

Heterocyclic Studies. Part 41.¹ Disproportionation of Acridinium Compounds and Mass Spectra of Some Acridines

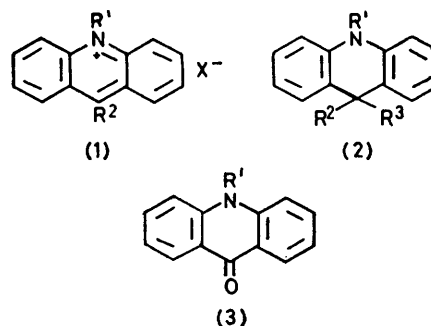
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Deuterium labelling is used to show that disproportionation of 10-methylacridinium iodide involves transfer of a hydride ion from the 9-position of the pseudo-base form of the compound to the 9-position of the 10-methylacridinium ion. Mass spectrometric fragmentations of some acridine and acridan derivatives have been elucidated with the aid of deuterium-labelled compounds.

ACRIDINIUM salts (1) undergo characteristic reactions at the highly electron-deficient 9-position.² For example they form 9-hydroxyacridan derivatives (2; R³ = OH) on treatment with hydroxide ions, as shown by conductimetric studies,³ u.v. spectroscopy,⁴ and fluorimetry.⁵ Such 9-hydroxy-derivatives may give corresponding 9-ethoxy-compounds on crystallisation from ethanol.⁶

In the absence of a 9-substituent, acridinium compounds may undergo base-induced disproportionation to the corresponding acridan (2; R² = R³ = H) and acridone (3) derivatives.⁷ A recent study of the disproportionation of some 10-alkylpyrimido[4,5-*b*]quinolinium compounds⁸ showed that the reactions involved transfer of a hydride ion from the 5-position of one molecule to the 5-position of another, and it seemed likely that the reaction undergone by acridinium salts is analogous. This has now been investigated for the case of 10-methylacridinium iodide (1; R¹ = Me, R² = H, X = I),

Acridone (3; R¹ = H) was reduced by sodium and butan[²H]ol to [9,9-²H₂]acridan (2; R¹ = H, R² = R³ = ²H)⁹ and the product was oxidised by dichromate to



[9-²H]acridine as described for unlabelled acridan.¹⁰ The final product was shown by ¹N n.m.r. and mass spectrometry to have an isotopic purity >98%. Methylation

¹ Part 40, J. Clark and M. Curphey, *J.C.S. Perkin I*, 1855.

² R. M. Acheson, 'Acridines,' Interscience, New York, 1956, p. 239.

³ J. G. Aston, *J. Amer. Chem. Soc.*, 1931, **53**, 1448; A. Hantzsch and M. Kalb, *Ber.*, 1899, **32**, 3109.

⁴ J. J. Dobbie and C. K. Tinkler, *J. Chem. Soc.*, 1905, 269.

⁵ R. J. Goldacre and J. N. Phillips, *J. Chem. Soc.*, 1949, 1724.

⁶ H. Decker and P. Becker, *Ber.*, 1913, **46**, 969.

⁷ A. Pictet and E. Patry, *Ber.*, 1902, **35**, 2534.

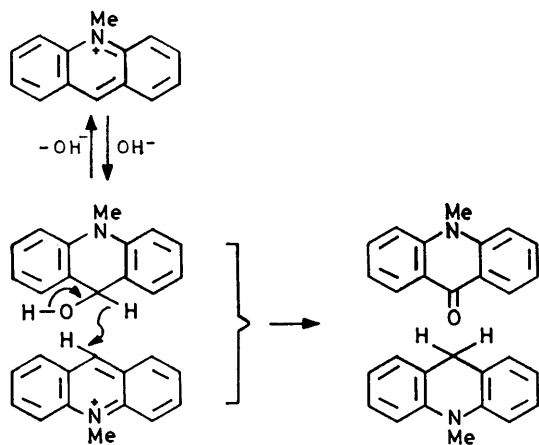
⁸ J. Clark and B. Parvizi, *J.C.S. Perkin I*, 1976, 131.

⁹ S. Steenken, *Tetrahedron Letters*, 1970, 4791.

¹⁰ A. Albert, 'The Acridines,' 2nd edn., Arnold, London, 1966, p. 27.

by methyl iodide gave 10-methyl[9-²H]acridinium iodide.

The salt (1; R¹ = Me, R² = ²H, X = I) underwent disproportionation on treatment with aqueous sodium hydroxide as described for the unlabelled analogue.⁷ The products were a steam-volatile compound which proved to be 10-methyl[9,9-²H₂]acridan (2; R¹ = Me, R² = R³ = ²H), with a high degree of isotopic purity (>95%), and the non-volatile 10-methylacridone (3; R¹ = Me). An unlabelled specimen of 10-methylacridinium iodide¹¹ (1; R¹ = Me, R² = H, X = I) underwent disproportionation in a mixture of sodium deuterioxide and deuterium oxide to give 10-methylacridan (2; R¹ = R² = R³ = H), with no detectable excess of deuterium, and 10-methylacridone (3; R¹ = Me). Each disproportionation yielded a quantity of acridone relative to acridan greater than the expected equimolar ratio. This was most probably due to partial oxidation of the acridan, which occurs readily,¹² in spite of some simple precautions to limit this. The two experiments, however, did make it clear that the extra hydrogen atom acquired by an acridinium compound during disproportionation comes exclusively from the 9-position of another acridine molecule and that the migrating hydrogen is never completely free. In view of the base-catalysed nature of the transfer, the fact that the transfer occurs to a cationic species, and that it proceeds in a good ionising medium, it is extremely probable that the hydrogen is transferred as hydride ion. The facts fit the mechanism shown in Scheme 1.

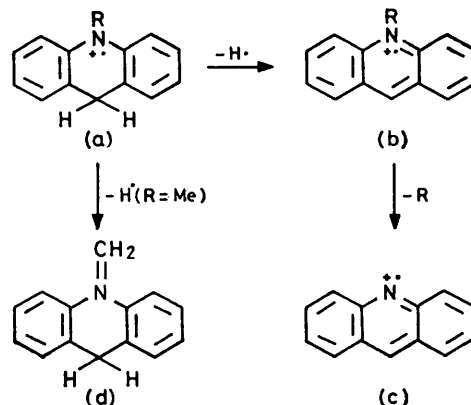


SCHEME 1

If the acridinium salt readily accepts a hydride ion at position 9, as suggested, then acridinium salts should be readily reduced by hydride ion donors; this proved to be the case. 10-Methylacridinium iodide was reduced to 10-methylacridan (2; R¹ = R² = H) with sodium formate in formic acid or formamide or by *N*-methylformamide

alone. Other acridinium salts have been reduced by similar reagents.¹³

Mass Spectra.—Mass spectrometry was used to examine the various labelled and unlabelled acridine derivatives; the results threw some light on the fragmentation



SCHEME 2

of the compounds as well as revealing the extent of isotopic labelling.

The spectrum of [9-²H]acridine is essentially similar to the published spectrum of acridine¹⁴ except that the *m/e* values of all the major peaks are one unit higher. This is in agreement with a suggested rationale.¹⁵

The mass spectrum of acridan (2; R¹ = R² = R³ = H) [Figure 1(a)]* was complex in the molecular ion region, with losses of 1, 2, and 3 hydrogen atoms giving peaks of appreciable intensity. Comparison with the spectrum of its 9,9-dideuterio-derivative (2; R¹ = H, R² = R³ = ²H) [Figure 1(b)] shows that the first loss occurs, as expected by analogy with other acridans,^{15,16} largely from the 9-position to give the ion (b; R = H) (Scheme 2). The 10-deuterio-derivative (2; R¹ = ²H, R² = R³ = H) [Figure 1(c)] chiefly loses a hydrogen atom and then a deuterium atom, so the second loss is mainly from the 10-position to give the ionised acridine (c) (Scheme 2). However the spectrum of the 9,9,10-trideuterio-derivative (2; R¹ = R² = R³ = ²H) [Figure 1(d)] shows losses of single mass units as well as the expected two successive losses of two mass units, so some hydrogen scrambling probably occurs between the 9- and 10-positions and the adjacent aromatic protons. The complicated molecular ion regions made it difficult to deduce the extent of labelling from the 70 eV spectra, but they were considerably simplified at lower ionising energies. In the 10 eV spectra (Figure 2) the molecular ion was the only significant peak from both unlabelled and 9,9-dideuterio-compounds.

* Figures 1—3 are available as Supplementary Publications No. SUP 22076 (5 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

¹¹ F. Kröhnke and H. L. Honig, *Chem. Ber.*, 1957, **90**, 2215.

¹² Ref. 10, p. 333.

¹³ M. Gomberg and D. L. Tabern, *J. Amer. Chem. Soc.*, 1926, **48**, 1345; G. M. Kosalopoff and C. S. Shoepfle, *ibid.*, 1954, **76**, 1276.

¹⁴ 'Registry of Mass Spectral Data,' vol. I, ed. E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Wiley, New York, 1974, p. 712.

¹⁵ Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds,' Wiley Interscience, New York, 1971, p. 419.

¹⁶ H. Mautsch and V. Zanker, *Tetrahedron Letters*, 1966, 4211.

The spectrum of 10-methylacridan (2; $R^1 = \text{Me}$, $R^2 = R^3 = \text{H}$) [Figure 3(a)] shows that the loss of a single hydrogen atom gives rise to the base peak, and comparison with the spectrum of its 9,9-dideuterio-derivative (2; $R^1 = \text{Me}$, $R^2 = R^3 = {}^2\text{H}$) [Figure 3(b)] proves that, at 70 eV, the loss occurs mainly from the 9-position (Scheme 2) to give an *N*-methylacridinium ion (b; $R = \text{Me}$). Hydrogen scrambling followed by loss of a proton, again from position 9, probably accounts for some of the $M - 1$ peak in the spectrum of the 9,9-dideuterio-derivative, but the $M - 1$ ion is fairly abundant and it is likely that an ion presumably analogous to (d) results from loss of a proton from the methyl group. At 20 eV [Figure 2(c)] the latter reaction is largely suppressed and only deuterium loss to give a labelled version of ion (b; $R = \text{Me}$) is apparent. The latter decomposes by loss of its methyl group to give ionised acridine (c). Spectra at 10 eV (Figure 2) again showed a greatly simplified molecular ion region which enabled the degree of labelling to be assessed.

EXPERIMENTAL

[9,9- ${}^2\text{H}_2$]Acridan.⁹—Acridone (1.5 g) was heated under reflux with butan[${}^2\text{H}$]ol (61.5 ml) while sodium (4.5 g) was added in six approximately equal portions at intervals of 5 min, and for a further 30 min. The cooled solution was cautiously diluted with water (65 ml) and the butanol removed by steam distillation. The solid was filtered off and crystallised from ethanol by slow addition of water to yield [9,9- ${}^2\text{H}_2$]acridan (0.96 g), m.p. 170–172°, τ 4.1br (1 H, s, NH) and 2.75–3.5 (8 H, m, aromatic) (Found: M^+ , 183.1019. $\text{C}_{13}\text{H}_9{}^2\text{H}_2\text{N}$ requires M , 183.1017).

[9- ${}^2\text{H}$]Acridine.—[9,9- ${}^2\text{H}_2$]Acridan (0.9 g) was stirred with water (108 ml) under reflux while a solution of potassium dichromate (0.44 g) in boiling water (7.5 ml) was added in two equal portions at 5 min intervals. The mixture was heated for a further 5 min, then more dichromate (1.25 g) was added and the mixture allowed to cool. Next day the precipitate was filtered off and suspended in hot water (35 ml); the suspension was treated with aqueous ammonia (9 ml; d 0.88), brought to the boil, and quickly cooled and filtered. The residue was dissolved in hot 0.5N-hydrochloric acid (60 ml), filtered from a trace of acridan, and reprecipitated with aqueous ammonia. The product (0.6 g) had m.p. 108–109°, τ 1.55–2.6 (m) (Found: M^+ , 180.0790. $\text{C}_{13}\text{H}_9{}^2\text{HN}$ requires M , 180.0798).

10-Methyl[9- ${}^2\text{H}$]acridinium Iodide.—A solution of [9-

${}^2\text{H}$]acridine (0.53 g) in hot dimethylformamide (2 ml) was treated with methyl iodide (0.6 g) and kept at room temperature for 16 days. The product (0.6 g), m.p. 224° (decomp.), was filtered off and washed with ether (Found: M^+ , 322.0067. $\text{C}_{14}\text{H}_{11}{}^2\text{HIN}$ requires M , 322.0079).

Disproportionation of 10-Methyl[9- ${}^2\text{H}$]acridinium Iodide.—The acridinium salt (1 g) was dissolved in warm water and kept under nitrogen while an excess of 2N-sodium hydroxide was added. The mixture was steam distilled and the non-volatile solid which remained was filtered off and crystallised from ethanol to yield 10-methylacridone (0.27 g), m.p. 190–192° (lit.,¹⁷ 199°), τ 6.2 (3 H, s, CH_3), 2.2–2.9 (6 H, m, 2-, 3-, 4-, 6-, and 7-H), and 1.50 (2 H, d, J 10 Hz, 2- and 8-H). The steam-volatile compound was filtered off and crystallised from ethanol by slow addition of water to give 10-methyl[9,9- ${}^2\text{H}_2$]acridan (0.12 g), m.p. 93–94°, τ 6.67 (3 H, s, CH_3) and 2.4–3.4 (8 H, m, aromatic) (Found: M^+ , 197.1179. $\text{C}_{14}\text{H}_{11}{}^2\text{H}_2\text{N}$ requires M , 197.1173).

Reduction of 10-Methylacridinium Iodide.—(a) The acridinium salt (1 g), formic acid (30 ml), and sodium formate (5 g) were heated under reflux for 5 h. The mixture was cooled and water added. The product was filtered off and crystallised from ethanol by slow addition of water to yield 10-methylacridan (0.33 g), m.p. 93–94° (lit.,⁷ 96°).

(b) In a similar reaction with formamide (30 ml) and sodium formate (5 g) the acridinium salt (1 g) yielded 10-methylacridan (0.33 g), m.p. 93–94°. When the experiment was repeated without sodium formate the yield was only 0.05 g.

(c) The acridinium salt (1 g) and *N*-methylformamide (30 ml) were heated under reflux for 5 h, and the mixture was treated as in (a) to yield 10-methylacridan (0.4 g), m.p. 93–94°.

Mass spectra were measured with an A.E.I. MS 902S spectrometer with source temperature *ca.* 220 °C, accelerating voltage 8 kV and ionising energy 70 eV except where otherwise stated. Low resolution spectra were measured at a resolving power of 1000 and accurate mass measurements at a resolving power of 10 000. Samples were introduced on a direct insertion probe.

The spectrum of [10- ${}^2\text{H}$]acridan was obtained by passing the unlabelled compound into a previously deuteriated source while deuterium oxide was admitted simultaneously through a separate inlet system. The spectrum of [9,9,10- ${}^2\text{H}_3$]acridan was similarly obtained by using [9,9- ${}^2\text{H}_2$]acridan as the compound admitted.

[7/300 Received, 21st February, 1977]

¹⁷ K. Lehmstedt and H. Hundertmark, *Ber.*, 1931, **64**, 2386.