108. *Absorption Spectra of Acridines. Part IV. Steric Interference with Ionisation.*

By D. P. Craig.

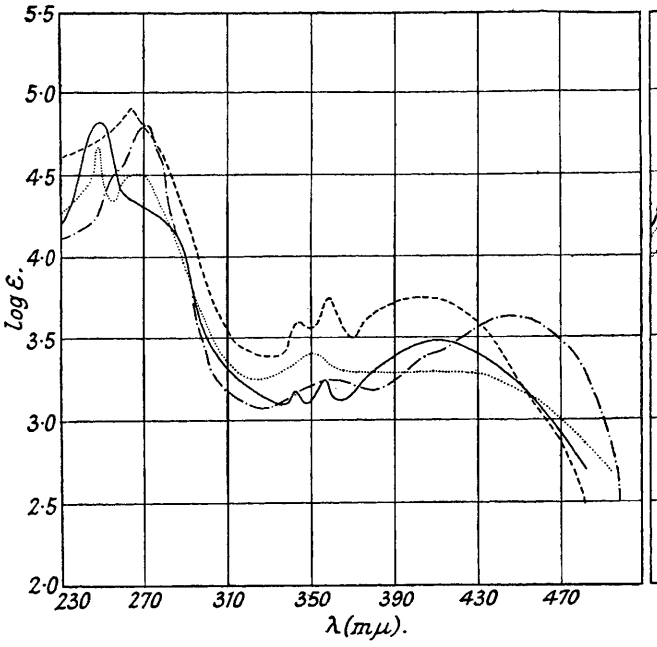
The absorption spectra of 1 : 9-diaminoacridine and 1-amino-9-methylacridine at different pH values are reported. The spectra of the former compound are interpreted to show that it differs from previously investigated mono- and di-aminoacridines in that the ring nitrogen atom is less basic than those of the primary amino groups and is ionised only under very strongly acid conditions. The second compound is shown to form monohydrochlorides involving either the primary amino group or the ring nitrogen, depending on the conditions of ionisation. The case is an unusual one in that a change of solvent causes a reversal in the relative pK values of the two possible ionising processes. The anomalies in ionising behaviour are shown to have their origins in steric hindrance.

Absorption spectra of the mono- and some di-aminoacridines previously reported in Parts I and II (Craig and Short, *J.*, 1945, 419; Turnbull, *J.*, 1945, 441) have established that in all the monoaminoacridines the ring nitrogen is more basic than the nitrogens of the primary amino groups and that it accepts the first proton on ionisation. The evidence provided by the absorption spectra of these compounds is that in the conversion from base to univalent ion the long wave band undergoes a shift towards the red as seen in the ionisation of acridine. On conversion to the bivalent ion, the monoaminoacridines (except the 5-isomeride which does not form a bivalent ion) show a shift to shorter wavelengths giving spectra almost identical with that of the ion of unsubstituted acridine. The inference is that only at the second ionisation is the amino group converted to $-NH_3^{\oplus}$ and thus prevented from participating in the resonance pattern of the structure.

The results for 1 : 9-diaminoacridine and for 1-amino-9-methylacridine are shown in Figs. 1—4 and in the Table.

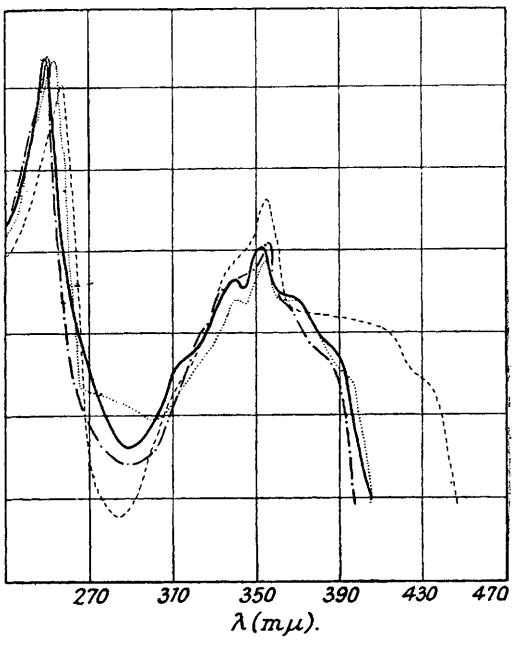
Dealing first with 1 : 9-diaminoacridine, the absorption in 5N-hydrochloric acid reverts almost exactly to that of acridine itself (not, like other aminoacridines, to that of the acridine *ion*) as shown in Fig. 2. The indication is that the two amino groups are not able to participate in the resonance (*i.e.*, are ionised to $-NH_3^{\oplus}$) and that the ring nitrogen is behaving as it does in acridine; the ring nitrogen, then, is not ionised in 5N-hydrochloric acid. The conclusion that in 1 : 9-diaminoacridine the ring nitrogen is the *least* basic is confirmed by the observation (Fig. 3) that in 18N-sulphuric acid the absorption is almost identical with that of the acridine

FIG. 1.



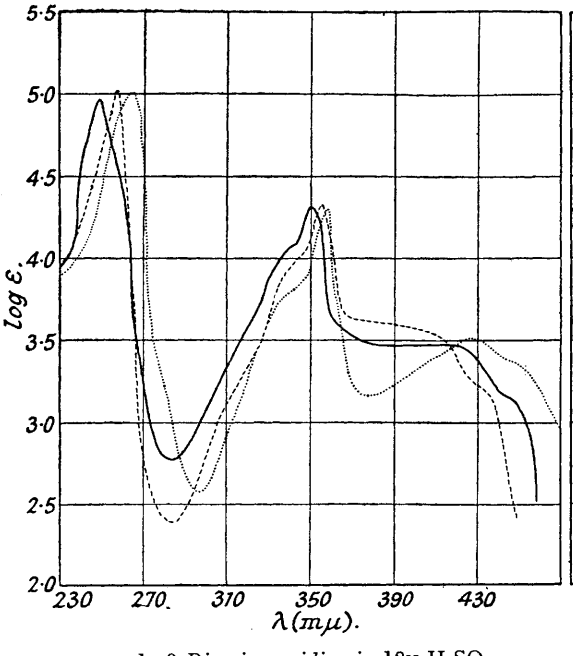
——— 1-*Amino*-9-*methylacridine in abs. alcohol.*
—·—·— 1 : 9-*Diaminoacridine in abs. alcohol.*
– – – – – – 1-*Aminoacridine at* pH 11 *in* 33% *methanol–water.*
· · · · · · · · 1 : 9-*Diaminoacridine at* pH 3·0.

FIG. 2.



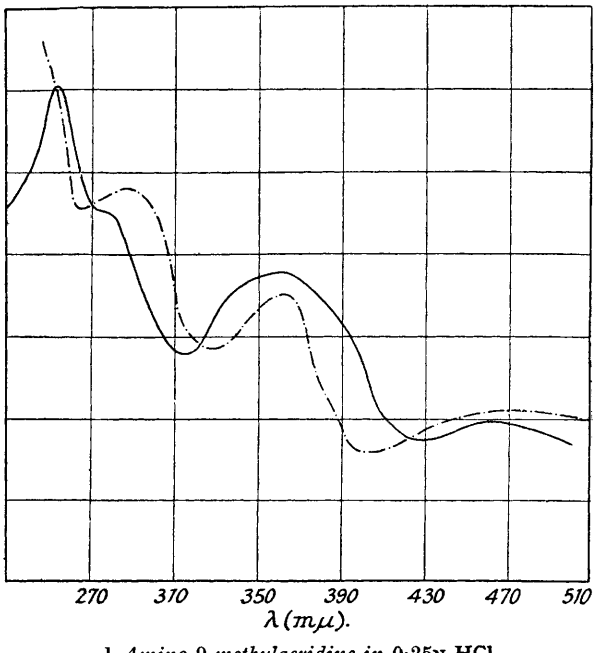
——— 1 : 9-*Diaminoacridine in* 5N-HCl.
—·—·— *Acridine at* pH 11.
· · · · · · · · 1-*Amino*-9-*methylacridine in alcoholic* N/15-HCl.
– – – – – – *Acridine ion in* 5N-HCl.

FIG. 3.



——— 1 : 9-*Diaminoacridine in* 18N-H_2SO_4.
· · · · · · · · 1-*Amino*-9-*methylacridine in* 5N-HCl.
– – – – – – *Acridine in* 5N-HCl.

FIG. 4.



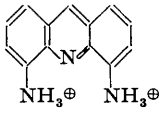
——— 1-*Amino*-9-*methylacridine in* 0·25N-HCl.
—·—·— 1-*Aminoacridine at* pH 2·5 (33% *methanol–water*).

Absorption maxima and significant inflexions.

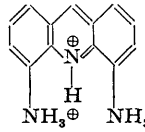
	$\lambda_{max.}$, mμ.	log ε.	$\lambda_{max.}$, mμ.	log ε.	$\lambda_{max.}$, mμ.	log ε.
			1 : 9-*Diaminoacridine.*			
In abs. alcohol	272	4·80	362	3·22	448	3·63
At pH 3 (33% methanol)	250	4·62	352	3·42	420	(Inflexion)
	268	4·51				
At pH 2·5 (33% methanol)	248	4·9	354	3·75	420	(Inflexion)
	268	4·28				
In 5N-HCl	249	5·17	353	4·03	(No band)	
In 18N-H_2SO_4	250	4·98	352	4·31	410	(Inflexion)
			1-*Amino-9-methylacridine.*			
In abs. alcohol	252	4·82	358	3·25	413	3·50
N/15-HCl in abs. alcohol	254	5·17	354	3·95	(No band)	
N/4-aqueous HCl	255	5·02	360	3·88	460	2·97
	278	(Inflexion)				
5N-HCl	264	5·01	358	4·31	426	3·50

ion. It is only under these extreme conditions of hydrogen-ion activity that the ring nitrogen accepts a proton.

(I.)



1 : 9-Diaminoacridine in 5N-HCl.



(II.)

1 : 9-Diaminoacridine in 18N-H_2SO_4.

The addition of half an equivalent of hydrochloric acid to 1 : 9-diaminoacridine (M/300) gives a pH of 3·65 (in 50% alcohol, Albert and Goldacre, unpublished); if this result, suitably corrected for hydrolysis, were taken to be the pK_a of the ionisation it would correspond with the ionisation of a primary amino group: the remaining resonating system should then be the same as that of 1-aminocridine. When the spectrum of 1-aminoacridine is compared with that of 1 : 9-diaminoacridine at pH 3·0 in Fig. 1, the agreement is poor, and the curves suggest strongly the existence of a mixture of base, univalent ion, and bivalent ion. It is in any case likely that the first and second basic constants would lie rather close together since the ionisation of one of the amino groups should not greatly affect the free energy change involved in the ionisation of the second amino group. The pH 3 absorption, then, is due to a mixture of base, bivalent ion, and a little univalent ion. That there is some of the latter present is shown by the fact that the pH 3 curve cannot be obtained exactly by linear combination (from a linear plot in ϵ) only of the base and bivalent ion curves, but requires the addition of a small percentage of the 1-aminoacridine curve.

1-Amino-9-methylacridine shows no special features in absolute alcohol solution (free base, Fig. 1) or in 5N-hydrochloric acid (bivalent ion, Fig. 3). However, two different univalent ions exist. In alcoholic N/15-hydrochloric acid the spectrum corresponds with that of acridine, indicating that the primary amino group is ionised and the ring nitrogen not ionised (Fig. 2). In aqueous N/4-hydrochloric acid, the spectrum is close to that of the univalent ion of 1-aminoacridine in which it is the ring nitrogen which is ionised (Fig. 4) and the primary amino group free. The $-NH_3^{\oplus}$ univalent ion is also obtainable to a small extent in very dilute aqueous hydrochloric acid, and there is a small concentration range within which the $-NH_3^{\oplus}$ form is stable in the cold and the $-\overset{\oplus}{N}=$ form in the hot solution. A striking feature of the present case is the fact that a proton shift of at most 2A., involving a very small overall energy change, causes so sweeping a change in the energy levels of excited states as reflected in the absorption spectrum.

Methyl-substituted aminoacridines having either the 1- or 9-position free differ to a negligible extent from the unsubstituted aminoacridine in their ionisation behaviour (Albert and Goldacre, unpublished). The anomalous ionisation of 1-amino-9-methylacridine in very dilute alcoholic acid is almost certainly due to steric hindrance to the close approach of an oxonium (or ethyloxonium) ion to the ring nitrogen atom. The primary amino group is accordingly ionised first. The case is an unusual one in that a change of solvent causes a reversal of the relative pK values of the two possible ionising processes.

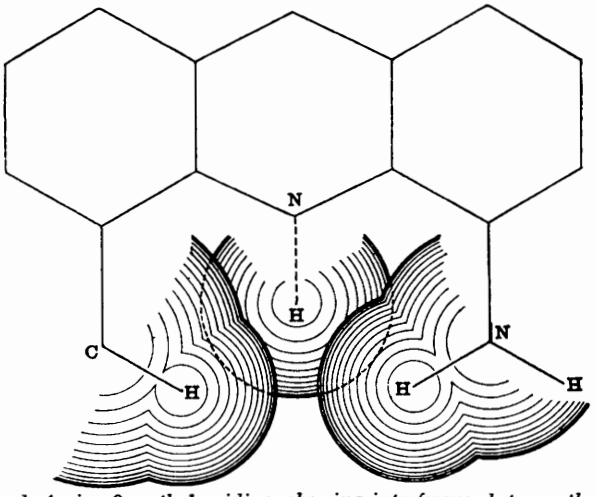
In 1 : 9-diaminoacridine the steric consideration is still more serious, even though the path of access to the ring nitrogen is faintly wider (see Fig. 5). Here the two amino groups are ionised at about the same pH value, and the approach of oxonium ions to the ring nitrogen is then hindered both by a steric effect and by the electrostatic repulsion of the two $-NH_3^{\oplus}$ groups to the approaching oxonium ion. The ring nitrogen atom is not ionised in 5N-hydrochloric acid but accepts a proton in 18N-sulphuric acid.

The steric implications in the case of 1-amino-9-methylacridine are illustrated in Fig. 5. The diagram has been drawn using the bond lengths of Pauling and Huggins (*Z. Krist.*, 1934, **87**, 205) as modified by Schomaker and Stevenson (*J. Amer. Chem. Soc.*, 1941, **63**, 37). The situation can also easily be visualised for 1 : 9-diaminoacridine. The effect of the ionisation of one primary amino group on the ionisation of the other in this substance is expected to be similar to that studied in some dicarboxylic acids (Gane and Ingold, *J.*, 1928, 1594). Since the resonance interaction between the 1- and 9-positions is small, the ruling effect should be the decrease in

active mass of oxonium ions in the vicinity of the second amino group due to electrostatic repulsion by the $-NH_3^{\oplus}$ group. The centres of the amino groups are about 5 A. apart, and the second amino group should differ in pK_a value by about one unit from the first on this count (Bjerrum, *Z. physikal. Chem.*, 1923, **106**, 219).

As far as the ring nitrogen is concerned, the process of ionisation involves the approach of an oxonium ion sufficiently close to the basic centre to enable the exchange of a proton to take place between the two. For this to be possible the proton must, in general, be transported up to about 1·5 A. from the nitrogen atom, *i.e.*, to about the hydrogen bond distance. Fig. 5, however, shows that the undistorted configuration would allow an approach no nearer than 3·5 A. in the plane of the molecule, and the required proximity will be attained only by energetic oxonium ions or at instants when the configuration is distorted by favourable vibrations. Approach to the nitrogen atom from directions out of the plane is not so difficult sterically, but is less likely to result in the formation of an N–H bond since the available *n* orbital is directed mainly in the plane of the rings. It seems reasonable to postulate that the low basicity of the ring nitrogen in 1 : 9-diaminoacridine and 1-amino-9-methylacridine is a steric effect and results from the blocking of approaching oxonium ions by the 1- and 9-groups.

FIG. 5.



1-Amino-9-methylacridine, showing interference between the Van der Waals spheres of the 1- and 9-subsituents and the hydrogen attached to the nuclear nitrogen.

EXPERIMENTAL.

The spectra were observed using a Hilger medium quartz spectrograph with a tungsten spark as light source. The pH 3·0 buffer solution used was a sodium citrate–HCl mixture made up in 33% methanol (International Critical Tables, Vol. 1) and the pH value measured with a glass electrode. The stated value is uncorrected for the effect of alcohol on the electrode.

Grateful acknowledgment is made to Dr. Adrien Albert for the 1-amino-9-methylacridine and for much helpful discussion; also to Dr. F. Lahey for the 1 : 9-diaminoacridine.

CHEMISTRY DEPARTMENT, UNIVERSITY OF SYDNEY. [*Received, November 26th*, 1945.]