673. *The Bromination and Nitration of Acridine 10-Oxide.*

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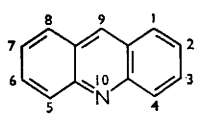
Acridine 10-oxide has been prepared. It undergoes bromination and nitration at position 9. The structures of the products were established by hydrolysis to 10-hydroxyacridone, by conversion into 9-chloroacridine with phosphorus trichloride, and in the case of the bromo-compound also by synthesis from 9-bromoacridine. The electric dipole moments of acridine, 9-phenylacridine, and their 10-oxides have been measured and used to study the electron shifts within the 10-oxides.

Electrophilic bromination and nitration of acridine (I) take place [1] quite rapidly at positions 2 and 7; further substitution at positions 4 and 5 occurs under more vigorous conditions. Electrophilic reagents attack pyridine slowly at position 3. Pyridine 1-oxide, however, is nitrated mainly at position 4, though bromination and sulphonation still occur largely at position 3 for reasons which are not entirely clear. It was therefore of interest to see if the conversion of acridine into its 10-oxide would alter the pattern of electrophilic substitution.



(I)

Acridine 10-oxide, erroneously called " acridol," was first obtained on reduction of 10-hydroxyacridone [2] by sodium amalgam and as a by-product from the reaction [3] between 2-nitrobenzyl chloride and benzene in the presence of aluminium chloride; its structure was recognised later.[4,5,6] Monoperphthalic acid has been used [7] for the oxidation of some acridines to their 10-oxides, but for acridine itself the best oxidant is stated to be perbenzoic acid in benzene [5] or chloroform.[7]

Our highest yield of the 10-oxide on use of perbenzoic acid in chloroform was 19%, in contrast to the 50% claimed earlier. This was obtained with a short reaction time at room

[1] Acheson, " The Acridines," Interscience Publ., Inc., New York, 1956, p. 60.
[2] Kliegl and Fehrle, *Ber.*, 1914, **47**, 1629.
[3] Drechsler, *Sitzungsber. Akad. Wiss. Wien*, 1914, **123**, 51.
[4] Tanasescu and Ramontianu, *Bull. Soc. chim. France*, 1934, **1**, 547.
[5] Kliegl and Brösamle, *Ber.*, 1936, **69**, 197.
[6] Lehmstedt and Klee, *Ber.*, 1936, **69**, 1155, 1514.
[7] Pushkareva and Varyukhina, *Doklady Akad. Nauk U.S.S.R.*, 1955, **103**, 257.

temperature, but even so the major product of the reaction was a yellow compound, also noted earlier,[5] the structure of which will be discussed in a later communication. Initially, great difficulty was experienced in obtaining the 10-oxide analytically pure and free from the yellow compound as they appear to crystallise together. This accounts for the low melting point and poor analytical data [8] obtained by others. Oxidation of 9-phenylacridine under the same conditions gave only the 10-oxide, which had previously been obtained by another route,[9] while 9-aminoacridine was unattacked. The last observation is in line with the failure [10] to convert 6,9-diamino-2-ethoxyacridine into its 10-oxide but is not in accord with the claims that Atebrin gives a di-*N*-oxide dihydrochloride (Found: C, 54·3; H, 6·7. Calc. for $C_{23}H_{30}O_3N_3Cl,2HCl$: C, 54·7; H, 6·3%) with either perbenzoic acid [7] or 3% aqueous hydrogen peroxide [11] although the products of these reactions are identical. It is consistent with the suggestion that the compound is the dihydrochloride

FIG. 1. FIG. 2.

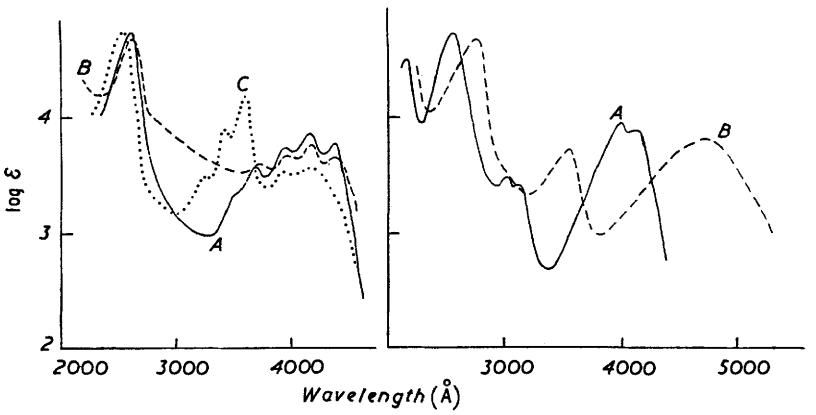


FIG. 1. *Acridine 10-oxide in methanol: A, neutral; B, basified; C, acidified.*
FIG. 2. *10-Hydroxyacridone in methanol: A, neutral; B, basified.*

monohydrate of the mono-*N*-oxide of the side-chain tertiary nitrogen atom (Calc. for $C_{23}H_{30}O_2N_3Cl,2HCl,H_2O$: C, 54·5; H, 6·7%); *N*-oxides are notorious for the ease with which they form hydrates.

The bromination of acridine 10-oxide in acetic acid gave a monosubstituted product which was identical with 9-bromoacridine 10-oxide, prepared from 9-bromoacridine and perbenzoic acid. The position of the bromine atom was confirmed by refluxing this latter oxide with phosphorus trichloride in chloroform: 9-chloroacridine was then obtained through deoxygenation and halogen exchange; further, heating it with dilute hydrochloric acid gave 10-hydroxyacridone. The ultraviolet absorption spectra of acridine 10-oxide (Fig. 1) and 10-hydroxyacridone (Fig. 2), prepared by a modification of a published method,[12] are shown as they differ significantly from earlier curves.[13,14]

Acridone did not dissolve in refluxing phosphorus tribromide, but reacted vigorously on the addition of bromine to yield 9-bromoacridine identical in melting point with that obtained earlier [15] from acridine-9-thione, red phosphorus, and bromine. 9-Bromoacridine with phosphorus trichloride in refluxing chloroform gave 9-chloroacridine.

[8] Euler and Hasselquist, *Arkiv Kemi*, 1959, **12**, 584.
[9] Lehmstedt and Dostal, *Ber.*, 1939, **72**, 1071.
[10] Khaletskii, Pesin, and Chou Tsing, *Zhur. obshchei Khim.*, 1958, **28**, 2821.
[11] Linkser and Bogert, *J. Amer. Chem. Soc.*, 1946, **68**, 192.
[12] Kliegl and Fehrle, *Ber.*, 1914, **47**, 1629.
[13] Dima and Pogâneanu, *Bull. Sect. sci. Acad. Roumanie*, 1939, **22**, 19.
[14] Lehmstedt and Dostal, *Ber.*, 1938, **71**, 2432.
[15] Edinger and Arnold, *J. prakt. Chem.*, 1901, **64**, 471.

Nitration of acridine 10-oxide in nitric–sulphuric acid gave the 9-nitro-derivative, as shown by its conversion into 9-chloroacridine by phosphorus trichloride, and into 10-hydroxyacridone by acid-hydrolysis.

The electric dipole moments of acridine, 9-phenylacridine, and their 10-oxides have been determined. These new measurements permit comparisons of the changes of electric dipole moment which occur when oxygen is attached to nitrogen in these compounds. The relevant values are tabulated.

Dipole moments (D).

	Base	*N*-Oxide	Difference
Pyridine	−2·22	−4·24	−2·02
Acridine	−2·13 ± 0·03	−3·90 ± 0·02	−1·77
9-Phenylacridine	−2·49 ± 0·03	−4·13 ± 0·01	−1·64

As the aromatic system increases in size the numerical difference between the *N*-oxide and the parent compound decreases. The moments may all be ascribed negative signs, meaning that the negative pole of the dipole is pointed towards the hetero-atom or -atoms; so the differences (μ *N*-oxide $-$ μ parent) are all negative. The change in these, when the aromatic system increases in size, is positive. This could mean that the importance of canonical structures containing the unit $\rangle N^+ = O$ and with formal negative charges on ring-carbon atoms increases with the size of the system. The increase between the acridine and the 9-phenylacridine case indicates in particular that there is an appreciable degree of conjugation across the transannular C–C bond, although Stuart models showing the effect of van der Waals radii indicate that the phenyl group cannot lie coplanar with the acridine ring system.

The procedure suggested by Bax, Katritzky, and Sutton [16] for evaluating the moment due to the inward " drift " of electrons from oxygen in the aromatic *N*-oxides cannot be employed here because there are no results for the acridine–BX_3 complexes. Linton's procedure,[17] involving comparisons with trimethylamine oxide by the relation

$$\Delta\mu = \mu(\text{acridine 10-oxide}) - \mu(\text{acridine}) - [\mu(\text{trimethylamine oxide}) - \mu(\text{trimethylamine})]$$

may not have as good absolute significance but gives results which are valuable for their relative significance, namely, as shown:

Compound	$\Delta\mu$ (D)	Fractional charge transferred
Pyridine 1-oxide	2·35	0·573
Acridine 10-oxide	2·60	0·634
9-Phenylacridine 10-oxide	2·73	0·666

Taking the probable length of the N–O bond as 1·32 Å, and assuming a part of the electron charge to be transferred from the oxygen atom to the carbon atom in the 4- or the 9-position in pyridine and acridine respectively, gives the approximate fractional charges transferred as in the last column.

Electrophilic attack on the acridine ring system at position 9, usually susceptible only to nucleophilic reagents, has not been recorded previously and it is noteworthy that both nitration and bromination of acridine 10-oxide occur at this position. This is in agreement with the comparatively large fractional charge transferred to position 9. In the case of pyridine 1-oxide the fractional charge transferred is smaller, and nitration, but not bromination, occurs at position 4.

Experimental

The ultraviolet absorption spectra were determined for MeOH solutions, and the infrared spectra for paraffin pastes in the 2·5—15 μ region.

Acridine 10-Oxide.—Acridine (20 g.) in chloroform (200 ml.) was treated with perbenzoic

[16] Bax, Katritzky, and Sutton, *J.*, 1958, 1258.
[17] Linton, *J. Amer. Chem. Soc.*, 1940, **62**, 1945.

acid (16·8 g., 10% excess) in chloroform (500 ml.) at room temperature. The mixture rapidly became bright red and after 10 min. was washed with 2N-sodium hydroxide (500 ml.), dried ($MgSO_4$) at 0° for 2 hr., and evaporated to dryness at room temperature; a tar was often formed but solidified on trituration with ether. The solid was washed with aqueous 2N-sodium hydroxide until the washings were colourless; crystallisation from aqueous ethanol followed by washing with alkali and one further recrystallisation gave acridine 10-oxide as hygroscopic yellow needles (4·1 g., 18·7%), m. p. 169° (Found: C, 80·0; H, 4·6; N, 7·4. Calc. for $C_{13}H_9NO$: C, 80·0; H, 4·7; N, 7·2%). $\nu_{max.}$ 3·05, 5·97, 6·20, 6·41, 6·52, 6·86, 6·96, 7·10, 7·29, 7·58, 7·80, 7·97, 9·04, 9·21, 10·25, 10·35, 10·99, 11·62, 12·84, and 13·42 μ; the maximum at 3·05 μ is due to water absorbed while the paste was being formed and that at 7·58 μ is probably the N–O stretching frequency.

9-*Bromoacridine* 10-*Oxide*.—(i) Bromine (3 ml.) was added to acridine 10-oxide (0·85 g.) in glacial acetic acid, and the mixture heated at 100° for 2½ hr.; then the excess of bromine and most of the acetic acid were removed *in vacuo*. Dilution with water (10 ml.) and pouring into 16% aqueous ammonia (100 ml.) gave a brown solid, which was washed, dried, and chromatographed in benzene on alumina. Evaporation of the eluate gave 9-*bromoacridine* 10-*oxide* (0·55 g.) which crystallised from acetonitrile in yellow needles, m. p. 174° (Found: C, 56·9; H, 3·0; N, 5·0; Br, 29·4. $C_{13}H_8ONBr$ requires C, 56·9; H, 2·9; N, 5·1; Br, 29·2%), $\lambda_{max.}$ 2180 (log ε 4·42), 2690 (4·58), 3775 (3·59), 4080 Å (3·70), 4250 (3·79), 4500 (3·68), $\nu_{max.}$ 6·19, 6·56 6·84, 7·01, 7·30, 7·58, 7·79, 9·07, 9·83, 10·90, 12·91, 13·10, and 13·22 μ. (ii) A mixture of 9-bromoacridine (0·2 g.) and perbenzoic acid (0·14 g.) in chloroform (9 ml.) was left for 1 hr. at room temperature and then washed with aqueous 2N-sodium hydroxide (2 × 50 ml.). The chloroform was dried ($MgSO_4$) and evaporation gave the 10-oxide which separated from acetonitrile in yellow needles (0·2 g.), m. p. and mixed m. p. 174°. The infrared absorption spectra of the two samples were identical.

9-*Bromoacridine*.—Bromine (13 ml.) was added to a mixture of acridone (2·5 g.) and phosphorus tribromide (30 ml.), a vigorous reaction occurring. The mixture was heated at 140° for 3 hr., cooled, diluted with chloroform, and filtered. The chloroform was dripped into an excess of a vigorously stirred mixture of ice and aqueous ammonia at 0°, the chloroform was collected and dried ($MgSO_4$), the solvent removed *in vacuo*, and the residue recrystallised from 1 : 1 ethanol–5% aqueous ammonia, giving 9-bromoacridine as colourless needles, m. p. 116° (Found: C, 60·8; H, 3·0; N, 5·2; Br, 31·2. Calc. for $C_{13}H_8NBr$: C, 60·5; H, 3·1; N, 5·4; Br, 31·0%) (lit.,[14] m. p. 116°), $\lambda_{max.}$ (in MeOH containing 5% of 5% aqueous ammonia) 2515 (log ε 5·01), 3430 (3·76), 3600 (4·40), 3870 Å (3·65), $\nu_{max.}$ 6·22, 6·58, 6·69, 6·92, 7·35, 7·40, 7·72, 7·93, 9·92, 10·80, 11·84, 12·51, 13·25, 13·40, and 13·55 μ. 9-Chloroacridine showed $\nu_{max.}$ 6·30, 6·56, 6·69, 6·91, 7·02, 7·25, 7·35, 7·70, 7·91, 8·78, 9·92, 11·80, 12·19, 12·91, and 13·18 μ. 9-Bromoacridine (50 ml.), when refluxed with phosphorus trichloride (0·5 ml.) in chloroform and worked up as above, gave 9-chloroacridine, m. p. and mixed m. p. 119°, and confirmed by its infrared absorption spectrum.

Bromination of acridine 10-oxide in the presence of iron filings gave an impure tribromo-derivative.

9-*Nitroacridine* 10-*Oxide*.—Nitric acid (0·65 ml.; *d* 1·42) was added dropwise with stirring to a solution of acridine 10-oxide (2·0 g.) in concentrated sulphuric acid (8 ml.) at 0° with cooling. After 2 hr. at room temperature the mixture was poured on to vigorously stirred ammonia, ice, and chloroform. The chloroform layer was washed, dried (Na_2SO_4), and evaporated to dryness and the residue, in benzene, was passed through an alumina column. Evaporation of the eluate gave the *nitro-compound*, which separated from acetonitrile in orange needles, m. p. 223° (Found: C, 64·9; H, 3·4; N, 11·7. $C_{13}H_8N_2O_3$ requires C, 65·0; H, 3·3; N, 11·7%), $\lambda_{max.}$ 2670 (log ε 4·60), 3540 (3·56), and 4525 Å (3·66), $\nu_{max.}$ 6·41, 6·50, 6·66, 6·89, 7·02, 7·32, 7·54, 7·77, 7·94, 8·98, 12·07, 12·96, 13·14, and 13·64 μ.

10-*Hydroxyacridone*.—(i) *o*-Nitrobenzaldehyde (5 g.) was added to a cooled mixture of concentrated sulphuric acid (20 g.) and benzene (20 g.). After 5 days' shaking at 20°, water (50 ml.) was added and the excess of benzene removed *in vacuo*. The residual black tar was extracted repeatedly by 2N-sodium hydroxide (total 600 ml.). Acidification precipitated 10-hydroxyacridone which separated from glacial acetic acid in dark yellow needles (1·0 g.), m. p. 256° (decomp.) (Found: C, 73·8; H, 4·5; N, 6·7. Calc. for $C_{13}H_9NO_2$: C, 73·9; H, 4·3; N, 6·6%), $\nu_{max.}$ 3·70, 6·19, 6·29, 6·42, 6·63, 6·80, 6·88, 7·26, 7·47, 7·70, 8·42, 8·59, 9·48, 9·68, 10·61, 11·42, 12·30, 13·23, and 14·80 μ.

(ii) 9-Bromoacridine 10-oxide (50 mg.), prepared from the 10-oxide, was heated for 5 hr. at 100° with 2N-hydrochloric acid (25 ml.). After cooling, the yellow solid material was collected and after one crystallisation from acetic acid was identical with authentic 10-hydroxyacridone in m. p., mixed m. p., and ultraviolet and infrared spectra.

(iii) 9-Nitroacridine 10-oxide was hydrolysed as in (ii), giving 10-hydroxyacridone, the same identification criteria being applied.

9-*Phenylacridine* 10-*Oxide*.—9-Phenylacridine (10 g.) in benzene (180 ml.) was allowed to react with perbenzoic acid (7·3 g.) in ether at 0° for 2½ hr. After being washed with 2N-sodium hydroxide the chloroform was dried and evaporated, the 10-oxide (6·5 g.), m. p. 227° (decomp.), being obtained. A pure specimen could not be prepared by direct crystallisation, but after passage through an alumina column (B.D.H.; deactivated with 5% of its weight of 10% acetic acid) in benzene the oxide was obtained as yellow needles, m. p. 227° (decomp.) (Found: C, 84·2; H, 5·1; N, 5·0. Calc. for $C_{19}H_{13}ON$: C, 84·1; H, 4·8; N, 5·2%) (lit.,[14] m. p. 227°), $\lambda_{max.}$ 2665 (log ε 4·37), 4000 (3·42), 4220 (3·49) and 4450 Å (3·37), or in acid MeOH 2600 (4·43), 3280 (3·11), 3430 (3·31), 3600 (3·66), 4210 Å (3·21).

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