Substituent Effects in Tautomerism. Part I. Acyl- and Sulphonyl-amidines

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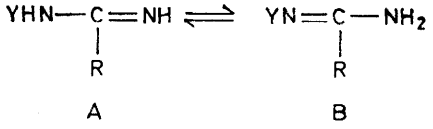
The tautomerism of acyl- and sulphonyl-amidines is reviewed. The structures of the cations of mobile and fixed forms of acetyl-, benzoyl-, mesyl-, and tosyl-amidines are established by u.v. spectroscopy. Quantitative pK_a measurements demonstrate that the H_2N–CR=N–Y form predominates for all series with K_T *ca.* 30 for the acyl- and *ca.* 10^7 for the sulphonyl compounds.

These results are compared with the tautomerism of 2-acylamino- and 2-sulphonamido-pyridines, and differences in tautomeric behaviour are rationalised.

QUANTITATIVE studies of the tautomeric structure of heteroaromatic compounds have been numerous and successful in explaining much of the pattern of substituent effects on such tautomeric equilibria.[1] By contrast, the study of non-heteroaromatic tautomeric equilibria, with the exception of keto–enol systems, has been less systematic and often merely qualitative.[2] Among the disadvantages of this situation is that comparisons, needed for aromaticity estimates,[3] between heteroaromatic equilibria and model systems cannot be made. This is the first of a series of papers attempting to fill this gap.

The present paper concerns acyl- and sulphonyl-amidines. The prototropic tautomerism of amidines has been reviewed recently by Schwenker and Bösl,[4] who concluded that the literature data were in part insufficiently based on experimental facts and that a new thorough investigation would be appropriate.

Prevorsek [5] has shown by i.r. spectral comparisons that alkyl groups tend to prefer attachment to the amino-nitrogen of the amidine system [*i.e.* (1A) preferred to (1B)] but that the reverse is true for aryl groups [*i.e.* (2B) preferred to (2A)]. The conclusions regarding *N*-arylamidines were in agreement with earlier work by Pyman,[6] and have recently been confirmed.[7] However, no quantitative information on the position of tautomeric equilibrium was obtained.



A B

Y = (1) alkyl, (2) aryl, (3) acyl, (4) sulphonyl

Schwenker and Bösl have also demonstrated [8] by i.r. spectroscopy that for a variety of sulphonyl-amidines, the tautomeric form predominates in which the sulphonyl group is attached to the imino-nitrogen [*i.e.* (4B)]. This situation also applies to acetylguanidine [9] [*cf.*

[1] 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, A. R. Katritzky, and P. Linda, *Adv. Heterocyclic Chem.*, in the press.

[2] No modern review is available; for an account of the older work see B. Eistert, 'Tautomerie and Mesomerie,' Stuttgart, 1938.

[3] *Cf.* M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J.C.S. Perkin II*, 1972, 1295.

[4] G. Schwenker and K. Bösl, *Pharmazie*, 1969, **24**, 653.

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

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

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

[8] G. Schwenker and K. Bösl, *Arch. Pharm.*, 1970, **303**, 980.

[9] R. Greenhalgh and R. A. B. Bannard, *Canad. J. Chem.*, 1961, **39**, 1017.

TABLE 1

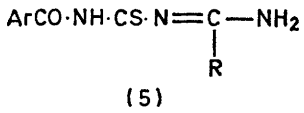
^{1}H N.m.r. chemical shift data [a]

Compound no.	Solvent	=C(Me)–	=C(H)–	YMeN–	MeN=	–N(Me)–	–[CH$_2$]$_n$–	YHN–/NH– [b]	Protons in Y group
(9)	CCl_4	7·8 (t) [c]					6·5 (t), 6·7 (m), [c] 8·2 (quint)		7·89 (3H, s)
(10)	CCl_4	8·2 (t) [c]					6·4 (t), 6·6 (m), [c] 8·2 (quint)		2·5 (5H, m)
(11)	$CDCl_3$	7·7 (t) [c]					6·3 (t), 6·6 (m), [c] 8·1 (quint)		6·93 (3H, s)
(12)	CCl_4	7·8 (t) [c]					6·3 (t), 6·7 (m), [c] 8·3 (quint)		2·3 (5H, m)
(13)	CCl_4	8·14		6·87	7·01				2·67 (5H, m)
(14)	$CDCl_3$	7·76		6·94	6·94				2·5 (4H, q)
									7·58 (3H, s)
(15)	$CDCl_3$		1·61			6·87, 6·94			7·85 (3H, s)
(16)	$CDCl_3$		1·35			6·84, 6·90			1·7 (2H, m)
									2·6 (3H, m)
(17)	$CDCl_3$		1·88			6·95, 7·07			6·85 (3H, s)
(18)	$CDCl_3$		1·83			6·90, 7·03			2·1 (2H, d)
									2·8 (2H, d)
(19)	D_2O						7·3 (4H, m)	5·34 (2H, s)	
(20)	$CDCl_3$	7·88						1·7 (2H, m)	2·5 (5H, q)
(21)	$CDCl_3$	7·89						3·3 (2H, b)	7·04 (3H, s)
(22)	$CDCl_3$	7·92						3·3 (2H, b)	2·2 (5H, m)

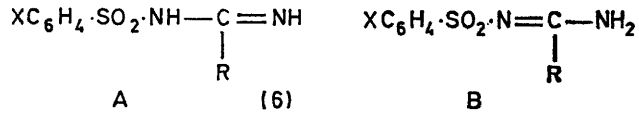
[a] All protons absorb as singlets except where indicated. [b] Time-averaged signal. [c] Homoallylic coupling ^5J *ca.* 1·4 Hz.

3B; R = NH_2)] and sulphanilyl-guanidine [10] [*cf.* (4B; R = NH_2)].

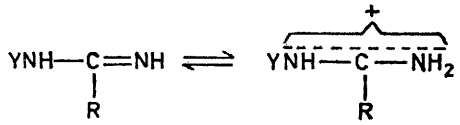
I.r. spectra of compounds (5) show bands for NH_2, which indicates their existence in the tautomeric form



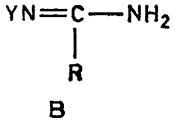
(5)



A (6) B



A (7) (8)

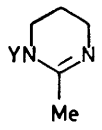


B

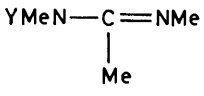
indicated.[11] Earlier claims [12,13] to have isolated individual tautomers (6A and B; R = Ph) of sulphonylamidines were disproven by Danilewicz and his coworkers; [14] they showed that for compound (6; R = Me) the tautomeric structure (6B) predominated by substituting ^{15}N for the terminal nitrogen and observation of N–H coupling. These results agree with earlier but less conclusive i.r. data reported by Tinkler.[15]

Aims of Present Work.—In contrast to the qualitative results previously reported, we wished to obtain quantitative energy differences between the two possible

Models for type A tautomers



Me

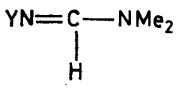


Me

(9) Y = COMe
(10) Y = COPh
(11) Y = SO_2Me
(12) Y = SO_2Ph

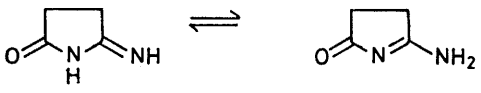
(13) Y = COPh
(14) Y = $SO_2 \cdot C_6H_4Me$-*p*

Models for type B tautomers

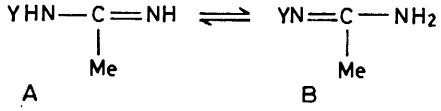


H

(15) Y = COMe
(16) Y = COPh
(17) Y = SO_2Me
(18) Y = $SO_2 \cdot C_6H_4Me$-*p*



A (19) B



Me Me

A B

(20) Y=COPh (21) Y = SO_2Me (22) Y = SO_2Ph

tautomers by application of the basicity method, which depends on the formation of the cation (8) for both the

[10] G. Schwenker, *Arch. Pharm.*, 1962, **295**, 753.
[11] J. Goerdeler and J. Neuffer, *Chem. Ber.*, 1971, **104**, 1580.
[12] H. J. Barber, *J. Chem. Soc.*, 1943, 101.
[13] S. J. Angyal and W. K. Warburton, *Austral. J. Sci. Res.*, 1951, **4**, 93.
[14] J. C. Danilewicz, M. J. Sewell, and J. C. Thurman, *J. Chem. Soc.* (*C*), 1971, 1704.
[15] R. B. Tinkler, *J. Chem. Soc.* (*B*), 1970, 1052.

tautomeric forms A and B. By preparing fixed models for A and B and comparing their basicities, K_T (= [B]/[A]) can be deduced (see ref. 1).

Preparation of Compounds.—Compounds (9)—(14) were prepared as models for type A tautomers; the series (15)—(18) provided models for type B tautomers. It also seemed desirable to examine some corresponding mobile tautomeric systems; accordingly we prepared (19) and the series (20)—(22). All compounds were prepared by literature methods, or by acylation or sulphonylation of the corresponding amidines. Structures were confirmed by n.m.r. spectroscopy (Table 1).

EXPERIMENTAL

I.r. spectra of suspensions in Nujol or of liquid films were obtained using a Perkin-Elmer 257 spectrophotometer. N.m.r. spectra (60 MHz) were recorded at 35° on a Perkin-Elmer R12 spectrometer. U.v. spectra were recorded using a Unicam SP 800 spectrophotometer and pK_a values were calculated [16] 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–sodium hydroxide (8·0—10·3), and sodium hydroxide (11·0—12·6). 1,4,5,6-Tetrahydro-2-methylpyrimidine was generously supplied by Pfizer Ltd.

Preparation of Compounds.—The following were prepared by literature methods: *N'*-acetyl-*NN*-dimethylformamidine [17] (15) (80%), b.p. 53° at 0·1 mmHg (lit.,[18] 60° at 0·25 mmHg); *N'*-benzoyl-*NN*-dimethylformamidine [17] (16) (93%), m.p. 72—74° (lit.,[18] 67—69°) (Found: C, 67·9; H, 6·8; N, 15·8. Calc. for $C_{10}H_{12}N_2O$: C, 68·2; H, 6·8; N, 15·9%); *N'*-methylsulphonyl-*NN*-dimethylformamidine [19] (17) (43%), m.p. 83—84° (lit.,[19] 80—81°) (Found: C, 32·0; H, 6·6; N, 18·7. Calc. for $C_4H_{10}N_2O_2S$: C, 32·0; H, 6·7; N, 18·7%); *NN*-dimethyl-*N'*-*p*-tolylsulphonylformamidine [19] (18) (80%), m.p. 134—135° (lit.,[20] 133—133·5°) (Found: C, 53·1; H, 6·4; N, 12·7. Calc. for $C_{10}H_{14}N_2O_2S$: C, 53·1; H, 6·2; N, 12·4%); 5-amino-$\Delta^{1(5)}$-pyrrolin-2-one [21] (19) (61%), m.p. 241—243° (decomp.) [lit.,[21] 250° (decomp.)] (Found: C, 48·7; H, 6·1; N, 28·3. Calc. for $C_4H_6N_2O$: C, 49·0; H, 6·1; N, 28·6%); *N*-methylsulphonylacetamidine (21) (12%), m.p. 70—75° (lit.,[22] 66—68°) (Found: C, 26·4; H, 5·8; N, 20·5. Calc. for $C_3H_8N_2O_2S$: C, 26·5; H, 5·9; N, 20·6%).

N-*Benzoylacetamidine* (20).—A solution of benzoyl chloride (2·8 g) in Me_2CO (15 ml) was added dropwise during 35 min to a stirred ice-cooled mixture of acetamidine hydrochloride (2 g), aqueous 50% NaOH (4 ml), and Me_2CO (20 ml). After a further 15 min stirring, the upper layer was separated and evaporated. Water (20 ml) was added to the residue and the mixture extracted with $CHCl_3$ (3 × 15 ml). Evaporation of the dried extract gave a solid which on recrystallisation from $CHCl_3$–light petroleum (b.p. 30—40°) afforded *N*-benzoylacetamidine (2·6 g, 96%) as prisms, m.p. 89—92° (lit.,[23] 92—93·5°) (Found: C, 66·7; H, 6·2; N, 17·5. Calc. for $C_9H_{10}N_2O$: C, 66·7; H, 6·2; N, 17·3%).

N-*Phenylsulphonylacetamidine* (22).—Benzenesulphonyl chloride (1·4 ml) was added to a mixture of acetamidine hydrochloride (1 g), aqueous 50% NaOH (2 ml), and Me_2CO (10 ml). The mixture was shaken vigorously for 10 min. The upper layer was removed and partially evaporated to precipitate N-*phenylsulphonylacetamidine* (1·15 g, 72%) as prisms (from EtOAc), m.p. 121·5—122·5° (Found: C, 48·6; H, 5·2; N, 13·9. $C_8H_{10}N_2O_2S$ requires C, 48·5; H, 5·1; N, 14·1%).

1-*Benzoyl*-1,4,5,6-*tetrahydro*-2-*methylpyrimidine* (10) *Hydrochloride.*—A solution of benzoyl chloride (1·9 g) in Me_2CO (10 ml) was added dropwise during 30 min to a stirred ice-cooled mixture of 1,4,5,6-tetrahydro-2-methylpyrimidine (1·35 g), aqueous 50% NaOH (8 ml), and Me_2CO (20 ml). The upper layer was evaporated off. Water (10 ml) was added to the residue and the whole was extracted with $CHCl_3$ (3 × 15 ml). Evaporation of the dried extract and distillation of the residue afforded 1-*benzoyl*-1,4,5,6-*tetrahydro*-2-*methylpyrimidine* (1·3 g, 47%) as a liquid, b.p. 126° at 0·5 mmHg, which formed a *hydrochloride* as prisms, m.p. 152—157° (decomp.) (from EtOH–Et_2O) (Found: C, 60·6; H, 6·4; N, 11·7. $C_{12}H_{14}N_2O$,HCl requires C, 60·4; H, 6·3; N, 11·7%).

1,4,5,6-*Tetrahydro*-2-*methyl*-1-*phenylsulphonylpyrimidine* (12) *Hydrochloride.*—A solution of benzenesulphonyl chloride (2·5 g) in Me_2CO (10 ml) was added dropwise during 30 min to a stirred, ice-cooled mixture of 1,4,5,6-tetrahydro-2-methylpyrimidine (1·35 g), aqueous 50% NaOH (8 ml), and acetone (20 ml). After 10 min stirring, the upper layer was evaporated, water (10 ml) was added to the residue, and the whole was extracted with $CHCl_3$ (3 × 15 ml). The extract was dried and the solvent removed; distillation of the residue afforded the *sulphonylamidine* (12) (1·5 g, 46%) as a pale yellow liquid, b.p. 145—147° at 0·7 mmHg. This gave a *hydrochloride* as needles (from EtOH), m.p. 158—159° (Found: C, 47·8; H, 5·4; N, 10·0. $C_{11}H_{14}N_2O_2S$,HCl requires C, 48·1; H, 5·5; N, 10·2%).

1-*Acetyl*-1,4,5,6-*tetrahydro*-2-*methylpyrimidine* (9).—1,4,5,6-Tetrahydro-2-methylpyrimidine (5 g) dissolved in benzene (10 ml) was cooled to 0°. Acetyl chloride (2 g) in benzene (10 ml) was added dropwise during 30 min with stirring, which was continued for a further 30 min at 0°. A precipitate was filtered off and the solvent was removed under vacuum. The liquid residue was distilled to give the *acetylamidine* (9) (2 g, 28%) as a liquid, b.p. 63·5° at 0·3 mmHg (Found: C, 59·8; H, 8·7; N, 20·0. $C_7H_{12}N_2O$ requires C, 60·0; H, 8·6; N, 20·0%).

N-*Benzoyl*-NN'-*dimethylacetamidine* (13).—*NN'*-Dimethylacetamidine hydrochloride [24] (0·61 g) was dissolved in aqueous 10% NaOH (10 ml). Benzoyl chloride (0·7 ml) was added and the mixture was vigorously shaken for 10 min, then extracted with $CHCl_3$ (3 × 10 ml). The extract was dried (Na_2SO_4) and evaporated under vacuum. The liquid residue was distilled in a microdistillation unit (oil-bath temp. 90°; 0·6 mmHg) to give N-*benzoyl*-NN'-*dimethylacetamidine* (0·3 g, 30%) as a liquid (Found: C, 69·5; H, 7·2; N, 14·3. $C_{11}H_{14}N_2O$ requires C, 69·5; H, 7·4; N, 14·7%).

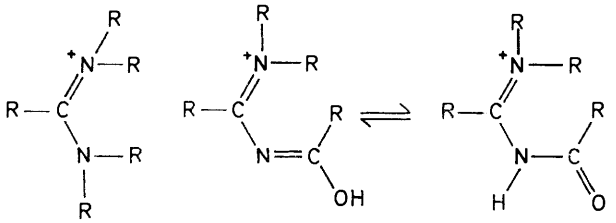
[16] A. Albert and E. P. Sergeant, 'The Determination of Ionisation Constants,' Chapman and Hall, London, 1971, p. 44.
[17] U.S.P. 3,121,084/1964 (*Chem. Abs.*, 1964, **60**, 13,197*d*).
[18] Belg.P. 629,972/1963 (*Chem. Abs.*, 1964, **61**, 1803*c*).
[19] G. Tosolini, *Chem. Ber.*, 1961, **94**, 2731.
[20] C. King, *J. Org. Chem.*, 1960, **25**, 352.
[21] J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 1954, 442.
[22] G.P. 839,493/1952 (*Chem. Abs.*, 1953, **47**, 1737*b*).
[23] G. Palazzo, G. Strani, and M. Tavella, *Gazzetta*, 1961, **91**, 1085.
[24] A. J. Hill and I. Rabinowitz, *J. Amer. Chem. Soc.*, 1926, **48**, 732.

1,4,5,6-*Tetrahydro*-2-*methyl*-1-*methylsulphonylpyrimidine* (11).—Methanesulphonyl chloride (1 ml) was added to a solution of 1,4,5,6-tetrahydro-2-methylpyrimidine (0·9 g) in Et_3N (2 ml) and benzene (15 ml) at 0°. The solution was heated under reflux for 3 h. The precipitate was removed and the solvent distilled off under vacuum. The liquid residue was distilled in a microdistillation unit (oil-bath temp. 100°; 1·0 mmHg) to give the *sulphonylamidine* (11) (0·16 g, 10%), as a liquid which solidified to white prisms, m.p. *ca.* 20° (Found: C, 41·4; H, 7·0; N, 15·9. $C_6H_{12}N_2O_2S$ requires C, 40·9; H, 6·9; N, 15·9%).

NN'-*Dimethyl*-N-p-*tolylsulphonylacetamidine* (14).—*NN'*-Dimethylacetamidine hydrochloride (1·3 g) was added to aqueous 50% NaOH (2 ml) and Me_2CO (10 ml). Toluene-*p*-sulphonyl chloride (1·9 g) in Me_2CO (10 ml) was added and the solution was shaken vigorously for 10 min, diluted with water (100 ml), and set aside for 1 h. The precipitate was filtered off and recrystallised from 95% EtOH to give the *sulphonylamidine* (14) (1·45 g, 57%) as prisms, m.p. 71·5—73·5° (Found: C, 55·1; H, 6·7; N, 11·6; S, 13·1. $C_{11}H_{16}N_2O_2S$ requires C, 55·0; H, 6·7; N, 11·7; S, 13·3%).

RESULTS AND DISCUSSION

Structure of Amidinium Cations.—Any discussion of tautomeric equilibria in terms of pK_a values must be based on knowledge of the structure of the cations formed. Whereas no doubt exists regarding the structure (23) of simple amidinium cations,[25] and sulphonyl-amidinium cations would be expected to be similar (as sulphonamides are protonated on nitrogen [26]), the matter is more open for the cations of acyl-amidines, where possibilities such as (24A) ⇌ (24B) exist. Additionally, amidinium cations [27] show restricted rotation about C–N bonds, and thus possibilities of *cis–trans* isomerism exist.

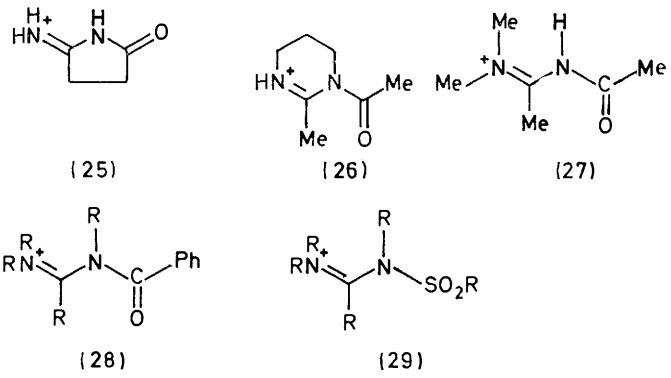


(23) A (24) B

In the acetyl-amidinium series, the close correspondence between the u.v. spectra of the cations of (9) and (15) (Figure 1) indicates similar structures, (26) and (27). The cation of the 5-amino-$\Delta^{1(5)}$pyrrolin-2-one (19) must have a different structure: the low intensity appears to preclude *O*-protonation, thus pointing to structure (25).

In the benzoyl-amidine series, all the cations possess similar u.v. absorption (Figure 2), and the same applies to each of the sulphonyl-amidine series (Figures 3 and 4). We believe that the cation structures are (28) and (29).

U.v. Spectra of the Neutral Species (*Figures* 5—8).—An unambiguous deduction of the predominant tautomer



(25) (26) (27)

(28) (29)

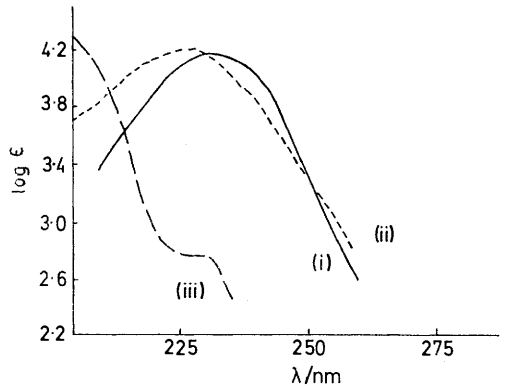


FIGURE 1 Cation species of (i) 1-acetyl-1,4,5,6-tetrahydro-2-methylpyrimidine (9) at pH 3, (ii) *N'*-acetyl-*NN*-dimethylformamidine (15) at pH 3 (half-life *ca.* 5 min), and (iii) 5-amino-$\Delta^{1(5)}$-pyrrolin-2-one (19) at pH 2·5

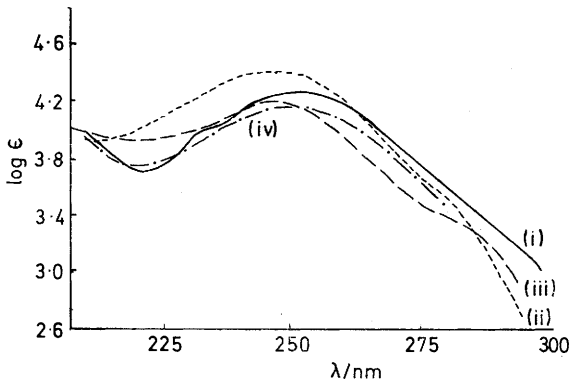


FIGURE 2 Cation species of (i) 1-benzoyl-1,4,5,6-tetrahydro-2-methylpyrimidine (10) at pH 4, (ii) *N'*-benzoyl-*NN*-dimethylformamidine (16) at pH 1·5, (iii) *N*-benzoylacetamidine (20) at pH 2·5, and (iv) *N*-benzoyl-*NN'*-dimethylacetamidine (13) at pH 1

from the u.v. spectra is possible for the benzoyl-amidine series. *N*-Benzoylacetamidine clearly exists predominantly in form (20B): its u.v. spectrum resembles that of

[25] J. C. Grivas and A. Taurins, *Canad. J. Chem.*, 1959, **37**, 1260.

[26] P. O. I. Virtanen and K. Heinamaki, *Suomen Kem.* (*B*), 1969, **42**, 142 (*Chem. Abs.*, 1969, **70**. 118,627*h*).

[27] R. C. Neuman, jun., G. S. Hammond, and T. J. Dougherty, *J. Amer. Chem. Soc.*, 1962, **84**, 1506.

(16) and not that of (13) (Figure 6). The opposite conclusion might be drawn from Figure 5 regarding the *acetyl-amidine* series; however we believe (see later discussion) that the potentially tautomeric compound exists as (19B), and that the dissimilarity of its u.v.

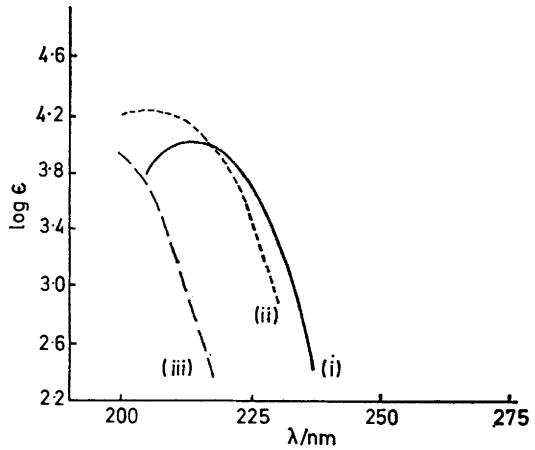


FIGURE 3 Cation species of (i) 1,4,5,6-tetrahydro-2-methyl-1-methylsulphonylpyrimidine (11) at pH 5·5, (ii) *NN*-dimethyl-*N'*-methylsulphonylformamidine (17) at H_0 −3·48, and (iii) *N*-methylsulphonylacetamidine (21) at H_0 −3·30

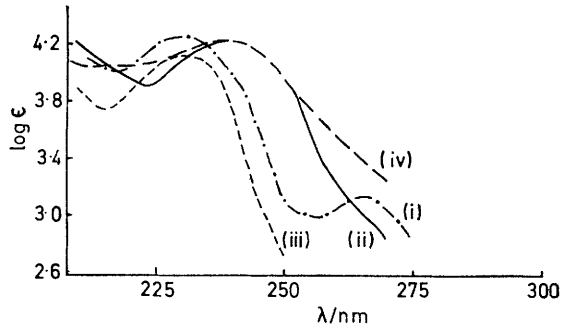
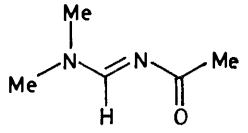


FIGURE 4 Cation species of (i) 1,4,5,6-tetrahydro-2-methyl-1-phenylsulphonylpyrimidine (12) at pH 4, (ii) *NN*-dimethyl-*N'*-*p*-tolylsulphonylformamidine (18) at H_0 −2·95, (iii) *N*-phenylsulphonylacetamidine (22) at H_0 −2·95, and (iv) *NN'*-dimethyl-*N*-*p*-tolylsulphonylacetamidine (14) at pH 3

spectrum to that of (15) is a consequence of the existence of the latter in the *cis,trans*-structure (30).



(30)

The u.v. spectra of the neutral species of the two sulphonyl series (Figures 7 and 8) are too similar to allow definite conclusions, although, when allowance is made for the bathochromic effects of alkyl substitution, the spectra do give some indication of the existence of the tautomeric compound in forms (21B) and (22B).

pK_a *Measurements.*—(a) *Acetyl and benzoyl series* (*Table* 2). Interpretation of the pK_a measurements is not straightforward: in the benzoyl series the parent compound (20) is considerably *more* basic than two of the

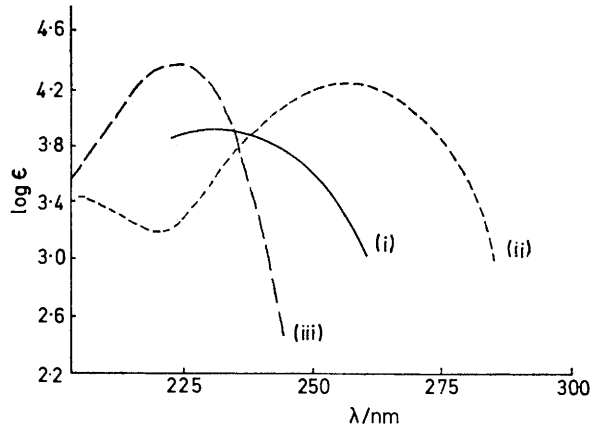


FIGURE 5 Neutral species of (i) 1-acetyl-1,4,5,6-tetrahydro-2-methylpyrimidine at pH 12 (half-life *ca.* 3 min), (ii) *N'*-acetyl-*NN*-dimethylformamidine at pH 8 (half-life *ca.* 30 min), and (iii) 5-amino-$\Delta^{1(5)}$-pyrrolin-2-one at pH 7

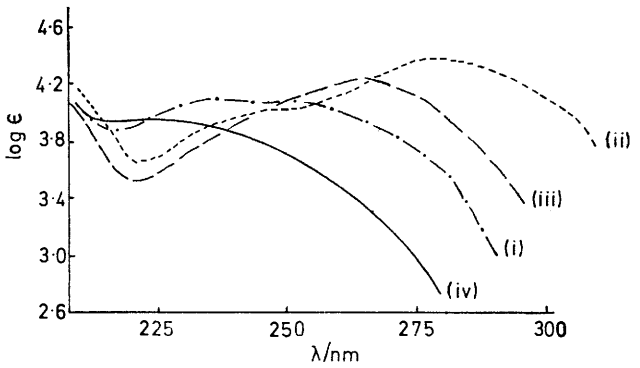


FIGURE 6 Neutral species of (i) 1-benzoyl-1,4,5,6-tetrahydro-2-methylpyrimidine at pH 11, (ii) *N'*-benzoyl-*NN*-dimethylformamidine at pH 8·5, (iii) *N*-benzoylacetamidine at pH 10·5, and (iv) *N*-benzoyl-*NN'*-dimethylacetamidine at pH 10

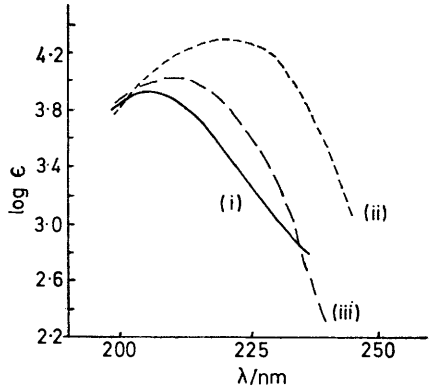


FIGURE 7 Neutral species of (i) 1,4,5,6-tetrahydro-2-methyl-1-methylsulphonylpyrimidine at pH 10, (ii) *NN*-dimethyl-*N'*-methylsulphonylformamidine at pH 3, and (iii) *N*-methylsulphonylacetamidine at pH 2

models [(13) and (16)] and further the two 'similar' models [(10) and (13)] show a considerable difference in basicity. The greater basicity of (20) as compared to

(16) is probably due to the cation (31) being stabilised by hydrogen-bonding with solvent water, as compared with (32).* Cation (33) is presumably destabilised relative to (31) by about the same amount. If this is assumed, then the most appropriate pK_a difference to use as an approximation for pK_T is that between (16) and (13). The conclusion is then that $K_T \simeq 30$ in favour of the 'conjugated' form (20B). The lower basicity of (13) compared to (10) is probably due to (13) existing as the free base in some more favoured rotameric form, possibly as (34).

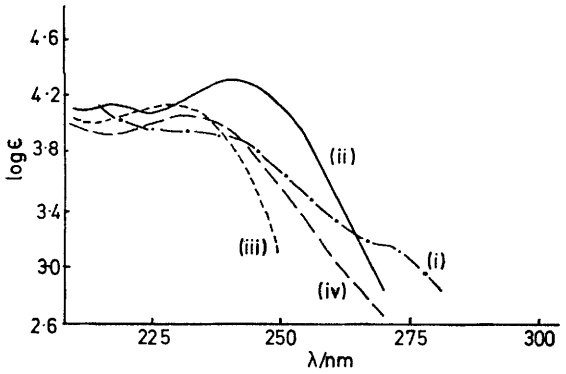
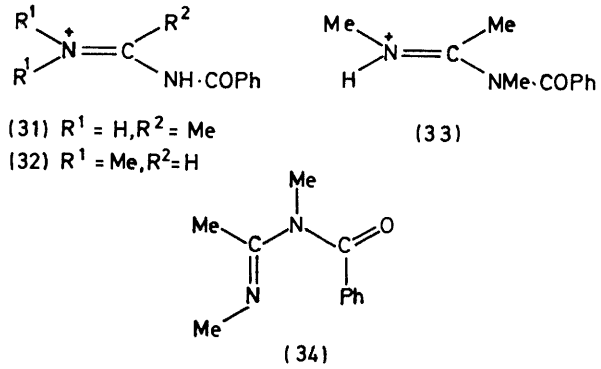


FIGURE 8 Neutral species of (i) 1,4,5,6-tetrahydro-2-methyl-1-phenylsulphonylpyrimidine at pH 10·5, (ii) *NN*-dimethyl-*N'*-*p*-tolylsulphonylformamidine at H_0 −0·65, (iii) *N*-phenylsulphonylacetamidine at pH 4·6, and (iv) *NN'*-dimethyl-*N*-*p*-tolylsulphonylacetamidine at pH 10

In models of both types, substitution of acetyl for benzoyl [*i.e.* (16) ⟶ (15); (10) ⟶ (9)] raises the pK_a by $1·4 \pm 0·1$ pK units: this suggests that the tautomeric equilibria in the two series are similar.



(b) *Methylsulphonyl and arylsulphonyl series* (*Table* 2). Here the qualitative interpretation is clear: the tautomeric compounds exist predominantly in forms (21B) and (22B) because they are weak bases, as are models of type B, whereas type A models are quite strong bases. Comparison of the arylsulphonyl and the benzoyl series is illuminating: the type A models are reduced in basicity by a mere 0·47 or 0·01 pK_a units on replacement of PhCO by $ArSO_2$. The reduction in basicity is 6·04 pK_a units for the type B model and 7·10 units for

TABLE 2

pK_a and u.v. spectral data

	Compound no.	Y	pK_a	Buffer	Concn. (10^{-3}M)	λ/nm [a]	Cation $\lambda_{max.}$ ε(× 10^{-3})	Neutral form $\lambda_{max.}$ ε(× 10^{-3})
Models for type A [YHN–C=NH] (R) tautomers	(9)	COMe	9·49 [b]				231 (decomp.) (pH 3)	230 (decomp.) (pH 12)
	(10)	COPh	8·04	KH_2PO_4–NaOH H_3BO_3–NaOH	5·3	250	250 17·8 (pH 4)	240 (decomp.) (pH 11)
	(11)	SO_2Me	7·9	KH_2PO_4–NaOH H_3BO_3–NaOH	12·0 (1% EtOH)	219	213 10·8 (pH 5·5)	205 8·2 (pH 10)
	(12)	SO_2Ph	7·57	KH_2PO_4–NaOH H_3BO_3–NaOH	6·8	230	230 18·2 (pH 4)	225[sh] 8·9 (pH 10·5)
	(13)	COPh	5·88	HOAc–NaOH KH_2PO_4–NaOH	7·0	250	248 13·5 (pH 1)	222 8·9 (pH 10)
	(14)	$SO_2C_6H_4$·Me·*p*	5·89	HOAc–NaOH KH_2PO_4–NaOH	8·3	247	239 17·6 (pH 3)	232 11·8 (pH 10)
Models for type B [YN=C–NH_2] (R) tautomers	(15)	COMe	5·91	HOAc–NaOH KH_2PO_4–NaOH	4·4	257	227 (decomp.) (pH 5)	257(decomp.) (pH 8·0)
	(16)	COPh	4·36	HCl HOAc–NaOH	4·3 (1% EtOH)	280	247 23·1 (pH 1·5)	277 22·1 (pH 8·5)
	(17)	SO_2Me	−1·47 [c]	H_2SO_4	5·2	225	206 13·6 (H_0 − 4·13)	221 16·5 (pH 4·6)
	(18)	$SO_2C_6H_4$·Me·*p*	−1·68 [d]	H_2SO_4	7·2	222	239 17·8 (H_0 − 2·95)	239 19·5 (H_0 − 0·65)
	(19)	$-CO\cdot CH_2CH_2-$	4·9	HCl HOAc–NaOH	3·4	224	None above 202 (pH 2·5)	224 23·9 (pH 7)
Tautomerically mobile systems	(20)	COPh	6·87	KH_2PO_4–NaOH H_3BO_3–NaOH	5·4	270	247 14·80 (pH 2·5)	265 16·1 (pH 10·5)
	(21)	SO_2Me	0·22 [e]	H_2SO_4	9·1	215	None above 200 (H_0 − 2·77)	211 9·89 (pH 4)
	(22)	SO_2Ph	−0·23 [f]	H_2SO_4	9·4	215	230 13·4 (H_0 − 2·95)	227 13·7 (pH 4·6)

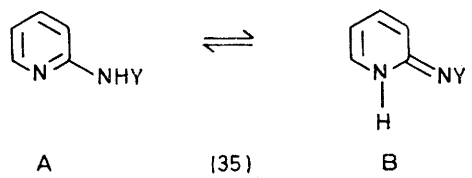
[a] Analytical wavelength used for pK_a determination. [b] Potentiometric titration (E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, 1962, **27**, 3764). [c] H_0 Acidity function assumed, $n = 1·21$. [d] H_0 Acidity function assumed, $n = 1·18$. [e] H_0 Acidity function assumed, $n = 1·13$. [f] H_0 Acidity function assumed, $n = 0·89$.

* The effect of *N*-methyl groups on amidine basicity has been little investigated, but appears not to be large for benzamidine [J. A. Smith and H. Taylor, *J. Chem. Soc.* (*B*), 1969, 64].

the mobile compound. Similar considerations as outlined above for the benzoyl series indicate that ΔpK_a between (18) and (14) is the best approximation to give $pK_T \doteq 7{\cdot}5$.

Again for the three cases where comparison is possible, substitution of $ArSO_2$ by $MeSO_2$ increases the pK_a by 0·33, 0·21, and 0·45 pK_a units. This, we believe indicates that pK_T for the methylsulphonyl amidine is similar to that deduced for the phenylsulphonyl analogues.

Comparison of Tautomerism of Corresponding 2-Acylamino- and 2-Sulphonamido-pyridines.—Relevant comparisons [28] are collected in Table 3. For the 2-acetamido- (35A) over (35B) as has previously been demonstrated for amide–imidol and related tautomeric systems.[3] Quantitatively the differences in resonance energies of the

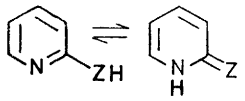


A (35) B

various types of structure of type (35B) are of doubtful significance in view of the approximations made, but the sulphonyl group does appear to have a similar stabilising effect as might be expected.

TABLE 3

Pyridinoid/pyridonoid resonance energy difference



Z	pK_a (Z–Me)	pK_a (N–Me)	log K_u	$\Delta G°_u$/ kcal mol^{-1}	log K_s [a]	$\Delta G°_s$/ kcal mol^{-1}	$A_{py} - A_x$ [b]
NH	6·86 [c]	13·02 [d]	6·16	−8·5	0	0	−8·5
N-Ac	2·01 [e]	7·12 [e]	5·11	−7·0	−1·5	1·8	−8·8
N-Ms	1·73 [f]	−0·33 [f]	−2·06	2·8	−7·5	10·3	−7·5
N-Ts	(Comparison of u.v. spectra)		−1·82 [g]	2·5	−7·5	10·3	−7·8

[a] See text. [b] Aromatic resonance energy differences are derived from $\Delta G°$ values according to method (i) in ref. 3. [c] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240. [d] Ref. 3. [e] Ref. 28*a*. [f] Ref. 28*b*. [g] Yu N. Sheinker, E. M. Peresleni, N. P. Zosimova, and Yu. I. Pomerantsev, *Russ. J. Phys. Chem.*, 1959, **33**, 303.

and 2-methylsulphonylamino-series, we have taken the pK_a values of both methylated models, on the same grounds as discussed above, and for consistency. Comparison of these results with those just discussed indicates that incorporation of the amidinium system into the pyridine ring stabilises the amino-form of type (35) by *ca.* 5—6 log K_T units (*ca.* 7—8 kcal mol^{-1}). This is due to the greater aromatic resonance energy of forms

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[28] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, (*a*) 1959, 1317; (*b*) 1961, 378.