The Bromination of Acridine.

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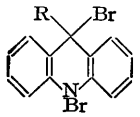
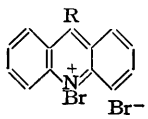
Acridine and 5-phenylacridine with bromine in carbon tetrachloride give addition compounds, formulated as *N*-bromoacridinium bromides. In acetic acid acridine gives a mixture of 3-bromo- and 3 : 7-dibromo-acridine, identical with synthetic specimens of undoubted constitution.

Acridine has been reported (Senier and Austin, *J.*, 1904, 1196) to react in chloroform with chlorine, bromine, and iodine to give a series of addition compounds. These compounds were inadequately characterised, and occasionally were formulated as acridans (I; R = H) on account of their non-fluorescence; attempts to prepare salts were stated to give the corresponding salts of acridine. Early accounts (Dunstan and Oakley, *Ber.*, 1906, **39**, 981; Dunstan and Hilditch, *J.*, 1907, 1659) of the bromination of 5-phenylacridine and derivatives are similar, and the addition compounds formed are stated to give *N*-methyl methosulphates of the original acridines with hot methyl sulphate.

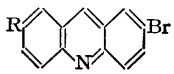
In order to clarify the situation, a carbon tetrachloride solution of acridine was treated with bromine. An orange addition compound was immediately precipitated, and a similar product was obtained from 5-phenylacridine. Analyses indicated that each acridine had combined with one mol. of bromine. The addition compounds did not fluoresce in chloroform, were unstable, and smelt of bromine; all the bromine was "available" on treatment of these compounds with acidified potassium iodide. Attempted crystallisation of the phenylacridine addition product from ethanol gave 5-phenylacridine hydrobromide in good yield. The extreme solubility of acridine hydrobromide in ethanol doubtless precluded its separation in the case of the acridine adduct. However, bromine was evolved when the latter was boiled with dilute hydrochloric acid and basification then precipitated acridine. Only two structures (I and II) can easily account for these results. The ultra-violet absorption spectra are, however, consistent only with the *N*-bromoacridinium bromide formulation (II). The spectrum of the acridine adduct is virtually identical with that of acridine hydrobromide (Fig. 1) while acridan is known to have only a flat maximum at *ca.* 2900 Å and no appreciable absorption near 3500 Å (Blout and Corley, *J. Amer. Chem. Soc.*, 1947, **69**, 763). Very similar results were obtained with the phenylacridine derivatives (Fig. 2); the small peak at 3600 Å in the phenylacridan curve is almost certainly due to the presence of some phenylacridine formed by aerial oxidation. The existence of these *N*-bromoacridinium bromides lends some support to the hypothesis of



(I)



(II)



(III)

Lehmstedt and Dostal (*Ber.*, 1939, **72**, 1071) that 10-chloro-5-phenylacridinium chloride is an intermediate product in the reaction between 5-phenylacridine 10-oxide and hydrochloric acid. Similar compounds may exist in the quinoline series (cf. Meisenheimer, *Ber.*, 1926, **59**, 1848; Bobranski, *Ber.*, 1938, **71**, 578), and *N*-bromopyridinium bromide may be the source of bromine cations in pyridine-catalysed brominations.

The substitutive bromination of acridine by *N*-bromosuccinimide in the presence of benzoyl peroxide, which presumably takes place by a free-radical mechanism, gives a mixture of two monobromoacridines and three dibromoacridines of unknown constitution among other products (Schmidt and Leutenegger, *Helv. Chim. Acta*, 1947, **30**, 1965). Nitration of acridine (Lehmstedt, *Ber.*, 1938, **71**, 808), in agreement with electron-density calculations (Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87), gives largely 3-nitroacridine and it was thought that cationoid bromination would effect substitution at the same position. Such was the case, and acridine with bromine in acetic acid gave a difficultly separable mixture of 3-bromo- (III; R = H) and 3 : 7-dibromo-acridine

FIG. 1. FIG. 2.

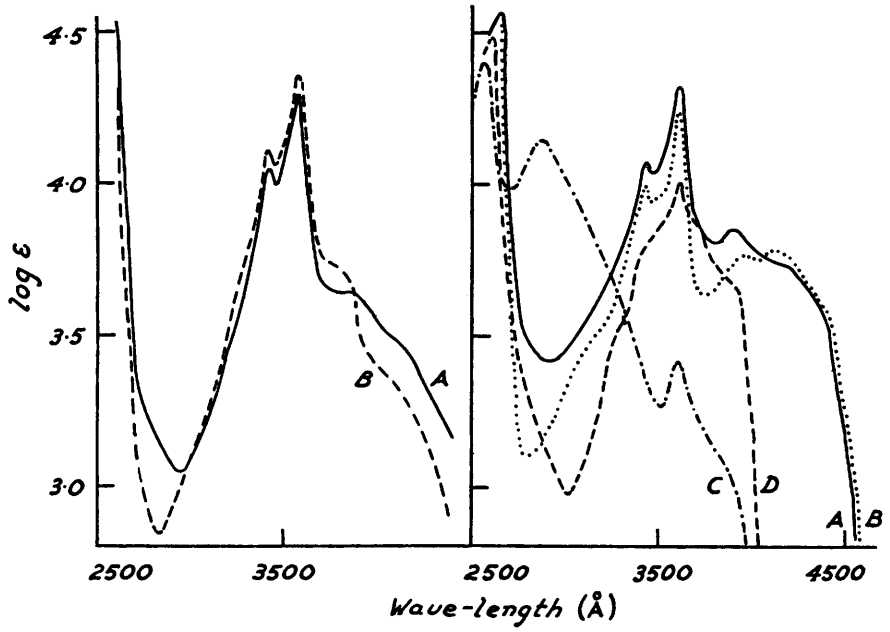


FIG. 1. *A*, 10-*Bromoacridinium bromide*. *B*, *Acridine hydrobromide*.
FIG. 2. *A*, 10-*Bromo-5-phenylacridinium bromide*. *B*, 5-*Phenylacridine hydrobromide*. *C*, 5-*Phenylacridan*. *D*, 5-*Phenylacridine*.

(III; R = Br), identical with authentic specimens. These acridines, which have almost the same melting points as two of those of Schmidt and Leutenegger, and 1 : 3 : 7 : 9-tetrabromoacridine were prepared from the corresponding 5-chloroacridines by reaction with toluene-*p*-sulphonhydrazide and subsequent decomposition with alkali (cf. Albert and Royer, *J.*, 1949, 1148).

The reduction of phenylacridine to phenylacridan by sodium dithionite (hydrosulphite), a reagent used by Scholl and Neuberger (*Monatsh.*, 1918, **39**, 238) for the reduction of acridine, deserves comment as this procedure is much more convenient than the usual catalytic hydrogenation.

EXPERIMENTAL

All ultra-violet absorption spectra were measured in dry, ethanol-free chloroform.

Acridine and Bromine.—(*a*) Bromine (2·0 g.) in carbon tetrachloride (10 ml.) was slowly added to acridine (2·0 g.) in carbon tetrachloride (25 ml.) at room temperature. The orange-yellow precipitate (3·6 g., 95%) of 10-*bromoacridinium bromide* was washed with carbon tetrachloride and, after drying *in vacuo* over potassium hydroxide and paraffin wax, had m. p. 108° (Found : C, 45·8; H, 2·6; Br, 47·7. $C_{13}H_9NBr_2$ requires C, 46·0; H, 2·7; Br, 47·2%). It showed $\lambda_{max.}$ 3410 and 3570 Å (log ε 4·05 and 4·30 respectively). All operations on 10-bromo-

acridinium bromide were carried out with freshly prepared material as the compound was unstable. The " available bromine " was determined by dissolving a weighed portion in dilute acetic–sulphuric acid. The iodine liberated by the addition of potassium iodide was estimated by titration with standard sodium thiosulphate. The end-point (starch) of the titration was not very clear (Found : Br, 41·8, 42·0%).

(*b*) Bromine (4·0 g.) was added to a solution of acridine (1·45 g.) in glacial acetic acid (70 ml.), and the mixture refluxed for 3 hr. Most of the solvent was then removed *in vacuo*, the residue poured into stirred aqueous ammonia, and the precipitate of bromoacridines (1·62 g.) collected and dried. It was almost completely soluble in chloroform, but chromatography from this solvent or benzene–light petroleum (b. p. 60—80°) over alumina effected little separation. The least soluble fraction obtained by repeated recrystallisation from ethanol was 3 : 7-*dibromoacridine*, m. p. 247°, mixed m. p. 249° (see below) (Found : C, 46·7; H, 2·1%). The infra-red absorption spectra of the two samples were identical.

The more soluble fraction had m. p. 167°, unchanged by further crystallisation. It was dissolved in the minimum volume of 2N-sulphuric acid and fractionally precipitated by aqueous sodium hydroxide. One fraction, after crystallisation from ethanol, had m. p. 172° and m. p. 173° on mixture with authentic 3-bromoacridine (see below). The infra-red absorption spectra of the substances in paraffin paste were identical. Various attempts to obtain a more homogeneous product from the bromination reaction by altering the conditions were unsuccessful.

Refluxing acridine (1·0 g.) with a large excess (10 ml., in two portions) of bromine in acetic acid for 14 hr. gave only a gum (2·4 g.). A black tar was obtained when the bromination conditions of Derbyshire and Waters (*J.*, 1950, 564) were applied to acridine.

Acridine hydrobromide was prepared from acridine and hydrobromic acid (60%). It was extremely soluble in ethanol but separated from aqueous hydrobromic acid (15%) in yellow needles of the monohydrate, m. p. 267° (decomp.) (Found, after drying at room temperature : C, 56·1; H, 4·4; N, 4·8. $C_{13}H_9N,HBr,H_2O$ requires C, 56·1; H, 4·3; N, 5·0%). It showed $\lambda_{max.}$ 3410 and 3575 Å (log ε 4·10 and 4·36 respectively).

3-*Bromoacridine*.—Hydrogen chloride gas was passed in a rapid stream through mixed saturated solutions of 3-bromo-5-chloroacridine (4·7 g.; m. p. 136°; Acheson and Robinson, *J.*, 1953, 232) and toluene-*p*-sulphonhydrazide (3·20 g.) in chloroform. Next day the yellow precipitate of the toluenesulphonhydrazide (6·45 g.) was collected, air-dried, and added to sodium hydroxide (10·9 g.) in water (81 ml.) and ethylene glycol (187 ml.). The mixture was heated on a steam-bath with intermittent stirring until no more nitrogen was evolved (3·5 hr.), poured into water (550 ml.), and refrigerated overnight. The precipitate of 3-*bromoacridine* separated from aqueous ethanol in yellow prisms (2·04 g., 49% overall yield), m. p. 175—175·5° (Found : C, 60·2; H, 3·1; Br, 30·9. $C_{13}H_8NBr$ requires C, 60·4; H, 3·1; Br, 31·0%).

3 : 7-*Dibromoacridine*.—This was prepared similarly from 3 : 7-dibromo-5-chloroacridine (6·1 g.; Acheson and Robinson, *loc. cit.*) and toluene-*p*-sulphonhydrazide (3·5 g.) in the minimum volume of boiling chloroform. The adduct (7·5 g.) was decomposed with sodium hydroxide (12·3 g.), water (93 ml.), and ethylene glycol (216 ml.) as before and the mixture poured into water (615 ml.). The precipitate, on crystallisation from aqueous ethanol, gave 3 : 7-dibromoacridine (3·07 g., 55%) as yellow plates, m. p. 249—250° (Found : C, 46·3; H, 2·4; N, 4·4, 3·9. $C_{13}H_7NBr_2$ requires C, 46·3; H, 2·1; N, 4·2%).

1 : 3 : 7 : 9-*Tetrabromoacridine*.—The corresponding 5-chloroacridine (2·4 g.; Acheson and Robinson, *loc. cit.*) was treated with toluene-*p*-sulphonhydrazide (0·95 g.) as before and the adduct (3·0 g.) decomposed by heating it with sodium hydroxide (4·0 g.), water (15 ml.), and ethylene glycol (35 ml.). The crude product (1·1 g., 49%) on crystallisation from benzene gave 1 : 3 : 7 : 9-*tetrabromoacridine* as pale yellow rhombs, m. p. 286—287° (Found : C, 31·5; H, 1·1. $C_{13}H_5NBr_4$ requires C, 31·5; H, 1·0%).

5-*Phenylacridines* (with K. A. Barnard).—5-Phenylacridine (Cohen, " Practical Organic Chemistry," Macmillan, London, 1924, p. 305), very pale yellow needles, m. p. 184°, showed $\lambda_{max.}$ 2600 and 3600 Å (log ε 4·49 and 4·01 respectively).

10-*Bromo-5-phenylacridinium bromide* was prepared by mixing 5-phenylacridine (3·0 g.) and bromine (1·9 g.) in carbon tetrachloride (100 and 50 ml. respectively). The yellow precipitate, dried over paraffin wax and potassium hydroxide, had m. p. 116° (Found : C, 55·3; H, 3·3; Br, 38·1, 38·9. $C_{19}H_{13}NBr_2$ requires C, 54·9; H, 3·1; Br, 38·6%). The ultra-violet absorption spectrum showed $\lambda_{max.}$ 2650, 3425, 3600, and 3900 Å (log ε 4·58, 4·09, 4·33, and 3·86 respectively). The " available bromine " was estimated by addition of excess of aqueous potassium iodide and chloroform, followed by titration with thiosulphate until the chloroform changed from orange-red to yellow. The end-point was sharp and reproducible in contrast to that obtained

by using starch (Found: Br, 37·1, 37·4%). Attempted crystallisation of the acridinium bromide from aqueous ethanol, or aqueous dioxan, gave brilliant yellow needles of *5-phenylacridine hydrobromide*, m. p. and mixed m. p. 296° (Found: C, 67·5; H, 4·1; Br, 24·3. $C_{19}H_{13}N,HBr$ requires C, 67·9; H, 4·2; Br, 23·8%). Its ultra-violet absorption spectrum showed $\lambda_{max.}$ 2650, 3425, 3600, 3975, and 4100 Å (log ε 4·58, 4·00, 4·25, 3·77, and 3·78 respectively).

5-Phenylacridan.—Aqueous sodium dithionite (cf. Scholl and Neuberger, *loc. cit.*) was added to 5-phenylacridine (3·0 g.) in refluxing ethanol (130 ml.) until the solution became colourless. On cooling, phenylacridan was precipitated, and on recrystallisation separated from ethanol in colourless prisms (2·75 g., 91%), m. p. 171° (Bergmann, Blum, and Christiani, *Annalen*, 1930, **483**, 80, give 170°). Its ultra-violet absorption spectrum showed $\lambda_{max.}$ 2500, 2875, and 3600 Å (log ε 4·41, 4·15, and 3·42 respectively).

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