Aromaticity and Tautomerism. Part II.[1] The 4-Pyridone, 2-Quinolone, and 1-Isoquinolone Series

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Aromatic resonance energies for 4-pyridone and its analogues are similar to those for the 2-pyridone series. For the bicyclic compounds, the differences in aromaticity between the quinolinoid and the quinolonoid forms are significantly less than for the monocyclic derivatives. A new acidity function $H_{-(q)}$ is derived for the deprotonation of methyl quaternary salts to neutral heterocyclic methide and imine bases. Quantitative tautomeric ratios are reported for the thioamide–thioimidate equilibrium in an Appendix.

PART I [1] presented quantitative data on the aromatic stabilisation of 2-pyridone and related compounds, derived from tautomeric equilibria. We now extend this approach to the 4-pyridone, 2-quinolone, and 1-isoquinolone series by comparing the tautomeric equilibria (1) ⇌ (2), (5) ⇌ (6), and (9) ⇌ (10) with (3) ⇌ (4), (7) ⇌ (8), and (11) ⇌ (12), respectively.

From the comparison of the ring currents in 1-methyl-2-pyridone and in 1-methyl-4-pyridone [2] Jackman and his co-workers concluded that the latter compound is less aromatic than the former and Batts and Spinner have recently concluded from n.m.r. data that neither 4-pyridone nor 4-pyridone imine have appreciable aromaticity.[3] MO calculations by Dewar [4] suggest to us that both pyridones have considerable aromatic character although 4-pyridone may be somewhat less delocalized than 2-pyridone.

Little quantitative data are available on the ' aroma-

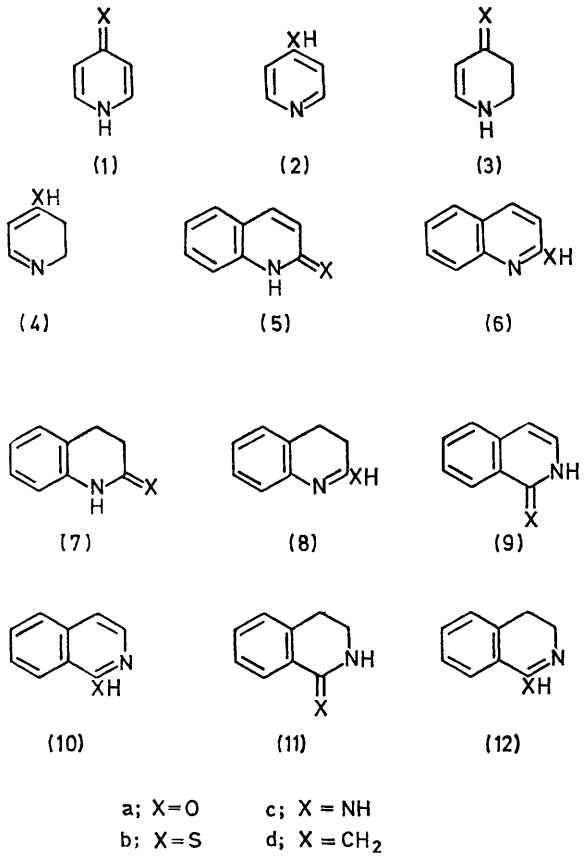
[1] Part I, M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J.C.S. Perkin II*, 1972, 1295.

[2] G. G. Hall, A. Hardisson, and L. M. Jackman, *Tetrahedron*, 1963, **19**, (suppl. 2), 101.

[3] B. D. Batts and E. Spinner, *Austral. J. Chem.*, 1969, **22**, 2595.

[4] N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Amer. Chem. Soc.*, 1970, **92**, 2929.

ticity ' of 2-quinolone, 1-isoquinolone, and related compounds. The different long-range coupling of the methyl



group to the *ortho*-hydrogen in 4-methyl-2-quinolone (J 1·3 Hz) and in 4-methyl-2-chloroquinoline (J 1·0 Hz) on 1-alkyl-2-quinolone and 1-alkyl-2-quinolone methide [6] and on 2-quinolone.[7] Dewar's calculation on the tautomeric 2-quinolone and 1-isoquinolone [4] suggested that the difference between the resonance energies of these compounds and quinoline or isoquinoline is less than for the monocyclic analogues.[8]

Tautomeric equilibrium constants follow from pK_a data of fixed models (normally the *N*-Me and *X*-Me analogues of the tautomers) and the present work has necessitated measurement of the pK_a values of many bases. We found that the deprotonation of quaternary salts (methiodides) of methyl- and amino-pyridines and methyl-quinolines and -isoquinolines to give neutral methides and imines did not follow the existing H_- scales and we therefore set up a new scale. Other pK_a values had to be obtained by special methods due to rapid hydrolysis (see Experimental section).

RESULTS AND DISCUSSION

4-Pyridone and Related Compounds (Table 1).—The pK_a values quoted for *N*- and *X*-methyl derivatives of the tautomeric pyridines are taken from the literature except for 1-methyl-4-pyridone imine and 1-methyl-4-pyridone methide which were redetermined. The previous value for 1-methyl-4-pyridone imine was subject to some uncertainty [3] (pK_a = 15—16). The only value for 1-methyl-4-pyridone methide previously reported [9] was >16·7: we measured the pK_a as 19·46 ± 0·04 using a procedure derived from that of Bowden and Cockerill [10] (see Experimental section).

The pK_a values for *N*- and *X*-Me derivatives of compounds (3) and (4) were not available. As models, we utilised the literature pK_a for 3-ethylaminocyclohex-2-enone [14] for (3a) and *N*-(3-methoxycyclohex-2-enyl-

TABLE 1

Results for 4-pyridone and related compounds [a]

	(1)	(2)	$\Delta G°_u$/	(3)	(4)	$\Delta G°_s$/	$(A_{py} - A_X)$/kcal mol^{-1} [b]			
X	pK_a	pK_a	kcal mol^{-1}	pK_a	pK_a	kcal mol^{-1}	(i)	(ii)	(iii)	(iv)
O	3·33 [c]	6·62 [c]	−4·5	3·10 [h]	11·19 [h]	−11·1	6·6	7·0	8·6	8·7
NH	17·87 [d]	9·12 [f]	12·0	*i*	*i*	0	12·0		15·6	15·8
CH_2	19·46 [e]	6·02 [g]	18·4	9·5 [j]	8·7 [i]	1·1	17·3	15·3	22·5	22·9

[a] All values refer to aqueous solutions. [b] The figures are respectively (i) uncorrected $\Delta G°$ values, (ii) $\Delta H°$ values from correlation of pK_a variation with temperature, (iii) $\Delta H°$ from Arnett's correlation, and (iv) $\Delta H°$ from temperature dependence of tautomeric equilibria. For full details see ref. 1. [c] *Cf.* ref. 11. [d] Present investigation. [e] Present investigation. [f] Value for 4-aminopyridine, ref. 12. [g] Ref. 13. [h] Value for 3-ethylaminocyclohex-2-enone, ref. 14. [i] Assumed equal by inspection. [j] Estimated value, see text. [k] Value for *N*-(3-methoxycyclohex-2-enylidene)ethylamine, ref. 14. [l] Value for *N*-n-butylcrotonaldimine, ref. 15.

has been attributed [5] to a lower aromaticity of the former compound. Some calculations have been performed

idene)ethylamine [14] for (4a). For the series X = CH_2, we used the literature pK_a of *N*-n-butylcrotonaldimine [15] for (4d) and estimated the pK_a of (3d) as 9·5 from the pK_a of 1,4,4-trimethyl-1,2,3,4-tetrahydropyridine [15] of

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10·45, making an allowance for the extra C=C by a reduction of one pK_a unit (*cf.* the pK_a values of 2-vinylpyridine and 2-ethylpyridine, 4·92 [16] and 5·97,[13] respectively). To a first approximation the pK_a values of the two compounds, (3c) and (4c), of the nitrogen 'non aromatic' series will be equal, as they are both imino-enamines.*

From the ΔG–ΔH correlations discussed in ref. 1† we calculate the following $(A_{py} - A_X)$ ‡ values: 4-pyridone, 7·7 ± 1·5 kcal mol^{-1}; 4-pyridone imine, 14·5 ± 3 kcal mol^{-1}, and 4-pyridone methide 19·5 ± 3·5 kcal mol^{-1}. Comparison with the data for the 2-pyridone analogues (see Table 2) shows that the aromaticities for the two series are very similar. While charge-separated structures have higher symmetry in the 4-series, the distance of charge separation is greater, and these two effects may approximately cancel.

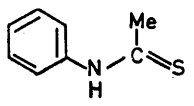
TABLE 2

Aromatic resonance energy differences for the 2- and 4-pyridone, 2-quinolone, and 1-isoquinolone series

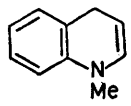
X	$(A_{py} - A_X)$/kcal mol^{-1} 2-Series	4-Series	$(A_q - A_X)$/ kcal mol^{-1}	$(A_{isoq} - A_X)$ kcal mol^{-1}
O	7·5 ± 1	7·7 ± 1·5	2·0 ± 0·5	4·4 ± 1·0
S	6 ± 1		2·9 ± 0·5	4·0 ± 1·0
NH	10 ± 2	14·5 ± 3	5·0 ± 1·0	6·2 ± 1·2
CH_2	17·5 ± 3·5 [a]	19·5 ± 4	7·9 ± 1·5	7·4 ± 1·5

[a] Redetermination of the pK_a of 2-pyridone methide (see Experimental section) modifies the mean value (18·6 kcal mol^{-1}) of the results reported in ref. 1.

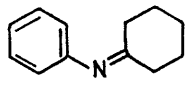
quinolone methide (15·23 ± 0·04) (5d). The pK_a values for many of the *N*- and *X*-alkylated models for compounds (7) and (8) are not available. Models have been therefore taken from the literature pK_a data for ethyl *N*-phenylthiobutyrimidate,[24] 1,3,3-trimethyl-2-iminoindoline,[22] and 2-aminoindolenine.[22,25] The pK_a values of *N*-phenylthioacetamide (13) and cyclohexanone anil (15) were determined (see Experimental section) as models for (7b) and (8d) respectively. For (7d), the pK_a of 1-methyl-1,4-dihydroquinoline (7·91 ± 0·09 experimental) (14) was considered as a first approximation. A terminal, *exo*-methylene group is less stable than an *endo* C=C; the n.m.r. spectrum of 1,2-dimethyl-1,4-dihydroquinoline confirms the predominance of the 1,4-dihydro-form. The model is therefore less basic than (7d), the pK_a of which was taken as 10·0.



(13)



(14)



(15)

The following $(A_q - A_x)$ values were calculated as in ref. 1: 2-quinolone, 2·0 ± 0·5 kcal mol^{-1}; quinoline-2-thione, 2·9 ± 0·5 kcal mol^{-1}; 2-quinolone imine, 5·0 ± 1 kcal mol^{-1}; and 2-quinolone methide, 7·9 ± 1·5 kcal mol^{-1}. Comparison with the data for 2-pyridone and its analogues (see Table 2) shows a decrease in $(A - A_x)$ values for the 2-quinolone series. This phenomenon is probably due to bond fixation in the quinoline ring compared with the completely delocalised pyridine ring: hence, less resonance energy is lost in passing from a quinolinoid to a quinolonoid ring than in the monocyclic series.

TABLE 3

Results for 2-quinolone and related compounds [a]

X	(5) pK_a	(6) pK_a	$\Delta G°_u$/ kcal mol^{-1}	(7) pK_a	(8) pK_a	$\Delta G°_s$/ kcal mol^{-1}	$(A_q - A_X)$/kcal mol^{-1} [b] (i)	(ii)	(iii)	(iv)
O	−0·71 [c]	3·17 [c]	−5·3	−0·50 [i]	4·63 [m]	−7·0	1·7	1·9	2·2	2·2
S	−1·6 [d]	3·71 [d]	−7·3	−3·34 [j]	3·84 [n]	−9·85	2·6	2·4	3·3	3·4
NH	11·68 [e]	7·34 [g]	5·9	9·25 [k]	8·15 [o]	1·5	4·4	4·0	5·7	5·8
CH_2	15·23 [f]	5·83 [h]	12·9	10·0 [l]	5·8 [p]	5·8	7·1	5·9	9·3	9·4

[a] All values refer to aqueous solutions. [b] (i), (ii), (iii), (iv) *cf.* Table 1. [c] *Cf.* ref. 17. [d] *Cf.* ref. 18. [e] Present investigation. [f] Present investigation. [g] Value for 2-aminoquinoline, *cf.* ref. 19. [h] *Cf.* value for 2-methylquinoline, ref. 20. [i] Value for *N*-methylacetanilide, *cf.* ref. 21. [j] Value for *N*-phenylthioacetamide, present investigation. [k] Value for 1,3,3-trimethyl-2-iminoindoline, *cf.* ref. 22. [l] Estimate, see text. [m] Value for ethyl *N*-phenylacetimidate, *cf.* ref. 23. [n] Value for ethyl *N*-phenylthiobutyrimidate, *cf.* ref. 24. [o] Value for 2-aminoindolenine, *cf.* refs. 22 and 25. [p] Value for cyclohexanone anil, present investigation.

2-Quinolones and Related Compounds (Table 3).—The pK_a values of the models for the tautomeric quinolines are taken from the literature except for 1-methyl-2-quinolone imine (11·68 ± 0·03) (5c) and 1-methyl-2-

* It is fundamental to this treatment that amides undergo protonation at oxygen. Further evidence has been provided recently (A. R. Fersht, *J. Amer. Chem. Soc.*, 1971, **93**, 3504).

† For further justification that $\Delta G°$ is a good estimate for ΔH_{int} see P. D. Bolton and L. G. Hepler, *Quart. Rev.*, 1971, **25**, 521.

‡ $A_{py} - A_X$ is the difference in aromatic resonance energy between the pyridine and pyridonoid structures: X refers to the exocyclic atom or group in the latter series (see ref. 1). Similar nomenclature follows for the benzo-fused series.

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[25] 2-Iminoindolines have been shown to exist as 2-aminoindolenines in $CDCl_3$; T. Hino, M. Nakagawa, T. Hashizume, N. Yamaji, Y. Miwa, K. Tsuneoka, and S. Akaboshi, *Tetrahedron*, 1971, **27**, 775.

1-Isoquinolone and Related Compounds (Table 4).—The pK_a values for isoquinolines and model compounds are from the literature or new measurements (see Experimental section). The pK_a values of the models for the amino-saturated compounds have been taken as equal as each is an alkylated benzamidine.

From these data the following $A_{isoq} - A_X$ values can be calculated: 1-isoquinolone, 4·4 ± 1 kcal mol^{-1}; isoquinoline-1-thione, 4·0 ± 1 kcal mol^{-1}; 1-isoquinolone imine, 6·2 ± 1·2 kcal mol^{-1}; and 1-isoquinolone methide, 7·4 ± 1·5 kcal mol^{-1}. These results can be explained as described above for the quinolone series.

General Conclusions.—On the basis of cumulative pK_a errors (maximum ±0·5 kcal mol^{-1}) and the spread of the ΔH° values obtained by the various methods, the $(A - A_X)$ values given are expected to be within *ca.* ±20%. The errors have been discussed in Part I.[1] Although gas-phase tautomerism of acetylacetone [28] and oxazolidines [29] varies little from that for the solution phase, Beak drew attention [30] to dangers in using aqueous solution data that could be considerably different from non-polar phase situations. However, Beak has recently concluded [31] that solvation effects, which are potential sources of error, could well cancel in the comparison of the equilibrium constants of the heteroaromatic and nonaromatic cases.

We therefore conclude that the aromatic resonance energies for 4-pyridone, 4-pyridone imine, and 4-pyridone methide are similar to those for the corresponding compounds of the 2-pyridone series. However, for all the compounds of the 2-quinolone and 1-isoquinolone series, the differences between the aromaticity of the quinolinoid and quinolonoid forms are considerably less than for the corresponding monocyclic analogues.

EXPERIMENTAL

M.p.s are uncorrected. pK_a Data were obtained using a Unicam SP 500 series 2 spectrophotometer.

Compounds.—1-Methyl-4-picolinium iodide, m.p. 154—155° (lit.,[32] 157—158°), 4-amino-1-methylpyridinium iodide, m.p. 188—190° (lit.,[33] 187—189°), 2-methylquinoline methiodide, m.p. 190—191° (lit.,[34] 195°) (Found: C, 46·3; H, 4·3; N, 4·8. Calc. for $C_{11}H_{12}IN$: C, 46·3; H, 4·2; N, 4·9%), 2-aminoquinoline methiodide, m.p. 258—261° (lit.,[35] 247°) (Found: C, 41·7; H, 3·9; N, 9·8. Calc. for $C_{10}H_{11}IN_2$: C, 42·0; H, 3·9; N, 9·8%), 1-methyl-3,4-dihydroisoquinoline methiodide, m.p. 199—202° (lit.,[36] 200—202°; [37] 191—193°), 1-methylisoquinoline methiodide, m.p. 207—210° (lit.,[38] 208°), *1-aminoisoquinoline methiodide*, m.p. 203—206° as needles from MeCN (Found: C, 42·3; H, 4·0; N, 9·8. $C_{10}H_{11}IN_2$ requires C, 42·0; H, 3·9; N, 9·8%) were prepared by the reaction of methyl iodide on the corresponding bases.

2-Aminoquinoline, m.p. 131·5—132·5° (lit.,[39] 130·5—131°), was prepared by the reaction of sodamide with quinoline in refluxing xylene; [40] 1-methyl-3,4-dihydroisoquinoline was prepared by reaction of $POCl_3$–P_2O_5 on *N*-phenethylacetamide in refluxing xylene [41] [hydrochloride, m.p. 195—198° (lit.,[41] 196—198°)]; 1-methylisoquinoline was prepared from 1-methyl-3,4-dihydroisoquinoline by dehydrogenation over Raney nickel [38] [sulphate, m.p. 246—249° (lit.,[42] 245°)].

1-Methyl-1,4-dihydroquinoline.—Sodium amalgam (27 g; 1·4%) was shaken with quinoline methiodide (1 g) in water (50 ml) and ether (50 ml). The ether layer was separated after 15 min and dried ($MgSO_4$). Evaporation gave 1-methyl-1,4-dihydroquinoline as a liquid which quickly

TABLE 4

Results for 1-isoquinolone and related compounds [a]

X	(9) pK_a	(10) pK_a	ΔG°_u/ kcal mol^{-1}	(11) pK_a	(12) pK_a	ΔG°_s/ kcal mol^{-1}	$(A_{isoq} - A_X)$/kcal mol^{-1} [b] (i)	(ii)	(iii)	(iv)
O	−1·80 [c]	3·05 [c]	−6·6	−1·62 [h]	5·8 [l]	−10·2	3·6	4·3	4·7	4·8
S	−2·13 [d]	3·93 [d]	−8·3	−2·61 [i]	6·04 [m]	−11·85	3·6	3·7	4·6	4·7
NH	11·38 [e]	7·62 [g]	5·15	*j*	*j*	0	5·15		6·7	6·8
CH_2	15·89 [f]	6·42 [f]	13·0	13·06 [k]	8·30 [n]	6·5	6·5	6·0	8·4	8·5

[a] All values refer to aqueous solutions. [b] (i), (ii), (iii), (iv) *cf.* Table 1. [c] *Cf.* ref. 17. [d] *Cf.* ref. 18. [e] Present investigation. [f] Present investigation. [g] Value for 1-aminoisoquinoline, *cf.* ref. 19. [h] Value for *NN*-dimethylbenzamide, *cf.* ref. 26. [i] Value for *N*-methylthiobenzamide, present investigation. [j] Assumed equal by inspection. [k] Value for 2-methyl-3,4-dihydro-1-isoquinolone methide, present investigation. [l] Value for methyl benzimidate, *cf.* ref. 27. [m] Value for ethylthiobenzimidate, *cf.* ref. 24. [n] Value for 1-methyl-3,4-dihydroisoquinoline, present investigation.

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coloured and became viscous, $\lambda_{max.}$ (EtOH) 303 nm (lit.,[43] 303 nm); τ ($CHCl_3$) 4·15 (1H, dt, $J_{2,3}$ 8, $J_{2,4}$ 1·5 Hz), 5·4—5·7 (1H, q, $J_{3,4}$ 4, $J_{2,3}$ 8 Hz), 6·35—6·55br (2H, d, $J_{3,4}$ 4 Hz), 7·05 (3H, s) [lit.,[43] τ 4·11 (1H, dt, $J_{2,3}$ 8, $J_{2,4}$ 1·6 **Hz**), 5·39—5·64 (1H, m), 6·43 (2H, d, $J_{3,4}$ 4 Hz), and 7·0 (3**H**, s)].

1,2-*Dimethyl*-1,4-*dihydroquinoline*.—Quinaldine methiodide was treated with sodium amalgam as above. The product decomposed rapidly in chloroform and carbon tetrachloride. The n.m.r. spectrum obtained in pyridine was similar to that of 1-methyl-1,4-dihydroquinoline, τ 5·55 (1·0H, t, 3-H), 6·55br (2·1H, s, 2 4-H), 6·1 (0·55H, d, impurity), 6·8—7·6 (m of impurity), 7·1 (*ca.* 3H, s, NCH_3), and 8·25br (*ca.* 3H, s, 2-CH_3); no signals in the region for terminal methylene protons (τ 4·3—5·4).

Cyclohexanone Anil.—Cyclohexane (48 g), aniline (46 g), toluene-*p*-sulphonic acid (1 g), and benzene (50 ml) were azeotropically distilled in a Dean and Stark apparatus until the theoretical amount of water (9 ml) had been collected. On fractional distillation, dimer distilled over and trimer remained as residue. The fraction containing aniline and the imine ($\nu_{max.}$ 1675 cm^{-1}) was redistilled to yield cyclohexanone anil, b.p. 95° at 1 mmHg (lit.,[44] b.p. 132° at 4 mmHg); $\lambda_{max.}$ (EtOH) 227 and 284 nm ($\log_{10}$ ε 3·98 and 3·30) [lit.,[45] (cyclohexane) 230 and 286 nm ($\log_{10}$ ε 3·93 and 3·33)]; τ (CCl_4) 2·6—3·5 (5H, m) and 7·4—8·9 (10H, m).

Ethyl Thionacetate.[46]—Ethanol (15 g), methyl cyanide (13 g), and hydrogen chloride (11 g) were kept 5 days at 0° to give ethyl acetimidate hydrochloride (28 g) which was filtered off and washed with dry ether. 6M-Potassium carbonate (45 ml) was added whilst stirring vigorously under ether at 0° until neutral. After removing the ether by evaporation, the imidate ester (10 g) in dry pyridine (20 ml) was cooled (ice–salt bath) and hydrogen sulphide was passed through it for 1·3 h. The yellow mixture was kept at 0° for 2 h and then poured onto ice with stirring and brought to pH 5 with hydrochloric acid (10%). The whole was extracted with ether (3 × 50 ml). The combined extracts were washed with hydrochloric acid (4%; 2 × 25 ml), dried (Na_2SO_4), and distilled to yield ethyl thionacetate (2·2 g), b.p. 109° (lit.,[46] b.p. 109°).

N-*Phenylthioacetamide*.—Aniline (3·7 g) in dry benzene (40 ml) was slowly added, with stirring, to ethylmagnesium bromide [from ethyl bromide (4·4 g) and magnesium (1·0 g)] in THF (20 ml) and the whole then heated under reflux for 5 min. Ethyl thionacetate (2·0 g) in dry THF (10 ml) was added and the mixture was heated under reflux for 1 h. The solvents were removed by evaporation (100° and 15 mmHg) and the residue was treated with ice (30 g), hydrochloric acid (36%; 16 ml), and brine (20 ml). The mixture was extracted with ether and, after removing the ether, the product was recrystallised from toluene–light petroleum (b.p. 60—80°) to yield *N*-phenylthioacetamide (1·2 g), m.p. 73—75° (lit.,[46] 75°).

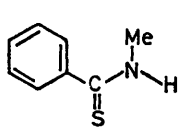
N-*Methylthiobenzamide*.—Benzonitrile (52 g) similarly gave ethyl benzimidate (31 g crude) and ethyl thionobenzoate (29 g), b.p. 114—116° at 10 mmHg (lit.,[46] 130° at 22 mmHg). Ethyl thionobenzoate (3·3 g) and methylamine (1·0 g) gave *N*-methylthiobenzamide (16) (0·5 g), m.p. 75—79° (3 recrystallisations from toluene) (lit.,[46] 79°) (Found: C, 63·3; H, 6·0; N, 9·2; S, 21·2. Calc. for C_8H_9NS: C, 63·5; H, 6·0; N, 9·3; S, 21·2%); $\lambda_{max.}$ (EtOH) 239 and 284·5 nm ($\log_{10}$ ε 4·03 and 3·88) [lit.,[47] 238 and 286·5 nm ($\log_{10}$ ε 4·03 and 3·86)].

TABLE 5

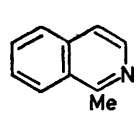
pK_a Values for proton addition at 20 ± 2°

Compound	pK_a	λ of pK_a measurement/nm	Method of measurement
1-Methyl-4-pyridone imine	17·87 ± 0·07	310	A
1-Methyl-4-pyridone methide	19·46 ± 0·04	306	A
1-Methyl-2-quinolone imine	11·68 ± 0·03	350	B
1-Methyl-2-quinolone methide	15·23 ± 0·04	390	A
2-Methyl-1-isoquinolone imine	11·38 ± 0·04	307·5	B
2-Methyl-1-isoquinolone methide	15·89 ± 0·07	370	A
1-Methyl-3,4-dihydroisoquinoline	8·30 ± 0·03	272	B
2-Methyl-3,4-dihydro-1-isoquinolone methide	13·06 ± 0·06	275	B and A
1-Methylisoquinoline	6·42 ± 0·04	332	B
1-Methyl-1,4-dihydroquinoline	7·91 ± 0·09	303	C
Cyclohexanone anil	5·8 ± 0·1		D
N-Phenylthioacetamide	−3·34 ± 0·17	275	E
N-Methylthiobenzamide	−2·61 ± 0·15	230 and 270	E

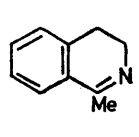
A = In Me_2SO–water, following the new $H_{-(q)}$ function (see Experimental section). B = In aqueous solution. C = In aqueous solution by a stop-flow method.[48] D = By potentiometric titration in methyl cyanide.[15,49] E = In sulphuric acid–water solutions.



(16)



(17)



(18)

pK_a *Measurements* (*Table* 5).—The spectroscopic method (u.v. absorbance) of determining pK_a values was used (*cf.* ref. 50). The pK_a of compounds (17) and (18) were measured in phosphate–alkali and boric acid–alkali buffers. The pK_a values of the *N*-Me derivatives of (5c) and (11d) were determined in sodium hydroxide solutions of known concentration and the activity of the hydrogen ions was determined from a plot of $-\log_{10} a_{H^+}$ *vs.* p[OH^-].[50] The pK_a of the *N*-Me derivative of (9c) was determined in boric acid–alkali buffers and sodium hydroxide solutions.

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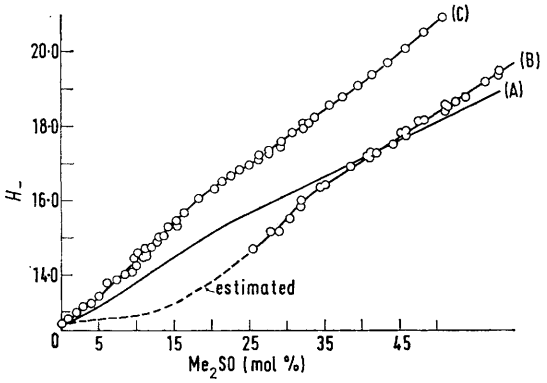
pK_a *Measurements of Strongly Basic Compounds and a New Acidity Function.*—The pK_a values of strongly basic compounds (pK_a > 13) were determined by a method similar to that already described by Bowden and Cockerill [10] using 0·047M-tetramethylammonium hydroxide in Me_2SO–water solutions. These workers set up a carbon acid H_- scale but the gradients of the plots of $\log_{10} I$ *vs.* H_- (where $I = [B]/[BH^+]$) for the bases studied here diverged considerably from −1·0. The gradients of plots of $\log_{10} I$ vs. mole % Me_2SO (*ca.* −0·165) in the present work differ substantially from those obtained by other workers for both carbon acids (*ca.* −0·133) and nitrogen acids (*ca.* −0·09) (see ref. 10 for data), and demonstrate that the deprotonation of our quaternary salts follows neither function.

For these reasons, the pK_a values for the *N*-Me derivatives of (1c), (1d), (5d), and (9d) were measured relative to that of the *N*-Me analogue of (11d), which had been measured in water, by a Hammett stepwise procedure. Results from the ionisation measurements on 1-methyl-2-pyridone phenylmethide and diphenylmethide [51] were included to improve the overlap. The measurements on



Acidity functions in aqueous Me_2SO containing tetramethylammonium hydroxide (0·047M): (A), nitrogen acid scale [54,*]; (B), carbon acid scale; (C), $H_{0(q)}$ scale (present investigation)

1-methyl-2-pyridone methide performed earlier [1] at a wavelength of 380 nm were repeated at a new wavelength (295 nm) because work currently in progress on the pseudobase formation of the pyridinium ion indicated that this effect had been interfering with the earlier measurements. The new data, when included in the stepwise procedure, lead to a value of 19·25 ± 0·04 for the pK_a which modifies our earlier value of 20·0 ± 0·2.[1] From the present study it is possible to set up a new scale for this class of compound (neutral bases derived from quaternary salts), which we term the $H_{-(q)}$ scale, and this is illustrated in the Figure together with the carbon acid [52] and nitrogen acid [53,54] H_- scales for comparison.

The $H_{0(q)}$ function rises more steeply with increasing mol % Me_2SO than either the *N*-acid or the *C*-acid H_- functions in the region so far studied (0·0—50·4 mol % Me_2SO; H_- = 12·7—21·0). This probably reflects an increase in the solvation of BH^+ by the increase in the proportion of Me_2SO, combined with the decrease in solvation by H bonding of B *via* the nitrogen lone pairs.

pK_a *Measurements for Weakly Basic Compounds.*—The pK_a values of the thioamides, (13) and (16), were determined in sulphuric acid–water solutions. The plots of log *I* *vs.* H_0 for (13) and (16) had gradients −1·45 and −0·90 and intercepts at H_0 −2·30 and −2·61, respectively. Therefore, a Yates type [55] correction was made for (13) but not for (16).

pK_a *Measurements for Compounds Susceptible to Rapid Hydrolysis.*—The pK_a of 1-methyl-1,4-dihydroquinoline (14) was obtained by a stop-flow [48] method in phosphate–alkali buffers because it was rapidly hydrolysed by aqueous media. The required quantity (0·2 ml) of a stock solution of the dihydroquinoline in absolute ethanol (which decomposed only slowly) was transferred to a dry u.v. cell (4 cm). The buffer (10 ml) was syringed into this sample cell in a Beckman DB spectrophotometer fitted with a Beckman '10 inch' recorder and absorbance at 303 nm *vs.* time was plotted automatically. This procedure gives reproducible absorbance values after 5 s; absorbance at the time of mixing and hence the pK_a were obtained by extrapolation.

The stop-flow method was inapplicable to the pK_a of cyclohexanone anil (15); benzylidene anils are hydrolysed with half lives of milliseconds in the region of their pK_a values.[56] For cyclohexanone anil Hall's method,[15,49] was therefore adopted: potentiometric titration of the base (5×10^{-4} mol) in methyl cyanide (50 ml) with perchloric acid in dioxan (0·5M) was carried out. The e.m.f. at half protonation ($E_{\frac{1}{2}}$) was plotted against the pK_a in water for 2,6-lutidine, pyridine, aniline, and *m*-nitroaniline and a straight line was obtained [57] (*cf.* Hall's results [49] and ref. 15 for a wide range of bases). Using this correlation, the pK_a of (15) was obtained from the value of its $E_{\frac{1}{2}}$. The protonation of cyclohexanone anil was shown to be reversible

TABLE 6

Thioamide tautomerism

Equilibrium	pK_a of model compounds: *NH*-Alkyl	*S*-Alkyl	log K_T [a]
Me–C(=S)–NH_2 ⇌ Me–C(SH)=NH	−1·76 [b]	7·01 [c]	8·77 (7·7 [h])
R–C(=S)–NHPh ⇌ R–C(SH)=NPh (R = alkyl)	−3·34 [e]	3·84 [f]	7·18 (5·13 [i])
Ph–C(=S)–NH_2 ⇌ Ph–C(SH)=NH	−2·61 [d]	6·04 [g]	8·65 (7·4 [j])

[a] Figures in parentheses refer to the corresponding amide-imidate equilibria. [b] $MeCSNH_2$, see D. Rosenthal and T. I. Taylor, *J. Amer. Chem. Soc.*, 1957, **79**, 2684. [c] MeCSNHPh, present investigation. [d] PhCSNHMe, present investigation. [e] MeC(SEt)NH, see ref. 24. [f] PrC(SEt)NPh, see ref. 24. [g] PhC(SEt)=NH, see ref. 24. [h] Obtained from data in Table 1 of ref. 1. [i] See Table 3. [j] See Table 4.

* The *N*-acid scale was originally for 0·011M base.[54] To correct to 0·047M base the plot has been moved up by 0·7H_- units.[52]

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[57] For full details see R. D. Tack, Ph.D. Thesis, Norwich, 1972

under these conditions by recording its u.v. spectrum in methyl cyanide alone ($4{\cdot}2 \times 10^{-4}$M), again after adding the perchloric acid (0·2 ml)–dioxan (3 ml), and once more after neutralising the acid with triethylamine (0·1 ml).

APPENDIX

Thioamide–Thioimidate Tautomerism.—U.v.[47] and i.r.[58] spectroscopic studies demonstrate that potentially tautomeric thioamides exist essentially as such rather than as the SH tautomer, but there appear to be no quantitative estimates of the equilibrium constants, K_T, for this fundamental equilibrium. K_T Can be estimated from pK_a data of fixed models or the pK_a of the mobile form and one fixed model, particularly when the model is one for the least favoured tautomer.[59] pK_a Data from the literature and the present work, together with values of K_T derived from these, are reported in Table 6. The results show that a phenyl substituent on nitrogen reduces the predominance of the thioamide form by a factor of *ca.* 10. Comparison of the data for tautomeric thioamides with those for corresponding tautomeric amides (Table 6) shows that the R'CXNHR tautomer is more favoured in the former series.

[2/2576 *Received*, 14*th November*, 1972]

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