, 769.

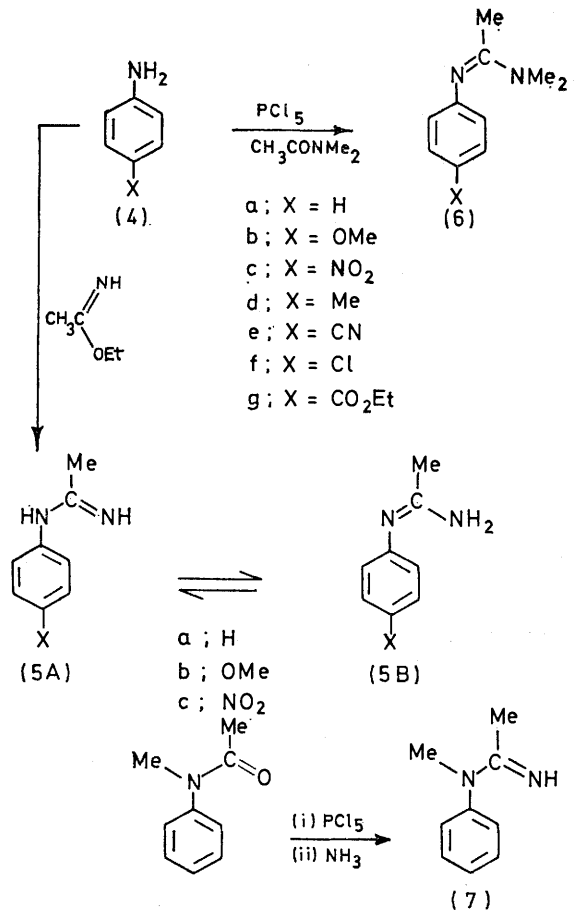
[6] J. A. Smith and H. Taylor, *J. Chem. Soc.* (*B*), 1969, **64**, 66.

[7] (*a*) R. L. Shriner and F. W. Neumann, *Chem. Rev.*, 1944, **35**, 363; (*b*) A. Bernthsen, *Annalen*, 1876, **184**, 321.

[8] A. J. Hill and I. Rabinowitz, *J. Amer. Chem. Soc.*, 1926, **48**, 732.

[9] A. Albert and E. P. Sergeant, ' The Determination of Ionisation Constants,' Chapman and Hall, London, 1971, p. 44.

sodium hydroxide (8.0—10.3), and sodium hydroxide (11.0—12.6).



SCHEME 1

N-*Arylacetamidines*(5).—Ethyl acetimidate (0.1 mol) and arylamine (0.1 mol) were kept 18 days in ether (50 ml). Solvents were evaporated and the residue distilled to give the amidine (see Table 1).

The *p*-methoxy-analogue (5b) was crystallized (benzene–light petroleum) instead of being distilled. For the *p*-nitro-compound (5c) the ethereal solution was heated under reflux for 20 days and the product separated on t.l.c. (alumina; chloroform–ethanol 5%).

N'-*Aryl*-NN-*dimethylacetamidines* (6).—*NN*-Dimethylacetamide (0.07 mol) was added to phosphorus pentachloride (0.05 mol), suspended in benzene, and dried over sodium (50 ml) with cooling. Arylamine (4) (0.1 mol) was then added and the whole heated under reflux for 3 h. Solvent was evaporated and the residue treated with excess of aqueous ammonia. The resultant paste was filtered and the residue extracted with ether (3 × 25 ml). The dried extract was distilled to give the amidine (see Table 2).

N-*Methyl*-N-*phenylacetamidine* (7).—*N*-Methylacetanilide (7.5 g) was added to phosphorus pentachloride (5.75 g) in benzene (30 ml), and the mixture heated under reflux for 6 h. After removal of most of the benzene the residue was added to an anhydrous solution of ammonia (9.0 g) in ethanol (50 ml) and the resulting mixture stirred for 6 h. The solvent was removed under reduced pressure and the residue extracted with chloroform. The chloroform extract was evaporated to dryness and the syrupy liquid chromatographed over alumina (preparative t.l.c. plate) to afford *N*-methyl-*N*-phenylacetamidine (1.2 g, 14%) as colourless needles, m.p. 72°. The base formed the hydrochloride salt, m.p. 249—252° (lit.,[10] m.p. 250°).

† The cations presumably have similar conformations: for recent studies of the conformations of amidinium cations and amidines see C. L. Perrin, *J. Amer. Chem. Soc.*, 1974, **96**, 5631; J. S. McKennis and P. A. S. Smith, *J. Org. Chem.*, 1972, **37**, 4173.

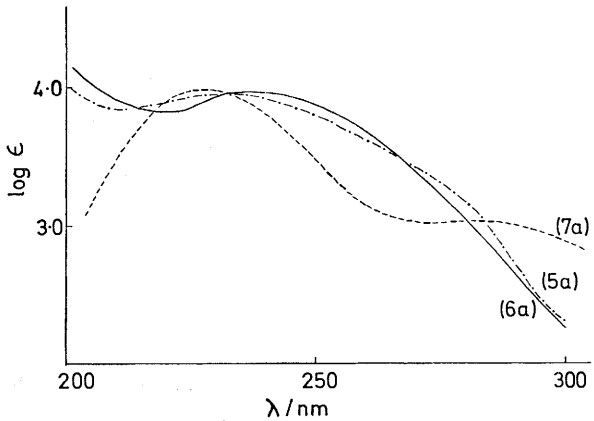


FIGURE 1 U.v. spectra (H_2O) of *NN*-dimethyl-*N'*-phenylacetamidine (pH 10.22) (6a); *N'*-phenylacetamidine (pH 10.22) (5a); and *N*-methyl-*N*-phenylacetamidine (pH 12.60) (7)

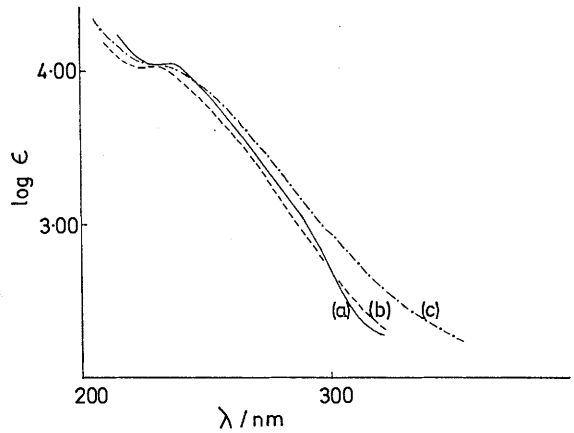


FIGURE 2 U.v. spectra (H_2O) of (a) *NN*-dimethyl-*N'*-phenylacetamidinium cation (pH 6.22); (b) *N'*-phenylacetamidinium cation (pH 6.05); and (c) *N*-methyl-*N*-phenylacetamidinium cation (pH 5.10)

RESULTS AND DISCUSSION

Tautomeric Structure of N-*Arylacetamidines*.—The u.v. spectrum of the neutral form of (5a) is compared with those of the two model compounds (6a) and (7) in Figure 1. Apart from a small bathochromic shift induced by *NN*-dimethylation the spectrum of (5a) resembles closely that of (6a) and confirms that the mobile compound exists predominantly as tautomer B. The same conclusion follows on comparison of the spectra of (5b and c) with those of (6b and c).

The spectra of the cations of (5a), (6a), and (7) (Figure 2) are all similar, demonstrating the formation of a common cation.† The pK_a values (Tables 1 and 3) for (5a)

[10] K. Matterstock and H. Jensen, Ger. P. 1,168,896/1964 (*Chem. Abs.*, 1964, **61**, 6991*f*).

and the model compounds (6a) and (7) further confirm that (5a) exists as tautomer B and provide a value for log K_T of 2.4. [$pK_T = pK_a$ (7) − pK_a (6a)].[2a] As the pK_a values for (5a) and (6a) are so close *N*-methylation appears to have little effect and this increases the reliability of the value for log K_T. In the absence of basicity data for *N*-aryl substituted derivatives of (7) it is not possible to derive values of K_T for other members of the series (5). However in a recent study of cyclic benzamidines (8), Fernandez *et al.*[11] showed that the basicity of the system (8) [which is analogous to (7)] is significantly less sensitive to *N*-aryl substituents than are the basicities of the series (5a) and (6a). Thus the pK_a values for the 4-methoxyphenyl (8a) and 4-nitrophenyl compound (8b), are 11.99 and 10.51 respectively. On this basis we predict that K_T for tautomeric *N*-arylamidines is less displaced towards tautomer (3B) when the *N*-phenyl group bears an electron-donating substituent and more in favour of tautomer (3B) when the substituent withdraws electrons. In the tautomeric equilibria of *N*-arylimines with *N*-aryleneamines, the imine forms predominate and K_T is raised on introducing a 4-methoxy-substituent, but lowered by a 4-nitro-group.[12]

An estimate of pK_T for *N*-phenylbenzamidine is possible from literature basicity data. Thus *NN*-dimethyl-*N'*-phenylbenzamidine, *N*-n-butyl-*N*-phenylbenzamidine, and the tetrahydropyrimidine (8c) have pK_a values of 7.8,[6] 10.4,[13] and 11.6 [11] respectively. Of the latter two values, that of 10.4 is probably to be preferred for tautomer A; in our previous study of *N*-acyl- and *N*-sulphonyl-amidines we found that tetrahydropyrimidine models were consistently more basic than open chain analogues.[1] This procedure then yields pK_T 2.6 for *N*-phenylbenzamidine, close to our value of 2.4 for *N*-phenylacetamidine. Analogously, there is no significant difference between K_T values for acetamides and benzamides, or between thioacetamides and thiobenzamides.[14]

Linear Free Energy Relationships.—Figure 3a and b

TABLE 1

p-Substituted *N*-phenylacetamidines and *N*-methyl-*N*-phenylacetamidine: physical constants, u.v. and basicity data

Compound no.	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	Ref.	U.v. spectra: Neutral form $\lambda_{max.}$/nm	Neutral form log ε	Cation $\lambda_{max.}$/nm	Cation log ε	pK_a
(5a)	40	68—70	70—71	*a*	235	4.06	231	4.02	9.95
(5b)	15	79—80	80—81	*b*	241	4.10	237	4.12	11.44
(5c)	12	170 Picrate	170 Picrate	*c*	357	4.12	282	4.16	7.56
(7)	14	249—252 Hydrochloride	250 Hydrochloride	10	376	4.17	234s	4.11	12.25

[a] F. C. Cooper and M. W. Partridge, *J. Chem. Soc.*, 1953, 255. [b] P. Reynaud, R. C. Moreau, and P. Fodor, *Compt. rend.*, 1966, **263C**, 788. [c] K. Brunner and F. Haslwanter, *Monatsh.*, 1927, **48**, 133.

TABLE 2

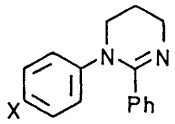
p-Substituted *NN*-dimethyl-*N'*-phenylacetamidines: physical constants and elemental analysis data

Compound no.	Crystal form	Yield (%)	M.p. (°C)	B.p. (°C)/[*p*/mmHg]	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
(6a)		20		86 [0.5]	73.72	8.5	17.3	$C_{10}H_{14}N_2$	74.0	8.7	17.3
(6b)	Prisms	30	30—32		68.95	8.0	14.5	$C_{11}H_{16}O_2$	68.7	8.4	14.6
(6c)	Prisms	18	95—97		58.30	6.4	20.0	$C_{10}H_{13}N_3O_2$	58.0	6.3	20.3
(6d)		23		88—90 [0.6]	75.38	9.1	16.1	$C_{11}H_{16}N_2$	75.0	9.0	15.9
(6e)	Prisms	30	51—53	122 [0.2]	70.25	6.9	22.4	$C_{11}H_{13}N_3$	70.4	7.0	22.6
(6f)		22		110—112 [1]	60.56	6.9	14.0	$C_{10}H_{13}N_2Cl$	61.0	6.6	14.2
(6g)		15		92—98 [0.1]	67.00	7.6	16.1	$C_{13}H_{18}N_2O_2$	66.7	7.7	15.9

TABLE 3

p-Substituted *NN*-dimethyl-*N'*-phenylacetamidines: u.v. spectral and basicity data

Compound no.	U.v. spectra: Neutral $\lambda_{max.}$/nm	Neutral log ε	Cation $\lambda_{max.}$/nm	Cation log ε	pK_a
(6a)	240	4.01	237	4.00	9.85
(6b)	245	4.08	242	4.05	11.15
(6c)	362	4.01	287	4.00	7.42
(6d)	245	4.04	230	4.06	10.81
(6e)	285	4.17	262	4.16	7.70
(6f)	247	4.17	240	4.16	9.28
(6g)	290	4.17	270	4.16	8.69



(8)

a; X = OMe
b; X = NO_2
c; X = H

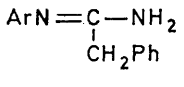
[11] B. Fernández, I. Perillo, and S. Lamdan, *J.C.S. Perkin II*, 1974, 1416; see also *idem.*, *ibid.*, 1973, 1371 for results for 1,2-diaryl-2-imidazolines.

[12] H. Ahlbrecht and S. Fischer, *Tetrahedron*, 1973, **29**, 659.

[13] E. Lorz and R. Baltzly, *J. Amer. Chem. Soc.*, 1949, **71**, 3992.

[14] M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J.C.S. Perkin II*, 1973, 1080.

shows plots of pK_a values for series (6) against σ^- (correlation coefficient, r 0.979) and σ (r 0.999), and demonstrates that the data are correlated better by the latter substituent parameter. As would be expected, the



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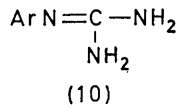

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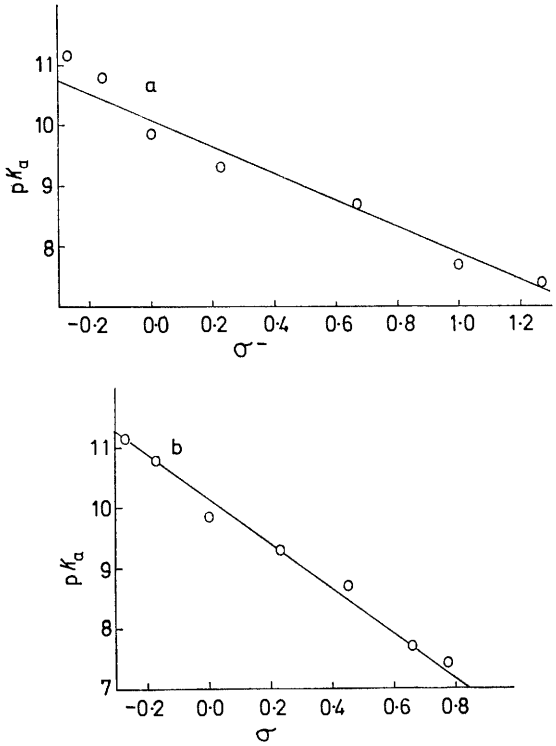
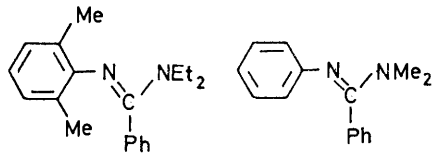


FIGURE 3 Plots of pK_a data against values for σ^- and σ (L. P. Hammett, 'Physical Organic Chemistry; Reaction Rates, Equilibria, and Mechanisms,' McGraw–Hill, New York, 1970, 2nd edn.)

value for ρ of -3.60 is significantly larger than that obtained elsewhere [11] for pK_a data of series (8) against σ (and σ^- for the 4-nitro-derivative) where $\rho = -0.948$. The implications of these trends for the variation of amidine K_T values with substituents was outlined above. Earlier Passem *et al.*[15] found that the pK_a values for series (9) are correlated by σ^0 values (ρ -2.09) and data for arylguanidines (10) [16] correlate significantly better against σ^0 than against σ^-.[17] The present data, when plotted against σ^0, have a slope of -3.36 with r 0.992. However discussion of the relative merits of using σ or σ^0 values for the range of substituents in series (6) hardly seems meaningful.

That the pK_a data for series (6), (9), and (10) are correlated by σ or σ^0 rather than σ^- implies that the amidine system and the *N*-aryl group are approaching coplanarity, or more strictly, that the site of protonation, the lone pair on the aryl substituted nitrogen, does not conjugate with the ring. This contention is contrary to the conclusion reached by Smith and Taylor [6] who reasoned that because the imino *N*-aryl group in (11) must be approximately at right angles to the plane of the amidine function, and because (11) and (12) have comparable basicity pK_a 7.7 and 7.8 respectively, then (12) must adopt the nonplanar conformation. However their discussion disregards the expected base strengthening effect of *o*-methyl substituents and, in our view, their similar basicities argue against (11) and (12) adopting similar conformations.



(11) (12)

Conclusions.—*N*-Phenylacetamidine (5a) favours the imino-tautomer (5aB) by log K_T $=2.4$. The variations of basicity with aryl substituent in the series (6), (8), and (9) suggest that K_T for *N*-arylamidines is larger when the aryl group carries an electron-withdrawing group but smaller when it bears an electron-donating substituent. The correlation of the basicity of series (6) with σ^0 implies that the *N*-aryl group and the amidine system approach coplanarity.

We thank Dr. C. D. Johnson for helpful discussions.

[5/1012 *Received*, 28*th May*, 1975]

[15] B. V. Passem, G. N. Kul'bitskii, N. A. Kalashnikova, and T. I. Vorobaeva, *Zhur. org. Khim.*, 1972, **8**, 1246.

[16] H. Koike, *Nippon Kagaku Zassahi*, 1962, **83**, 917 (*Chem. Abs.*, 1963, **58**, 13301*f*).

[17] S. Nadji, M.Sc. Thesis, University of East Anglia, 1974.