The Reaction between Acridine and Methyl Acetylenedicarboxylate.

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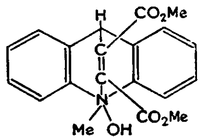
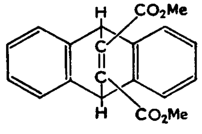
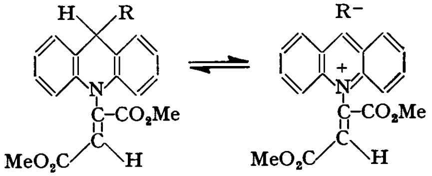
Reinvestigation of the reaction between acridine and methyl acetylenedicarboxylate has shown that in methanol the product is largely 10-(*trans*-1 : 2-dimethoxycarbonylvinyl)acridinium methoxide, but that in ether methyl 5 : 10-dihydro-5-oxoacridinyl-fumarate and -maleate are formed. Hydrogenolysis of the fumarate yielded acridone and methyl fumarate. The configurations of the acridone derivatives were established by conversion into the anhydride followed by hydrolysis, which gives only the *cis*-acid.

Although many reagents are known to add to the 9 : 10-positions of anthracene comparatively few addition reactions of acridine have been systematically investigated. Acridine is reported (Barnett, Goodway, Higgins, and Lawrence, *J.*, 1934, 1224) not to react with maleic anhydride but gives, according to Diels and Thiele (*Annalen*, 1939, **543**, 79), largely the adduct (I) with methyl acetylenedicarboxylate in the presence of methanol. This structure was presumably based on that of the anthracene–methyl acetylenedicarboxylate adduct (II) (Diels and Alder, *Annalen*, 1931, **486**, 191). Possible alternative structures for the latter adduct, which are also consistent with the chemical degradations, those of methyl 9-anthryl-fumarate or -maleate, were not considered by these workers; they have now been excluded as the ultra-violet absorption of the adduct is compatible with the 9 : 10-dihydroanthracene (cf. Phillips and Cason, *J. Amer. Chem. Soc.*, 1952, **74**, 2934), but not with the anthracene, formulation. The bright red acridine adduct, formulated as (I), was obtained by Diels and Thiele in 80—90% yield, along with 2—3% of a yellow isomer. The red compound was reported to contain three methoxyl groups, and on mild oxidation to give (VI), containing two methoxyl groups. Only one of the methoxyl groups in the bright red adduct was replaced by an ethoxyl group simply on crystallisation from ethanol. These observations cannot be explained satisfactorily by the structure (I) given by Diels and Thiele, and it was thought that the bright red adduct was probably (III) on the basis of which the experimental data can be explained.

Repetition of the acridine–methyl acetylenedicarboxylate reaction in methanol gave the bright red compound in high yield but we were unable to isolate any yellow isomer. The ultra-violet absorption spectrum of this adduct was of the acridinium-ion type in neutral methanol, and of the 5-methoxyacridan type after the addition of potassium hydroxide. As this behaviour was similar to that of 10-methylacridinium chloride (cf. Tinkler, *J.*, 1906, 856) structure (III) was confirmed. Recrystallisation of the adduct from ethanol gave another red compound (IV), which was also obtained when the original addition reaction was carried out in ethanol, and both the compounds (III) and (IV) with picric acid gave the same quaternary picrate showing that both were in equilibrium with an acridinium ion. This ready exchange of 5-alkoxyl groups is characteristic of the 5-alkoxy-10-alkylacridans (Decker, *Ber.*, 1902, **35**, 3068).

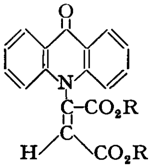

(I)

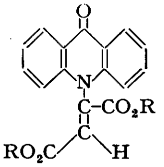

(II)

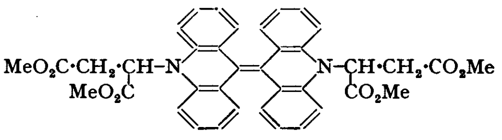

(III) : R = OMe
(IV) : R = OEt

Diels and Thiele (*loc. cit.*) claimed that the bright red adduct (III) was degraded by concentrated hydrochloric acid to 10-methylacridinium chloride, but this could not be confirmed. Degradation of the adduct (III) with hot concentrated hydrochloric acid, methanolic hydrogen chloride, or concentrated sulphuric acid gave only the corresponding salts of acridine in 20—60% yield. Further, treatment of the ethanol adduct (IV) with hot ethanolic hydrogen chloride gave acridine hydrochloride although 10-ethylacridinium chloride would have been expected from Diels and Thiele's observations. No trace of a 10-alkylacridinium salt or 10-alkylacridone was detected as a product from any of these degradations. Both compounds (III) and (IV) were readily oxidised by air or hydrogen peroxide in neutral solution to the orange acridone ester (VIII). This behaviour is typical of 5-alkoxy-10-alkylacridans (cf. Decker, *J. pr. Chem.*, 1892, **45**, 161). Alkaline hydrolysis of the acridan (III) was also accompanied by aerial oxidation and gave the acridone acid (VII).

The ultra-violet absorption spectrum of the acridone ester (VIII) closely resembled that of acridone. Both compounds also showed the same infra-red absorption maxima (6·10 μ), which may be characteristic of the acridone-carbonyl group. Alkaline hydrogen peroxide oxidised the orange ester (VIII) to acridone itself, showing that the aliphatic part of the molecule was attached to the heterocyclic nitrogen atom; a small yield of acridone was also obtained from the acid (VII) and potassium permanganate in cold acetone, but much of the acid was recovered. These results were unexpectedly confirmed by the interesting hydrogenolysis of the ester (VIII) in ethanol over freshly prepared Raney nickel to acridone and methyl fumarate. This reaction, which does not appear to have any parallel, took place very readily at room temperature and atmospheric pressure. The orange acridone (VIII), in contrast to the acridinium methoxide (III), gave only a mixture of half esters with hot concentrated sulphuric acid.


(V) : R = H
(VI) : R = Me


(VII) : R = H
(VIII) : R = Me


(IX)

Diels and Thiele (*loc. cit.*) reported that acridine and methyl acetylenedicarboxylate reacted in ether to give a mixture of the orange acridone (VIII), a creamy-white geometric isomer (VI) [stated erroneously to be (VI) and (VIII) respectively], and a third compound alleged to be formed from one molecule of acridine and two of the ester. Repetition of this experiment gave roughly equal amounts of the first two adducts in *ca.* 40% total yield but we were unable to confirm the formation of the third adduct. The ultra-violet absorption spectra of the two compounds were almost indistinguishable and the infra-red absorption spectra showed the presence of the same principal groups. Boiling methyl 5 : 10-dihydro-5-oxo-10-acridinylmaleate (VI) with pyridine for several hours converted it into the fumarate (VIII) but the reverse change could not be detected under these conditions. As reported by Diels and Thiele, both compounds were reduced by zinc and hydrochloric acid in the usual manner of 10-alkylacridones (cf. Decker and Dunant, *Ber.*, 1909, **42**, 1176) to the binuclear compound (IX), the structure of which was confirmed by two observations. The ultra-violet absorption spectrum of the solution obtained by oxidising it with dilute nitric acid showed a close resemblance to that of 10 : 10′-dimethyl-5 : 5′-diacridinium dinitrate, and the oxidised solution, presumably containing 10 : 10′-di-(1 : 2-dimethoxycarbonylethyl)-5 : 5′-diacridinium dinitrate, gave an intense blue chemiluminescence with alkaline 30% hydrogen peroxide. This is characteristic of most 10 : 10′-dialkyl-5 : 5′-diacridinium dinitrates (Gleu and Nitzsche, *J. pr. Chem.*, 1939, **153**, 233).

The stereochemistry of the compounds was established as follows. The dibasic acids (V) and (VII), gave the same anhydride when heated with acetic anhydride. As this anhydride was converted into the dicarboxylic acid (V) on hydrolysis with warm alkali, the white adduct must have the *cis*- (VI) and the orange acridone (VIII) the *trans*-configuration. The possibility that stereochemical rearrangement had taken place during the alkaline hydrolysis of the esters was eliminated by reconversion of the acids into the original esters by treatment with diazomethane.

The structures of the compounds obtained in these addition reactions suggest that the reactions are closely analogous to Michael additions which are well known to take place with acetylenedicarboxylic esters, and to give mainly *trans*-adducts (cf. A. W. Johnson, " Acetylenic Acids," Edward Arnold and Co., London, 1950). This behaviour contrasts with the quite different behaviour of pyridine, quinoline, and *iso*quinoline, which react with acetylenedicarboxylic esters to give pyrrocoline and pyridocoline derivatives (Johnson, *loc. cit.*). It is possible that the blocking of both carbon atoms α- to the nitrogen atom inhibits cyclisation to pyrrocolines, etc., but on the other hand such products must arise from the reaction of one molecule of the base with two of the ester, and no compounds of this type, either cyclised or otherwise, were obtained from acridine under the conditions used in this investigation.

EXPERIMENTAL

Methyl 9 : 10-dihydroanthracene-9 : 10-*endo*maleate (II), prepared according to Diels and Alder (*Annalen*, 1931, **486**, 191), had m. p. 160° (Found : C, 75·3; H, 5·1. Calc. for $C_{20}H_{16}O_4$: C, 75·0; H, 5·0%). In methanol it showed $\lambda_{max.}$ 2700 (log ε 3·36) and 2800 Å (log ε 3·34).

10-(trans-1 : 2-*Dimethoxycarbonylvinyl*)*acridinium Methoxide* (III).—Acridine (7·5 g.), methyl acetylenedicarboxylate (5·0 ml.), and methanol (30 ml.) were refluxed from a steam-bath for 3 hr. The deep red solid which separated at 0° crystallised from methanol, giving the *acridinium methoxide* (III) as ruby-red rhombs (12·0 g.), m. p. 101—102° (Found : C, 68·3; H, 5·4; N, 4·0. $C_{20}H_{19}O_5N$ requires C, 68·0; H, 5·4; N, 4·0%). In neutral methanol it showed $\lambda_{max.}$ 2600, 3600, and 4300 Å (log ε 4·64, 4·36, and 3·61), and after the addition of sodium hydroxide 2720 (log ε 4·32) and 3150 Å (log ε 3·63). Treatment of the methoxide with methanolic hydrogen chloride followed by ether gave a precipitate of 10-(trans-1 : 2-*dimethoxycarbonylvinyl*)*acridinium chloride* which separated from 1 : 1 ether–ethanol as small orange-yellow rhombs, m. p. 114—116° (decomp.) (Found: C, 63·6; H, 4·7; N, 3·9; Cl, 10·1. $C_{19}H_{16}O_4NCl$ requires C, 63·8; H, 4·5; N, 3·9; Cl, 9·9%), freely soluble in water giving a yellow green fluorescing solution. The corresponding *perchlorate*, yellow plates (from acetone), m. p. 215—216° (decomp.) (Found : C, 54·2; H, 4·1; N, 3·3; Cl, 8·4. $C_{19}H_{16}O_8NCl$ requires C, 54·2; H, 3·9; N, 3·3; Cl, 8·4%), and *picrate*, orange-yellow needles (from methanol), m. p. 185—186° (decomp.) (Found : C, 54·6; H, 3·4; N, 10·3. $C_{25}H_{18}O_{11}N_4$ requires C, 54·6; H, 3·3; N, 10·2%), were prepared similarly.

The acridinium methoxide (III) (1·0 g.) was dissolved in 7N-methanolic hydrogen chloride and evaporated to dryness on a steam-bath. The black residue, on crystallisation from dilute hydrochloric acid, gave yellow needles of acridine hydrochloride (Found, after drying at 120° : Cl, 16·6. Calc. for $C_{13}H_{10}NCl$: Cl, 16·5%) which on basification gave acridine (0·29 g., 58%), m. p. and mixed m. p. 109°, also identified as *picrate*, m. p. and mixed m. p. 258—259° (decomp., bath initially at 250°) (Found : C, 56·1; H, 3·0; N, 13·5. $C_{19}H_{12}O_7N_4$ requires C, 55·9; H, 2·9; N, 13·7%) [the usual literature value, 208° (Albert, "The Acridines," p. 128, Edward Arnold and Co., London, 1951) is incorrect]. Similar degradations of the acridinium methoxide (III) (1·0 g.) with hydrochloric acid (36%) at 150° (2 hr.) and with concentrated sulphuric acid at 100° (several hours) gave 0·27 and 0·1 g. of acridine respectively.

The acridinium methoxide (III) (1·0 g.), potassium hydroxide (0·5 g.), water (5 ml.), and methanol (5 ml.) were refluxed for 2 hr. The oil, precipitated on acidification, solidified when warmed. Crystallisation from aqueous ethanol gave 5 : 10-*dihydro*-5-*oxo*-10-*acridinylfumaric acid* (VII) as feathery yellow needles, m. p. 254—255° (decomp.) (Found : C, 66·2; H, 3·8; N, 5·0. $C_{17}H_{11}O_5N$ requires C, 66·0; H, 3·6; N, 4·5%).

10-(trans-1 : 2-*Dimethoxycarbonylvinyl*)*acridinium Ethoxide* (IV).—Acridine (2·0 g.), methyl acetylenedicarboxylate (1·4 ml.), and ethanol (10 ml.) were refluxed for 2 hr. On cooling of the solution in a refrigerator a red syrup separated which on trituration with more ethanol solidified. Crystallisation from ethanol gave the *ethoxide* (IV) as crimson rhombs, m. p. 70—71° (Found : C, 68·2; H, 5·9; N, 3·3. $C_{21}H_{21}O_5N$ requires C, 68·5; H, 5·7; N, 3·8%). In ethanol it showed $\lambda_{max.}$ 2550, 3600, and 4300 Å (log ε 4·65, 4·31, and 3·54). On crystallisation from methanol it yielded the methoxide (III), red rhombs, m. p. and mixed m. p. 101—102°. With ethanolic picric acid the ethoxide (IV) gave the picrate, m. p. 185—186° (decomp.) alone or mixed with the picrate obtained from the methoxide (III); the infra-red absorption spectra of the two picrates in paraffin paste were identical.

Evaporation of the ethoxide (1·0 g.) with ethanolic hydrogen chloride, as for (III) above, gave only acridine (0·29 g., 60%), identified by a mixed m. p. determination and as picrate.

Methyl 5 : 10-*Dihydro*-5-*oxo*-10-*acridinylfumarate*.—(*a*) A solution of the methoxide (III) in methanol or benzene became brown after a few weeks in air at room temperature. The residue obtained on evaporation was dissolved in a little methanol and refrigerated; the *fumarate* (VIII) slowly separated as orange rhombs, m. p. 141—142° (fast heating), m. p. 160—161° (slow heating) with a transition point at 138—139° (Found : C, 67·5; H, 4·6; N, 3·6; OMe, 18·5. $C_{19}H_{15}O_5N$ requires C, 67·7; H, 4·4; N, 4·1; OMe, 18·3%). The ultra-violet absorption spectrum in methanol showed $\lambda_{max.}$ 2550, 3750, and 3900 Å (log ε 4·66, 4·08, and 4·11). The infra-red absorption spectrum in paraffin paste showed strong maxima at 5·76 (ester-carbonyl) and 6·09 μ (acridone-carbonyl).

Unlike the methoxide, the ethoxide (IV) was rapidly oxidised by air in the solid state (the *iso*propoxide could not be obtained pure because of this very ready oxidation). The product obtained after 14 days' exposure to air gave likewise the methyl fumarate when purified chromatographically over alumina from benzene.

(*b*) The acridinium methoxide (III) (5·0 g.), aqueous hydrogen peroxide (3·0 ml.; 30%), and methanol (30 ml.) were refluxed (1 hr.). After evaporation the residue was extracted with hot ethyl acetate. The insoluble material (50 mg.) was acridone, m. p. and mixed m. p. 350°. The brown solid obtained on cooling of the ethyl acetate solution, when crystallised from methanol, yielded the methyl fumarate, identical with the specimen described above. No trace of the deep red by-product, $C_{38}H_{30}O_8N_2$, claimed by Diels and Thiele, could be found. Similar results were obtained when the methoxide (III) was replaced by the ethoxide (IV).

(*c*) The acridone (VIII), or Diels and Thiele's "orange adduct," was best prepared according to their directions. A trace of the maleate (VI) was also formed.

(*d*) The maleate (VI) was refluxed with pyridine for several hours, then poured into excess of dilute aqueous acid. The fumarate (VIII), identical with an authentic specimen, was precipitated.

Hydrolysis of methyl 5 : 10-dihydro-5-oxo-10-acridinylfumarate with boiling methanolic potassium hydroxide (2 hr.), followed by acidification, gave the corresponding acid (VII), which separated from dilute aqueous ethanol as golden needles, m. p. 254—255° (decomp.) (Found : C, 66·0; H, 3·5; N, 4·2%), mentioned above.

Heating the methyl fumarate (1·0 g.) with concentrated sulphuric acid (6 ml.) on a steam-bath for 3 hr. gave an orange solution which was poured into water. The yellow precipitate was collected and on fractional crystallisation from dilute aqueous ethanol gave a mixture of hydrogen esters. The more soluble *ester* crystallised in fine orange needles, m. p. 115—116° (decomp.) (Found : C, 60·1; H, 4·9; N, 4·6. $C_{18}H_{13}O_5N,2H_2O$ requires C, 60·2; H, 4·7; N, 3·9%). The less soluble *ester* separated in small pale-yellow rhombs, m. p. 247—248° (decomp.) (Found: C, 66·4; H, 4·2; N, 4·5. $C_{18}H_{13}O_5N$ requires C, 66·8; H, 4·0; N, 4·3%). Both half-esters with diazomethane in ether gave the original diester (VIII).

Degradation of Methyl 5 : 10-*Dihydro*-5-*oxo*-10-*acridinylfumarate to Acridone.*—(*a*) The ester (0·2 g.), aqueous hydrogen peroxide (30%; 3 ml.), and methanol (3 ml.) were refluxed for several hours but there was no change in colour. The addition of some aqueous sodium hydroxide (2N), however, caused a vigorous reaction with the evolution of much oxygen. The solution developed a strong blue fluorescence. The solution was cooled and the yellow precipitate, after crystallisation from much ethanol, yielded acridone (50 mg.), m. p. 350° (Found: C, 79·8; H, 4·9. Calc. for $C_{13}H_9ON$: C, 80·0; H, 4·6; N, 7·2%).

(*b*) The ester (1·0 g.) in ethanol (50 ml.) was shaken with hydrogen over fresh Raney nickel at atmospheric pressure and temperature. After one mol. of hydrogen had been taken up (15 min.) the solution was filtered and the filtrate largely evaporated. It deposited pale yellow needles of acridone (0·3 g.), m. p. 350° (Found: C, 79·7; H, 4·8; N, 7·0%). The mother-liquor was evaporated and the residue distilled at atmospheric pressure on to a cold finger. The yellow sublimate on crystallisation from methanol gave colourless needles of methyl fumarate, m. p. and mixed m. p. 102°.

Methyl 5 : 10-*Dihydro*-5-*oxo*-10-*acridinylmaleate* (VI).—Acridine (2·0 g.), methyl acetylenedicarboxylate (1·4 ml.), and ether (20 ml.) were kept together at room temperature for 2 days. Evaporation of the orange solution and trituration with methanol gave a red solid, which on crystallisation from acetonitrile yielded colourless rhombs of the *maleate* (VI) (0·75 g.), m. p. 222—223° (Found: C, 67·3; H, 4·4; N, 4·7; OMe, 18·3. $C_{19}H_{15}O_5N$ requires C, 67·7; H, 4·4; N, 4·1; OMe, 18·3%). The ultra-violet absorption spectrum in methanol showed $\lambda_{max.}$ 2550, 3740, and 3900 Å (log ε 4·73, 4·02, and 4·06). The infra-red absorption spectrum in paraffin paste showed strong maxima at 5·75 (ester-carbonyl) and at 6·10 μ (acridone-carbonyl). Evaporation of the methanol from the trituration and trituration of the residue with ether gave a buff solid (0·75 g.) which proved to be very largely the fumarate.

5 : 10-*Dihydro*-5-*oxo*-10-*acridinylmaleic acid*, obtained from the ester by reaction with methanolic potassium hydroxide, separated from dilute aqueous ethanol as fine pale yellow needles, m. p. 227—228° (decomp.) (Found, after drying at 120° *in vacuo*: C, 64·5; H, 3·8; N, 4·1. $C_{17}H_{11}O_5N,\frac{1}{2}H_2O$ requires C, 64·2; H, 3·8; N, 4·4%).

5 : 10-*Dihydro*-5-*oxo*-10-*acridinylmaleic Anhydride.*—The fumaric acid (VII) (1·0 g.) and acetic anhydride (1·5 ml.) were refluxed from an oil-bath for 2 hr. On cooling, a brown solid separated. This on crystallisation from acetic anhydride yielded orange-brown rhombs of the *maleic anhydride*, m. p. 231—232° (decomp.) (Found: C, 70·0; H, 3·2; N, 4·6. $C_{17}H_9O_4N$ requires C, 70·0; H, 3·1; N, 4·8%). Treatment of 5 : 10-dihydro-5-oxo-10-acridinylmaleic acid (V) in the same way yielded the same anhydride, m. p. 231—232° (decomp.) (Found: C, 69·9; H, 3·2; N, 4·9%). A mixed m. p. determination with the previous specimen showed no depression and the infra-red absorption spectra (paraffin paste) of the substances were identical and showed large absorption maxima at 5·40 and 5·60 μ.

The anhydride was hydrolysed in warm 2N-sodium hydroxide. Acidification gave a white precipitate which on crystallisation from dilute aqueous ethanol yielded pale yellow needles of the maleic acid, m. p. 227—228° (decomp.) (Found, after drying at 120°: C, 64·3; H, 3·8; N, 4·7%). Treatment of an ethereal suspension of the acid with diazomethane, followed by evaporation and crystallisation of the residue from acetonitrile, gave methyl 5 : 10-dihydro-5-oxo-10-acridinylmaleate as white rhombs, m. p. and mixed m. p. 222—223°.

10 : 10′-*Di*-(1 : 2-*dimethoxycarbonylethyl*)-5 : 5′ : 10 : 10′-*tetrahydro*-5 : 5′-*diacridinylidene* (IX).—The fumarate (VIII) (2·0 g.), zinc dust (1·7 g.), methanol (60 ml.), and concentrated hydrochloric acid (8 ml.) were heated on a steam-bath for 2 hr. After cooling, the green residue was collected and crystallisation from acetonitrile gave green rhombs of the diacridinylidene, m. p. 255° (decomp.) (Found: C, 70·7; H, 5·1; N, 4·3. Calc. for $C_{38}H_{34}O_8N_2$: C, 70·6; H, 5·3; N, 4·3%). Diels and Thiele give m. p. 260° (decomp.). The ultra-violet absorption spectrum in methanol showed $\lambda_{max.}$ 2350, 2650, 2800, 3750, and 4000 Å (log ε 4·27, 4·10, 3·83, 3·71, and 3·75). The ultra-violet absorption spectrum of the (cooled) solution in hot dilute nitric acid showed $\lambda_{max.}$ 2650, 3700, and 4400 Å (log ε 4·71, 4·42, and 3·92).

The same product was obtained when the maleate was treated similarly. It had m. p. 255° (decomp.) alone or mixed with the above specimen and the infra-red absorption spectra (paraffin paste) of the two specimens were identical and showed the ester-carbonyl absorption maximum at 5·76 μ.

10 : 10′-Dimethyl-5 : 5′-diacridinium dinitrate was prepared according to Decker and Petsch

(*J. pr. Chem.*, 1935, **143**, 211). The ultra-violet absorption spectrum showed $\lambda_{max.}$ 2550, 3700, and 4300 Å (log ε 4·85, 4·28, and 3·75).

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