

Some Tautomeric Acridines.

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Contrary to the conclusions reached by other workers using other methods, ultra-violet absorption measurements on solutions of 5-dimethyl-amino-, 5-imino-10-methyl-5 : 10-dihydro-, and 5-amino-acridine indicate that the last compound is largely present in the tautomeric form of 5-iminoacridan under the conditions of examination. Similar experiments indicate that acridone and thioacridone are present in solution in the CO and the CS form respectively.

THE question whether 5-aminoacridine is better represented as (I) or as (II), or as a tautomeric mixture, has been disputed. Attempts to decide it from chemical reactions have not been successful and could at best provide only negative evidence in favour of one formulation (cf. Angyal and Angyal, *J.*, 1952, 1461). Although physical methods are usually a better approach to questions of imine-amine tautomerism (cf. Angyal and Angyal, *loc. cit.*), dipole-moment determinations were inconclusive in this case (Short, *J.*, 1952, 4584; Pushkarev and Kokoshko, *Doklady Akad. Nauk S.S.S.R.*, 1953, 93, 77). The similarity of the ultra-violet absorption spectra of 5-aminoacridine and 9-aminoanthracene led Craig and Short (*J.*, 1945, 419) to conclude that the imine form of the acridine played an insignificant part under the conditions of the examination. Similarly, the infra-red absorption spectra of 9-aminoanthracene, 5-aminoacridine, and various other amino-heterocycles were considered by Short (*loc. cit.*) to support the thesis that 9-aminoanthracene

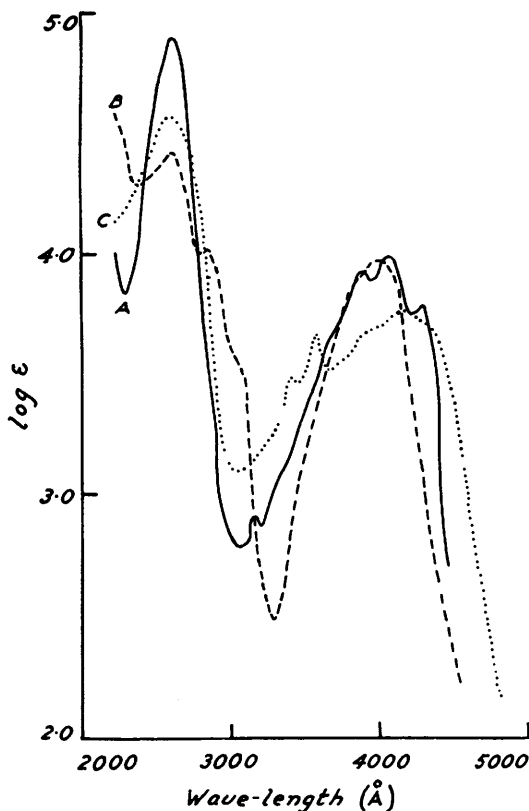


was best represented as such, rather than as anthrone imine, and to confirm his earlier view that 5-aminoacridine did not contain appreciable quantities of the imine form under the conditions of the examination; however, Karyakin, Grigorovskii, and Yaroslavskii (*Doklady Akad. Nauk S.S.S.R.*, 1949, 67, 679) came to the opposite conclusion, after

examination of the infra-red absorption spectra of a number of compounds in the 1—2- μ region.

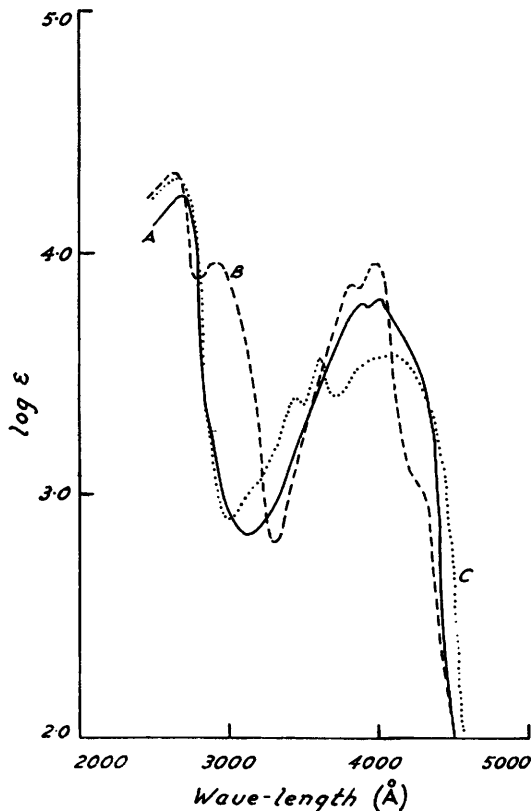
It appeared to us that the similarity between the ultra-violet absorption spectra of 5-aminoacridine and 9-aminoanthracene was insufficiently close to warrant definite structural conclusions, while the similarity of the spectrum of 5-aminoacridine with that of acridone, but not with those of 1-, 2-, 3-, and 4-aminoacridine (Craig and Short, *loc. cit.*), appeared significant. The observations by King, Gilchrist, and Tarnoky (*Biochem. J.*, 1946, 40, 706) that the ultra-violet absorption spectra of 2-chloro-5-diacetylaminoacridine,

FIG. 1.



A, 5-Aminoacridine in alkaline methanol. B, 5-Imino-10-methylacridan in methanol. C, 5-Dimethylaminoacridine in methanol.

FIG. 2.



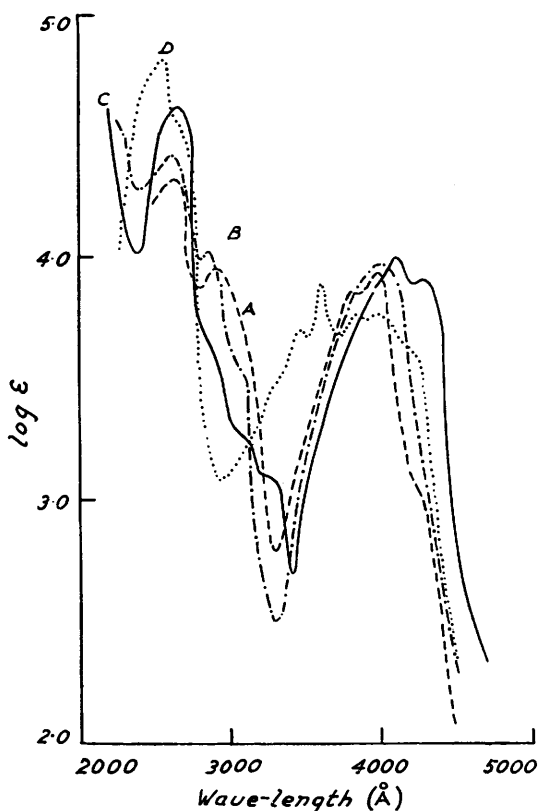
As for Fig. 1, but all in ethyl acetate.

the structure of which was proved by analogy (Wilkinson and Finar, *J.*, 1946, 115), in neutral and acid solution were very similar to those of acridine but dissimilar from those of 5-aminoacridine under the same conditions suggested, although inconclusively, that the latter compound had the imine structure. The absorption spectrum of 5-aminoacridine (I and/or II) was therefore compared (Figs. 1 and 2) with those of 5-imino-10-methylacridan (IV) and 5-dimethylaminoacridine (III), which cannot tautomerise, in methanol and ethyl acetate solution [only 5-dimethylaminoacridine was sufficiently soluble in *cyclohexane* (Fig. 3)]. While the spectra of 5-aminoacridine and the imino-compound (IV) have much in common, that of 5-dimethylaminoacridine (III) is quite different and is remarkably similar to those of 1-, 2-, 3-, and 4-aminoacridines which also exhibit maxima at 3450 and 3600 Å, and have broad bands in the 4000-Å region. The latter comparison indicates that 5-dimethylaminoacridine can be used as a fair spectral model for the amine form. It therefore appears that the unmethylated compound is probably very largely present as the

imine under the conditions of examination. If much of the amine form were present inflexions or maxima would be expected at *ca.* 3400 and 3600 Å as in the case of 5-dimethyl-aminoacridine. It is interesting that similar methods applied to 2- and 4-aminopyridine have shown that the imino-forms can be present in, at most, very small proportion (Anderson and Seeger, *J. Amer. Chem. Soc.*, 1949, 71, 340).

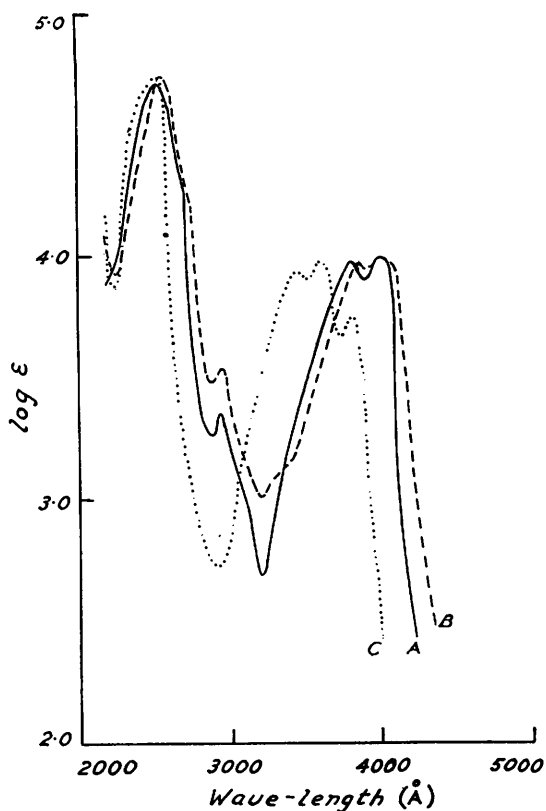
Infra-red absorption spectra of these three acridines (in paraffin pastes) in the carbonyl region appear superficially neither to confirm nor to discredit this conclusion which

FIG. 3.



5-Imino-10-methylacridan, (A) in ethyl acetate, (B) in alkaline methanol. C, 5-Amino-10-methylacridinium iodide in methanol. D, 5-Dimethylaminoacridine in cyclohexane.

FIG. 4.



A, Acridone in methanol. B, 10-Methylacridone in methanol. C, 5-Methoxyacridine in cyclohexane.

receives some support from their fluorescences (see Table). Attempts to measure the infra-red absorption spectrum of 5-aminoacridine and 5-imino-10-methylacridan in chloroform in the 3- μ region failed because of their low solubility. The solid iminoacridan

Acridine	Fluorescence in aqueous ethanol		
	Alkaline	Neutral	Acid
5-Aminoacridine (I or II)	Intense green	Green	Blue
5-Imino-10-methylacridan (IV)	Weak blue-green	Blue-green	Blue-green
5-Dimethylaminoacridine (III)	None	None	None

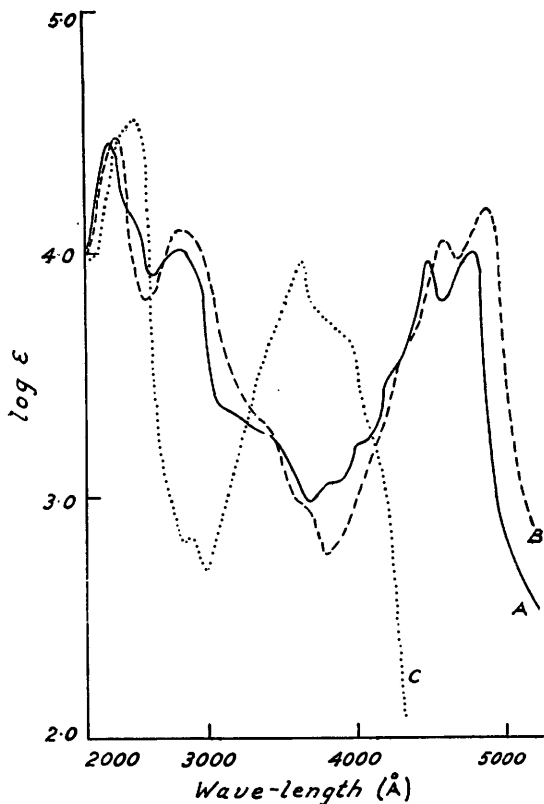
showed two very small maxima in this region in paraffin paste, in contrast to the one which would be expected by analogy with Angyal and Werner's observations (*J.*, 1952, 2911) on the dihydroiminopyridines. For 5-aminoacridine two maxima were found. From this it

might be inferred that the amino-form was present in the solid lattice but such a conclusion requires much further substantiation in view of the likelihood of "mesohydric tautomerism" (cf. Hunter, *J.*, 1945, 806) under these conditions.

The expression used by Angyal and Angyal (*loc. cit.*) to determine the equilibrium constants of the amine-imine system in the pyridine series can be applied to the acridine problem. The approximate pK_a values available (Albert and Goldacre, *J.*, 1943, 454; 1946, 706) for 5-amino-10-methylacridinium bromide and 5-aminoacridine suggest that both the amine and the imine of the latter have the same order of stability. (Incidentally this approach confirms conclusions drawn from optical data in the pyridine series.)

There is also a great similarity between the spectra of 10-methylacridone (Fig. 4) and

FIG. 5.
A, Thioacridone.
B, 10-Methyl(thioacridone).
C, 5-(Methylthio)acridine.
All in methanol.



5-imino-10-methylacridan (Fig. 3). The spectra of the latter compound in ethyl acetate and methanol solutions are similar (Fig. 3), the second being identical with that of 5-amino-10-methylacridinium iodide in methanolic potassium hydroxide. This suggests that dehydration of the acridinium hydroxide first formed is rapid, and provides no evidence for the formation of the intermediate acridan as postulated by Albert and Ritchie (*J.*, 1943, 458); the "acridan" precipitated by aqueous sodium hydroxide from 5-amino-10-methylacridinium salts is presumably the imine hydrate. Acridan itself has a structureless maximum at 2900 Å (Blout and Corley, *J. Amer. Chem. Soc.*, 1947, 69, 763) falling slowly with decrease in wave-length, as is found with other acridans (Tarnoky, *Biochem. J.*, 1950, 46, 297).

Similarly a comparison of the ultra-violet absorption spectra of acridone, 10-methylacridone, and 5-methoxyacridine (Fig. 4) shows that acridone is much better represented as such rather than as 5-hydroxyacridine. Similar conclusions regarding the structure of thioacridone can be drawn from the data on Fig. 5. It is of interest that 5-methoxy-

acridine crystallises from aqueous solvents as the hydrate, which is claimed (Drozdov and Cherntsov, *J. Gen. Chem., U.S.S.R.*, 1944, **14**, 181; cf. Barber, Wilkinson, and Edwards, *J. Soc. Chem. Ind.*, 1947, **66**, 411) to react much more readily than the anhydrous compound with hydrogen cyanide to give 5-cyanoacridine; this led to the supposition that the hydrate was best represented as 5-hydroxy-5-methoxyacridan. As the ultra-violet absorption spectra of anhydrous 5-methoxyacridine in *cyclohexane* and of the hydrate in aqueous methanol are very similar and differ very much from those of acridans this suggestion can no longer be upheld.

EXPERIMENTAL

Aminoacridines.—5-Aminoacridine, m. p. 234°, was prepared from 5-methoxyacridine hydrate according to Barber, Wilkinson, and Edwards (*loc. cit.*). In paraffin paste infra-red max. were at 2.88, 3.04, 6.02, 6.04, 6.19, 6.40, 6.45, 6.59, 6.73, 6.86, 7.15, 7.30, and 7.90 μ .

5-Dimethylaminoacridine (Dupré and Robinson, *J.*, 1945, 529) separated from light petroleum in pale yellow rhombs, m. p. 60° (Found: C, 81.0; H, 6.3; N, 12.0. Calc. for $C_{16}H_{14}N_2$: C, 81.2; H, 6.3; N, 12.5%). In paraffin paste infra-red max. were at 6.15, 6.20, 6.42, 6.50, 6.60, 6.66, 6.82, 6.92, 7.00, 7.10, 7.21, 7.28, and 7.98 μ . There was no maximum near 3 μ .

5-Imino-10-methylacridan (Albert and Ritchie, *loc. cit.*) was a pale brown friable solid, m. p. 134° (Found: N, 13.4. Calc. for $C_{14}H_{12}N_2$: N, 13.5%). Attempted crystallisation from methanol caused gradual decomposition to 10-methylacridone. In paraffin paste the infra-red max. were at 3.02 (very small), 3.08 (very small), 5.98, 6.24, 6.28, 6.46, 6.71, 6.83, 7.32, 7.42, 7.76, 7.90 μ .

5-Amino-10-methylacridinium iodide in methanolic potassium hydroxide showed λ_{max} . 2625 (log ϵ_{max} . 4.42), 2850 (4.22), and 4000 Å (3.97).

Acridones.—Acridone, m. p. 350°, was prepared from 9-chloroacridine according to Albert and Ritchie (*Org. Synth.*, 1942, **22**, 5) and in paraffin paste showed max. at 6.11, 6.26, 6.43, 6.54, 6.87, 7.28, 7.45, and 7.95 μ . 10-Methylacridone, m. p. 203—204° (Eckert and Steiner (*Sitzungsber. Akad. Wiss., Vienna*, 1914, IIb, 1141), in paraffin paste showed max. at 6.13, 6.26, 6.71, 6.84, 7.31, 7.47, 7.76, and 7.89 μ . The absorption max. at 6.11 and 6.13 in the last two compounds is probably due to the carbonyl group. 5-Methoxyacridine hydrate, m. p. 103° (decomp.) (Lehmstedt, *Ber.*, 1935, **68**, 1455), in methanol showed λ_{max} . 2450 (log ϵ_{max} . 4.77), 3560 (4.03), and 3700 Å (3.87); prolonged drying over phosphoric oxide *in vacuo* at 60° yielded anhydrous 5-methoxyacridine, m. p. 65°.

Thioacridones.—Thioacridone (Edinger and Arnold, *J. pr. Chem.*, 1901, **64**, 196) separated from 2% aqueous sodium hydroxide or from methanol in red needles, m. p. 265—267°, which in the former case were ground with boiling water to remove sodium hydroxide (Found, after drying over potassium hydroxide *in vacuo* at room temperature: C, 74.1; H, 4.4. Calc. for $C_{13}H_9NS$: C, 73.9; H, 4.3%). No monohydrate was obtained (cf. Edinger and Arnold). 5-(Methylthio)acridine formed yellow needles, m. p. 113—114° (Edinger and Arnold, *loc. cit.*). 10-Methyl(thioacridone) formed red needles m. p. 263° (cf. Gleu and Schaarschmidt, *Ber.*, 1939, **72**, 1249).

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