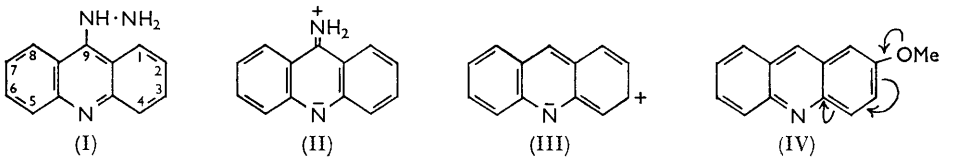
864. *Acridine Syntheses and Reactions. Part VI.*[1] *A New Dehalogenation of 9-Chloroacridine and its Derivatives. Further Acridine Ionisation Constants and Ultraviolet Spectra*

By Adrien Albert

A new oxidative method is described for converting 9-chloroacridines (and hence acridones) into acridines through the corresponding 9-hydrazinoacridines. Contradictions in the literature are resolved regarding the properties of 9-hydrazinoacridine.

Ultraviolet spectra and ionisation constants of several acridines in water are recorded and discussed.

Non-reductive elimination of a halogen atom is often required in heterocyclic chemistry to conserve easily reducible groups. The only known reaction of this kind in the acridine series [1] is to treat 9-chloroacridine in turn with toluene-*p*-sulphonylhydrazine and N-sodium hydroxide at 100°. To open up an alternative route, 9-chloroacridines have now been converted into 9-hydrazinoacridines and these have been oxidised to acridines. Copper salts proved ineffective as oxidising agents, although highly effective in the benzene,[2] pyridine, quinoline, cinnoline, and naphthyridine series.[3] However, oxygen (in the presence of platinum and a trace of alkali at 25°) gave acridine and its 4-methoxy- and 2-cyano-derivatives from the corresponding 9-chloroacridines in 44, 22, and 30% yields, respectively, compared with 73, 70, and 65% by the toluene-*p*-sulphonyl hydrazide method.[1] The new method may be advantageous when substituents sensitive to hot alkali are present.



The identity of 9-hydrazinoacridine, which was in doubt, had first to be established. This substance, first mentioned [4] in 1920 and prepared by condensing 9-chloroacridine with hydrazine (conditions not given), was said to form orange needles, m. p. 169°; 1,2-di-(9-acridyl)hydrazine, produced in the same reaction, was described as dark red crystals, m. p. 265° (both from ethanol). However, in a more recent Paper,[5] "9-hydrazinoacridine" (prepared by heating 9-chloroacridine with hydrazine hydrate in phenol at 130°) was described as pale red prisms, m. p. 265° (from methanol).

In the present work, 9-chloroacridine, refluxed with hydrazine hydrate in ethanol, gave a 78% yield of pale yellow needles, m. p. 171—172° (decomp.) and 15% of dark red

[1] Part V, A. Albert and R. Royer, *J.*, 1949, 1148.
[2] F. D. Chattaway, *J.*, 1907, **91**, 1323.
[3] E. Thielepape and O. Spreckelsen, *Ber.*, 1922, **55**, 2929; A. Albert, *J.*, 1960, 1790.
[4] Meister, Lucius, and Brüning, G.P. 364,031/1920, per Friedländers, *Fortschr. der Teerfarbenfabrik.*, 1926, **14**, 801.
[5] R. M. Acheson and C. W. Jefford, *J.*, 1956, 2676.

Physical properties of some acridines

Acridine	Species *	Ionisation (H_2O; 20°) pK_a	Concn. (M)	A.w.l.†	Spectroscopy in water ‡ $\lambda_{max.}$ (mμ)	log ε	pH
9-Hydrazino	0	—	—	—	230, 288, 384	4·72, 3·92, 3·91	9·5
	+	7·15 ± 0·02	10^{-5}	264	223, 264, 394 + 409 + 431	4·41, 4·69, 3·83 + 4·03 + 3·99	5·0
[1,2-Di-(9-acridyl)hydrazine]	0	—	—	—	235, 299, 468	4·92, 4·18, 4·37	—§
(Unsubstituted)	0	—	—	—	209, 249, *324*, 338 + 346 + 354 + *366*, *380*	4·21, 5·25, *3·61*, 3·83 + 3·85 + 4·02 + *3·66*, *3·44*	8·0
	+	(5·60) ¶	—	—	255, 324 + 338 + 354, 386, 402	5·10, 3·50 + 3·99 + 4·34, 3·50, 3·48	3·0
1-Amino	0	—	—	—	238, 262, 325 + 343 + 349 + 358, 413	4·56, 4·64, 3·14 + 3·37 + 3·32 + 3·57, 3·49	11·0
	+	(6·04)	—	—	236, 287, 343, 358, 524	4·50, 4·55 3·68 3·95, 3·45	2·5
	++	(0·6)	—	—	258, 341 + 358, 389, 403	5·01, 3·97 + 4·29, 3·51, 3·52	5N-HCl
2-Amino	0	—	—	—	*242*, 260, *325* + 339 + 355	*4·42*, 4·89, *3·32* + 3·56 + 3·76	11·0
	+	(5·88)	—	—	256, 273, 356 + 371, 462	4·50, 4·69, 3·81 + 3·92, 3·55	2·5
	++	(1·1)	—	—	257, 339 + 355, 384	5·03, 3·96 + 4·27, 3·50	5N-HCl
3-Amino‖	0	—	—	—	237, 262, 321 + 337 + 353, 410	4·46, 4·83, 3·35 + 3·65 + 3·92, 3·79	11·0
	+	(8·04)	—	—	233, 274, 349 + 365, 454	4·62, 4·65, 4·03 + 4·15, 4·10	2·5
4-Amino	0	—	—	—	239, 262, 327 + 342 + 359, 405	4·27, 4·33, 3·13 + 3·33 + 3·47, 3·46	11·0
	+	(4·40)	—	—	243 + 250, 277, 363, 463	4·48 + 4·49, 4·53, 3·92, 3·20	2·5
	++	(0·5)	—	—	259, 338, 355, 396, 412	4·99, 3·97, 4·30, 3·51, 3·53	5N-HCl
9-Amino (aminoacrine) ‖	0	—	—	—	218, 260, 389 + 406 + 425	4·33, 4·86, 3·83 + 3·89 + 3·66	12, 13, 14
	+	(9·99)	—	—	217, 260, 311, 326, 381 + 401 + 423	4·36, 4·92, 3·21, 3·24, 3·81 + 4·00 + 3·90	6·0
2,6-Diamino	+	8·11 ± 0·03	10^{-4}	485	—	—	—
3,6-Diamino (proflavine) **	0	—	—	—	262, *282*, *292*, 395	4·76, *4·52*, *4·40*, 4·25	12, 13, 14
	+	9·65 ± 0·02	10^{-5}	444	211, 261, *277*, 444	4·32, 4·73, *4·38*, 4·59	7·0
4,5-Diamino	0	—	—	—	270, *362*, 425	4·84, *3·22*, 3·57	7·0
	+	4·12 ± 0·07	10^{-5}	270	(238, 405) ††	—	3·4
	++	2·68 ± 0·04	10^{-5}	270	213, 249, *323*, 337 + *347* + 353 + *366*, *385*	4·11, 5·23, *3·47*, 3·79 + *3·84* + 3·99 + *3·70* *3·44*	0·0
9-Amino-1,2,3,4-tetrahydro	0	—	—	—	218, 237, 313 + 317	4·40, 4·54, 3·85 + 3·85	12
(tacrine)	+	10·00 ± 0·05	10^{-5}	335	218, 240, 323, 336	4·21, 4·58, 4·04, 3·99	7
9-Amino-3-chloro	+	9·34 ± 0·03	10^{-5}	275	—	—	—
9-Amino-3-chloro-7-methoxy	+	8·99 ± 0·05	10^{-4}	340	—	—	—
9-Amino-2-methoxy	+	9·66 ± 0·04	10^{-4}	435	—	—	—
4-Amino-5-methyl	+	3·95 ± 0·04	10^{-5}	262	—	—	—
9-Amino-4-methyl	+	10·29 ± 0·03	10^{-5}	300	—	—	—
4,5-Dimethyl	+	4·56 ± 0·05	10^{-5}	358	—	—	—
9-Dimethylamino	+	9·13 ± 0·04	10^{-5}	242	—	—	—
2-Methoxy	+	5·52 ± 0·03	10^{-5}	364	—	—	—
4-Methoxy	+	5·31 ± 0·03	10^{-5}	358	—	—	—
2-Methyl	+	5·79 ± 0·04	10^{-5}	351	—	—	—
4-Methyl	+	5·65 ± 0·03	10^{-5}	357	—	—	—
1,2,3,4-Tetrahydro	+	6·43 ± 0·03	10^{-4}	318	—	—	—

* Neutral species (0), cation (+), or dication (++). † Analytical wavelength (mμ), spectrometric determination. ‡ Inflections are in italics. § In methanolic 0·01N-potassium hydroxide. ¶ Values in parentheses from A. Albert and R. Goldacre, *J.*, 1946, 706, and 1943, 454. ‖ The second pK_a values of 3- and 9-aminoacridine are about −1·4, and < −2, respectively. ** The second pK_a is 1·5 (G. R. Haugen and W. H. Melhuish, *Trans. Faraday Soc.*, 1964, **60**, 386. †† From difference spectra, see text.

prisms, m. p. 265° (decomp.). Both substances gave satisfactory analytical figures (C, H, and N), the former for 9-hydrazinoacridine, and the latter for 1,2-di-(9-acridyl)hydrazine. Ethanolic solutions of the former gave intense orange and scarlet colours with benzaldehyde and *p*-nitrobenzaldehyde, whereas those of the substance of m. p. 265° were unaffected. Recently, 1,2-di-(9-acridyl)hydrazine was made [6] by reducing 9,9′-azoacridine and had the same ultraviolet spectrum as had this higher-melting substance. Clearly, the substance m. p. 171—172° is 9-hydrazinoacridine, as is the substance so named in ref. 4.

The ultraviolet spectrum and pK_a of 9-hydrazinoacridine are reported in the Table. The magnitude of the pK_a (7·15), compared with those of 9-aminoacridine (9·99) and phenylhydrazine (5·27) does not establish the position of protonation in the mono-cation. The hypsochromic displacement of the ultraviolet spectrum of the neutral molecule relative to that of 9-aminoacridine suggests that the latter has less contribution [7] of the type (II) in the resonance hybrid than has 9-hydrazinoacridine. The spectrum of the cation of 9-hydrazinoacridine resembles that of 9-aminoacridine. The large bathochromic shift on protonation of 9-hydrazinoacridine is more indicative of protonation on (*a*) the ring-nitrogen atom (as in 9-aminoacridine [7]) than on (*b*) the primary amino-group. Interpretation (*b*) is discounted by the feeble hypsochromy of phenylhydrazine (from 283 to 276, and from 241 to 227 mμ without much loss of intensity [8]) when converted into the cation.

Ultraviolet spectra (in water) of acridine, the five monoaminoacridines, and 3,6- and 4,5-diaminoacridine have been redetermined because previous determinations [9] lacked sufficient resolution. The results (see Table) show how closely the spectra of 1- and 4-aminoacridine agree, as do those of 2- and 3-aminoacridine, as would be expected. The di-cations, because the protonation of the primary amino-group cancels its contribution to the spectrum, have spectra closely similar to that of the cation of acridine. It has not previously been possible to demonstrate these points (summarised in ref. 9) so convincingly. The spectrum of the di-cation of 4,5-diaminoacridine (see Table) is remarkable in resembling that of the *neutral species* of acridine, steric hindrance preventing protonation of the ring nitrogen atom.[10] Because of the proximity of the two ionisation constants, the spectrum of the mono-cation, now examined for the first time, has been obtained as a "difference spectrum" by working at a pH value intermediate between the two pK_a values, and subtracting the contributions (17 and 42%, respectively) of the neutral species and the di-cation. The two characteristic peaks (238 and 405 mμ; log ε 4·06 and 3·39) occur also in the neutral species of 4-aminoacridine indicating that the mono-cation is (most unusually) protonated on a primary amino-group.

The Table also shows that the spectrum of the neutral species of 9-aminoacridine (also that of 3,6-diaminoacridine) does not change as the pH is varied from 12 to 14, thus discounting a prediction [11] of an anionic pK of 12 for both substances on the basis of polarographic reduction at these high pH values.

The hitherto unrecorded spectrum of 9-amino-1,2,3,4-tetrahydroacridine (tacrine) is similar to that of 4-aminoquinoline.[12] Like the spectrum of the latter, but unlike that of 9-aminoacridine, it shows a pronounced bathocrhomic shift on protonation.

pK_a values of many acridines hitherto examined only in 50% ethanol have now been determined in water (see Table). The striking feature emerges that a methoxy-group in the 2-position does not exert the $+M$ base-strengthening effect seen in 4-methoxyaniline (and equally manifest as an acid-weakening effect in 4-methoxyphenol and 4-methoxybenzoic acid). Instead it exerts a base-weakening effect (compare the pK_a values of

[6] G. Cauquis and G. Fauvelot, *Bull. Soc. chim. France*, 1964, 2014.
[7] S. J. Angyal and C. L. Angyal, *J.*, 1952, 1461.
[8] N. A. Valyashko and I. T. Depeshko, *Zhur. obshchei Khim.*, 1950, **20**, 479.
[9] A. Albert, "The Acridines," Edward Arnold, London, 1951.
[10] D. P. Craig, *J.*, 1946, 534.
[11] R. C. Kaye and H. I. Stonehill, *J.*, 1951, 2638.
[12] E. A. Steck and G. W. Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397.

2-methoxy-, 9-amino-2-methoxy-, and 9-amino-3-chloro-7-methoxy-acridine with those of acridine, 9-amino-, and 9-amino-3-chloro-acridine, respectively). It is concluded that forms such as (III), which contribute to the base strength of acridine, are electronically incompatible with the form (IV) through which the $+M$ effect of a 2-methoxy-group is exerted. Hence either (*a*) form (IV) is suppressed, and the methoxy-group exerts a $-I$ effect, or (*b*) partial antagonism of form (III) by form (IV) takes place. These substances were examined as prototypes of the antimalarial, mepacrine, in which the base-weakening character [9] of the 2-methoxy-group was unexpected.

The pK_a of 4,5-dimethylacridine is notable for being 1·68 units greater than the value in 50% ethanol; acridine is greater by 1·49, a difference that has been considered unusually large but explicable by differential solvation, the lipophilic neutral species preferring ethanol and the cation water.[13]

Experimental

Microanalyses were performed by Dr. J. E. Fildes, ionisation constants by Dr. D. D. Perrin (using methods developed in this Department [14,15]), and spectra by Dr. E. Spinner, and their respective staffs. The determination of the two pK_a values of 4,5-diaminoacridine, difficult because of their closeness, necessitated the use of a single analytical wavelength (at which the plot of optical density against pH showed two discontinuities). These results, by the solution of three simultaneous equations, gave preliminary values for the two pK_a values and for the density of the mono-cation. The pK_a values were then refined in the appropriate pH regions 4·25—3·45, and 3·45—2·56.

Ultraviolet spectra were measured first on a Shimadzu model RS27 recording spectrophotometer and then $\lambda_{max.}$ and ε values were redetermined on a Hilger "Uvispek" manual instrument.

9-Hydrazinoacridine.—9-Chloroacridine [16] (5 g.) was added, with stirring, to a refluxing solution of hydrazine hydrate (10 ml., 99%) in ethanol (250 ml.) during 10 min., and refluxing continued for 20 min. more. Water (1 l.), preheated to 75°, was then added and the suspension was quickly filtered. The filtrate, refrigerated, gave orange needles (3·8 g.), and extraction of the liquor with chloroform gave 0·6 g. more. The combined crops, recrystallised from 30 parts of benzene, gave *9-hydrazinoacridine* (78% yield) as pale yellow needles, m. p. 171—172° (effervesces), very soluble in cold ethanol and in N-acetic acid; the sulphate and hydrochloride (orange) are poorly soluble in water (Found, for material dried at 80°/0·01 mm.: C, 74·4; H, 5·4; N, 19·9. $C_{13}H_{11}N_3$ requires: C, 74·6; H, 5·3; N, 20·1%). Nitrogen analysis was carried out by the Kirsten–Dumas procedure.

The cake from the hot dilute ethanolic filtration, recrystallised from 200 parts of ethanol, gave *1,2-di-(9-acridyl)hydrazine* (15% yield) as red prisms, m. p. 265° (effervesces) (Found, for material dried as above: C, 80·8; H, 4·7; N, 14·7. $C_{26}H_{18}N_4$ requires: C, 80·8; H, 4·7; N, 14·5%). The purple hydrochloride is insoluble in cold water.

Acridine from the Hydrazine.—9-Hydrazinoacridine (0·5 g.) in ethanolic N-sodium hydroxide (15 ml.) was stirred with platinum (from 0·1 g. PtO_2) for 24 hr. at 25° while oxygen was bubbled through the mixture, which was finally evaporated to dryness in a slight vacuum. The residue, sublimed at 98°/0·01 mm., gave a 55% yield of acridine, m. p. 107—109° (lit.,[9] 110°).

9-Hydrazino-4-methoxyacridine.—9-Chloro-4-methoxyacridine [17] (2 g.) was refluxed with hydrazine hydrate (20 ml.), water (40 ml.), and ethanol (40 ml.) for 30 min. Kieselguhr was added and the suspension quickly cooled and filtered. The filtrate, refrigerated, deposited crystals which, after recrystallisation from 22 parts of ethanol, gave the scarlet *9-hydrazino-4-methoxyacridine* (55%), m. p. 145° (Found, for material dried in air at 110°; C, 70·35; H, 5·2; N, 17·4. $C_{14}H_{13}N_3O$ requires C, 70·3; H, 5·5; N, 17·6%). A solution of this substance (0·5 g.) and sodium hydroxide (0·01 g.) in ethanol (30 ml.) was oxygenated over platinum for 3 hr. as above. Repeated sublimation at 130°/0·05 mm. gave 4-methoxyacridine (40% yield), m. p. and mixed m. p. 134° (lit.,[9] 134°).

[13] A. Albert and R. J. Goldacre, *J.*, 1946, 706.
[14] A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962.
[15] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.
[16] A. Albert and B. Ritchie, *Org. Synth.*, 1942, **22**, 5.
[17] K. Gleu and S. Nitzsche, *J. prakt. Chem.*, 1939, **153**, 200.

2-*Cyano*-9-*hydrazinoacridine*.—9-Chloro-2-cyanoacridine [9] (1 g.), pyridine (30 ml.), and hydrazine hydrate (0·5 ml.) were heated on a steam-bath for 5 min., then poured into water (400 ml.). After refrigeration, the crystals, filtered off and recrystallised from pyridine trihydrate (b. p. 93°), gave 2-*cyano*-9-*hydrazinoacridine* as red-brown crystals, partial decomp. about 210°. It is soluble in 100 parts of boiling ethanol (Found, for material dried in air at 110°: C, 71·5; H, 4·4; N, 24·3. $C_{14}H_{10}N_4$ requires C, 71·8; H, 4·3; N, 23·9%). This substance, oxygenated as the 4-methoxy-analogue, gave 2-cyanoacridine (35%), m. p. and mixed m. p. 208° (lit.,[9] 209°).

For the preparation of the other substances in the Table, see ref. 9.

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