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THE TAUTOMERISM OF 9-HYDROXY- AND 9-MERCAPTO-ACRIDINE 10-OXIDE*

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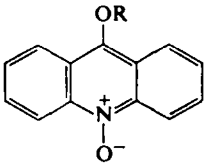
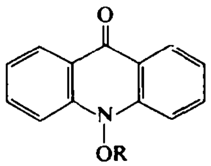
Abstract—Spectra and basicity measurements indicate that in aqueous solution 9-hydroxyacridine 10-oxide exists in equilibrium with an approximately equal amount of 10-hydroxyacridone. 9-Mercaptoacridine 10-oxide exists in aqueous solution as such, in equilibrium with a comparable amount of 10-hydroxythioacridone.

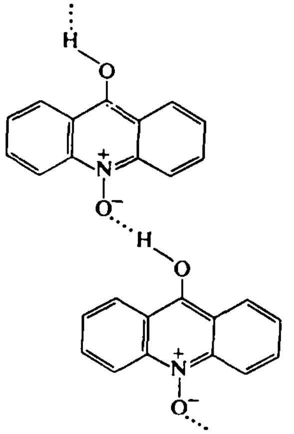


I, R = H II, R = CH_3

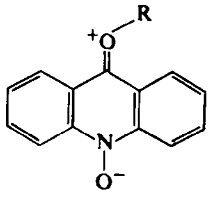


III, R = H IV, R = CH_3

THE tautomeric structure of 9-hydroxyacridine 10-oxide (I $\rightleftharpoons$ III) was a subject of considerable controversy during the third decade of this century: Tanasescu and Ramontianu[1] favoured the N-oxide formulation (I) and Kliegl and Brösamle[2] the 10-hydroxyacridone structure (III). In addition, the constitution of the alternative methyl ethers, and other derivatives, was contentious. A previous publication[3] by one of us clarified the latter matter, and indicated, from IR spectral evidence, that in the crystalline state 9-hydroxyacridine 10-oxide did exist in the 10-oxide form, strongly hydrogen bonded (cf. V). We have now applied the standard UV and p*K* methods



V



VI

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[*] N-Oxides and Related Compounds, Part XXIX. For part XXVIII see A. J. Boulton, P. B. Ghosh and A. R. Katritzky, *J. Chem. Soc.* C, 971 (1966).

[1] I. Tanasescu and E. Ramontianu, *Bull. Soc. Chim. Fr.* [5], 1, 547 (1934).

[2] A. Kliegl and A. Brösamle, *Chem. Ber.* 69, 197 (1936).

[3] M. Ionescu, H. Mantsch and I. Goia, *Chem. Ber.* 96, 1726 (1963).

(cf.[4]) to determine the equilibrium constant in solution so that a comparison could be made with 4-hydroxypyridine 1-oxide.[5] We have similarly investigated 9-mercapto-acridine 10-oxide.

RESULTS

The pK_a values in Table 1 were determined by the spectrophotometric method. For the hydroxy series, qualitatively, the closeness of the three values shows that there can be little difference between the stability of the hydroxy-10-oxide (I) and 10-hydroxyacridone (III) form in aqueous solution. Quantitatively, the effect of replacing H by CH_3 on the intrinsic basicity of the two tautomers I and III must be considered. The inductive effects of OH and OMe are similar in substituted anilines, but the mesomeric effect of OH is considerably more base strengthening that that of OMe—by ca. 0·3 pK units in *o*- and *p*-substituted anilines.[6] For the 10-oxides, canonical forms of type VI are important, and steric hindrance where R = Me will reduce their effect in the methylated compound. We conclude that the intrinsic pK of I is higher than 1·25 by something over 0·3 pK units, whereas that of III is probably near that of the Me analogue, 1·68. If the two forms I and III contributed equally to the tautomeric equilibrium, the observed pK would be lowered by the statistical factor of $\log_{10}2 =$ 0·30 pK units from the (equal) pK of the two individual forms I and III, and this interpretation best fits the pK evidence.

The pK_a values of the two available sulphur compounds (Table 1) likewise indicate that 9-mercaptoacridine 10-oxide exists either as such, or in equilibrium with up to an approximately equal amount of the thione form.

UV spectral maxima are recorded in Table 2, and curves for the oxygen compounds as conjugate acids and neutral forms are shown in Figs. 1 and 2. There are no large

TABLE 1. pK_a VALUES

No.	Compound	pK_a	Spread(±)	Conc (10^4M)	Wavelength (mμ)	pK of corresp. pyridine
1	9-hydroxyacridine 10-oxide	1·26	0·04	4·8	257	2·45
2	9-mercaptoacridine 10-oxide	0·89	0·06	4·2	256	1·53
3	9-methoxyacridine 10-oxide	1·25	0·03	3·9	257	2·05
4	9-methylthioacridine 10-oxide	2·79	0·07	4·1	264	2·09
5	10-methoxyacrid-9-one	1·68	0·06	4·0	259	2·57

AcONa–HCl buffers and H_2SO_4 of known H_0 were used. Solutions contained up to 2% EtOH. Spectra were obtained on a Unicam SP 500 spectrophotometer at 20°.

TABLE 2. UV SPECTRAL MAXIMA (mμ)

	Cations						Neutral species			
No.[a]	λ_{max}	$10^{-3}\,\varepsilon$	λ_{max}	$10^{-3}\,\varepsilon$	λ_{max}	$10^{-3}\,\varepsilon$	λ_{max}	$10^{-3}\,\varepsilon$	λ_{max}	$10^{-3}\,\varepsilon$
1	260	71·7	338	3·9	411	4·3	261	39·0	404	4·1
2	266	55·5					269	26·7		
3	258	100·6	338	6·5	400	5·2	252	84·2	403	5·1
4	264	140·6					269	82·7		
5	260	106·3	339	9·7	413	6·3	255	58·7	407	8·54

[a] Numbers refer to compounds in Table 1.

Measurements were on a Unicam S.P. 500 spectrophotometer.

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[4] A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* **1**, 311 (1963).

[5] J. N. Gardner and A. R. Katritzky, *J. Chem. Soc.* 4375 (1957).

[6] A. Albert and J. N. Phillips, *J. Chem. Soc.* 1294 (1956).

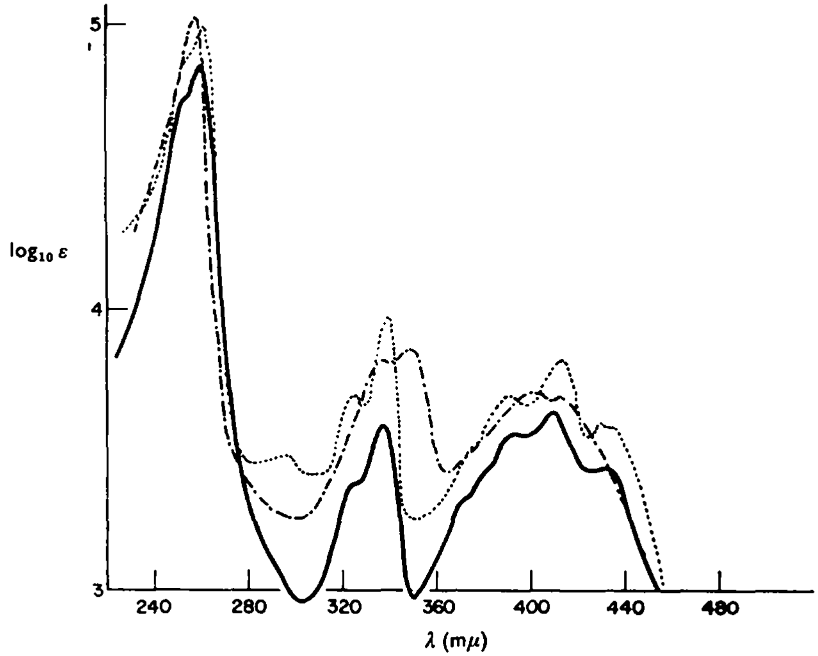


FIG. 1. 9-Hydroxyacridine 10-oxide ———, 9-methoxyacridine 10-oxide – · – · –, and 10-methoxyacrid-9-one .... in 15N H_2SO_4.

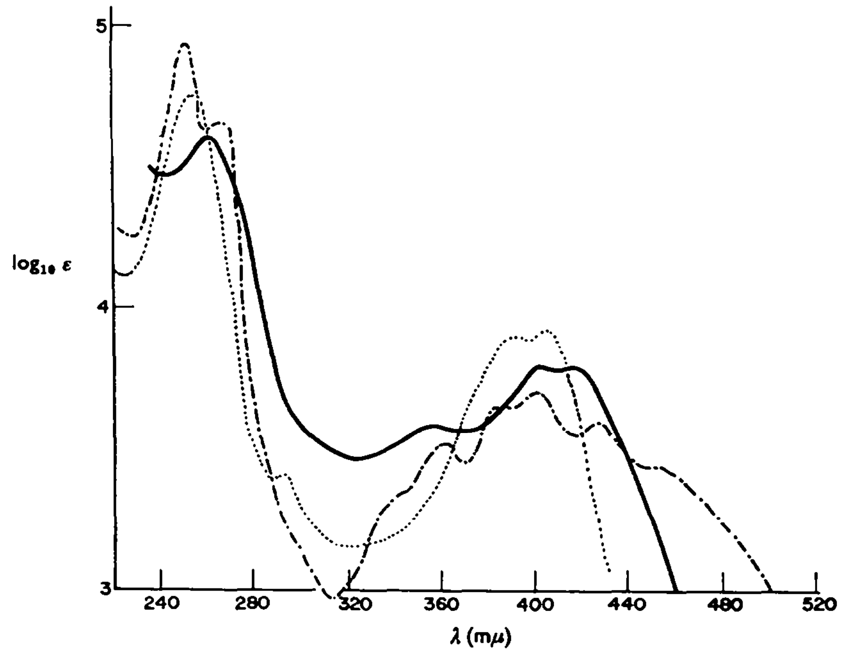


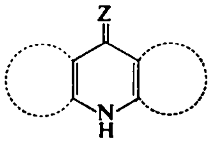
FIG. 2. 9-Hydroxyacridine 10-oxide ———, 9-methoxyacridine 10-oxide – · – · – and 10-methoxyacrid-9-one .... in 50% EtOH–AcONa aq–HCl buffer of pH 4·8.

differences in the spectra of the neutral forms, but their shape does support the conclusion that both tautomers I and III contribute in comparable amounts to the equilibrium.

DISCUSSION

In aqueous solution, the tautomeric composition of 9-hydroxyacridine 10-oxide resembles that of 4-hydroxypryidine 1-oxide[5] in that each co-exists with a comparable amount of the N-hydroxy form. For 9-mercaptoacridine 10-oxide, the tautomeric composition is probably a little more favourable towards the mercapto form than for the pyridine analogues, where there is a factor of ca. 4 towards 1-hydroxy-4-pyridinethione.[7]

This pattern differs from that found in the corresponding non-N-oxides (for full discussion and Refs[8]). The pyridine derivitaves (VII ⇌ VIII, Z = 0 or S) exist, by rather large factors, in the oxo or thione forms (VII). Annelation of one or two benzene rings (cf. VII, VIII) considerably *increases* the relative stability of the oxo and (probably) the thione forms. This is explained by the stabilization of the uncharged canonical forms VII, relative to VIII; however, it should be noted that the effect on the charge-separated forms IX and X is in the opposite direction.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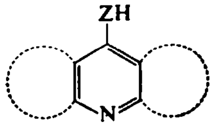
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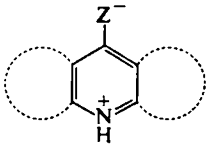
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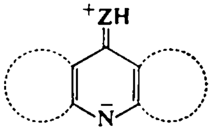
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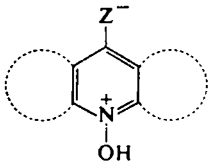
For the N-oxides, canonical forms of type XI (analogues to IX) are relatively less important, but those of type XII are more important (than those of type X), and there is a further type of charge-separated form XIII, which will also be stabilized by the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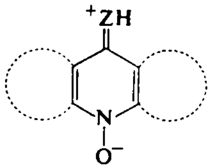
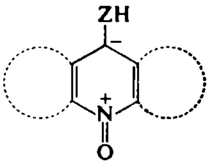

XII


XIII

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[7] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* 2937 (1960).

[8] A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* 1, 339 (1963).

annelation of benzene rings. Evidently it is the stabilization of forms of type XII and XIII which makes the N-oxide forms so important in the tautomerism of 9-hydroxy- and 9-mercapto-acridine 10-oxide.

EXPERIMENTAL

For the preparation of 9-hydroxy- and 9-methoxy-acridine 10-oxide and 10-methoxyacridone see Ref. 3.

For the preparation of 9-mercaptoacridine 10-oxide and 9-methylthioacridine see Ref. 9.

Basicity measurements were obtained by the spectrophotometric method (Unicam SP 500 spectrophotometer). Solutions were AcONa–HCl buffers or in H_2SO_4 of known H_0, and contained up to 2% of EtOH. UV spectra (Unicam SP 500 and Perkin–Elmer 136 spectrophotometers).

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I. Goia, H. Mantsch and M. Ionescu, *Rev. Roumaine Chim.* in press.