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Compounds Related to Acridine. VII.1) The Synthesis of 9-Ethynylacridine and Its Reaction with *p*-Nitrosodialkylaniline

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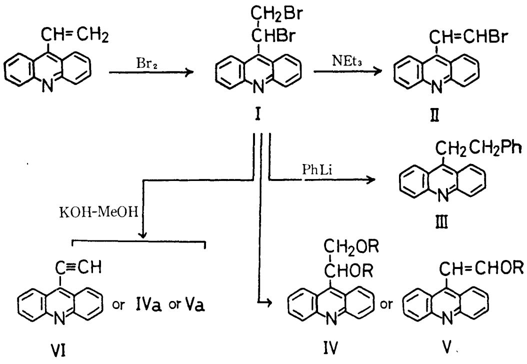
The dehydrobromination of 9-(1,2-dibromoethyl)acridine, which had easily been obtained by the bromination of 9-vinylacridine, to 9-ethynylacridine was attempted by several methods, and it has been established that this transformation can be effected in a 55% yield by the use of methanolic potassium hydroxide in dioxane. It has been found that the reaction of 9-ethynylacridine with *p*-nitrosodialkylaniline under the influence of hydrochloric acid in ethanol leads to the formation of the corresponding 1-(9-acridinyl)-1,2-bis(*p*-dialkylaminophenylimino)ethane N^1,N^2-dioxide. In addition, the configuration of the dioxide has also been proposed on the basis of spectroscopic studies and an inspection of the Dreiding models.

Previously, it has been found that hydrochloric acid (HCl) is an extremely effective catalyst for the condensation of acridine having an active methyl group with an aromatic nitroso compound.2) Furthermore, even 9-ethylacridine reacts with two moles of *p*-nitrosodimethylaniline under the influence of HCl to give a mixture of 1-(9-acridinyl)-1,2-bis(*p*-dimethylaminophenylimino)ethane and its N^1-oxide.3)

We decided to investigate the reactions of various acridine derivatives with aromatic nitroso compounds over a wider range. In the present work, several methods of the dehydrobromination of 9-(1,2-dibromoethyl)acridine to 9-ethynylacridine were studied, and a convenient synthetic method was established. It has been found that 9-ethynylacridine reacts with two moles of *p*-nitrosodialkylaniline to give 1-(9-acridinyl)-1,2-bis(*p*-dialkylaminophenylimino)ethane N^1,N^2-dioxide. In addition, the most reasonable configurations for the dioxide and for analogous compounds were decided upon.

Results and Discussion

Dehydrobromination Reactions of 9-(1,2-Dibromoethyl)acridine (I). No information has been available regarding the preparation and properties of 9-ethynylacridine (VI). The preparation of VI from 9-(1,2-dibromoethyl)acridine (I) which had easily been prepared by the bromination of 9-vinylacridine1), by several manners was investigated, as is shown in Scheme 1.



a : R=Me b : R=Et c : R=*n*-Pr
a : R=Me b : R=*t*-Bu

Scheme 1

The acetylene VI was not obtained by the attempted dehydrobromination with triethylamine or phenyllithium. Instead, *trans*-1-(9-acridinyl)-2-bromoethylene (II) or 1-(9-acridinyl)-2-phenylethane (III) was obtained in a 97 or 57% yield in the respective reaction. The structures of II and III were confirmed by spectral studies as well as by elemental analyses.

Mitchell and Sondheimer4) found that the dehydrobromination of 1,8-bis(1,2-dibromoethyl)naphthalene to 1,8-diethynylnaphthalene in a 79% yield could be effected by the use of potassium *t*-butoxide in boiling *t*-butyl alcohol and dioxane. However, the treatment of the dibromide I with several potassium alkoxides in the corresponding boiling alcohol and dioxane did not give the expected acetylene VI, but rather, 9-(1,2-dialkoxy-

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1) Part VI: O. Tsuge, A. Torii and T. Tomita, *Nippon Kagaku Zasshi*, **90**, 1263 (1969).

2) O. Tsuge, M. Nishinohara and M. Tashiro, This Bulletin, **36**, 1477 (1963).

3) O. Tsuge, M. Nishinohara and K. Sadano, *ibid.*, **38**, 2037 (1965).

4) R. H. Mitchell and F. Sondheimer, *Tetrahedron*, **24**, 1397 (1968).

ethyl)acridine (IV) or *trans*-1-(9-acridinyl)-2-alkoxyethylene (V) depending on the nature of the alkoxides; the reactions with methoxide, ethoxide, and *n*-propoxide gave the corresponding diether IVa—IVc respectively, while the treatment with *t*-butoxide afforded the vinylether Vb.

Although the dehydrobromination of the dibromide I to the acetylene VI caused such difficulties, it has been found that I reacted with methanolic potassium hydroxide in dioxane to give the corresponding diether IVa, *trans*-vinylether Va, or the expected acetylene VI, depending on the reaction conditions; the results are summarized in Table 1.

TABLE 1. CONDITIONS AND YIELDS OF PRODUCTS IN THE REACTION OF I WITH METHANOLIC POTASSIUM HYDROXIDE[a)]

MeOH:I mole ratio	Temp. (°C)	Time (min)	Yield (%)		
			IVa	Va	VI
11:1	65	120	80	0	0
9:1	75—80	120	0	75	0
2:1	94—96	120	0	0	27
2:1	94—96	40	0	+[c)]	34
2:1	94—96	20	0	0	55
0[b)]	100	120	0	0	0

a) Mixtures of I (5.0 g), KOH (5.0 g), and specified amounts of MeOH were heated under definite conditions.
b) I was recovered.
c) A plus-sign, +, indicates a trace amount.

The data in Table 1 indicate that differences in the amounts of methanol result in serious differences. As the acetylene VI was proved to be a rather unstable substance, a considerable reduction in reaction time is desirable.

The structures of IV, V, and VI were confirmed by spectral studies as well as by elemental analyses. The infrared spectrum of VI showed the characteristic bands due to the ethynyl group at 3200 and 2130 cm^{-1}, while the NMR spectrum in deuteriochloroform ($CDCl_3$) exhibited signals at τ 5.8 (1H, ethynyl-proton, singlet) and 1.4—2.5 (8H, aromatic protons, multiplet).

Reaction of 9-Ethynylacridine (VI) with the Nitroso Compound VII. The reaction of VI with *p*-nitrosodimethylaniline (VIIa) was investigated under various conditions.

The acetylene VI did not react with VIIa in either the absence or presence of a basic catalyst such as potassium carbonate in ethanol, but the presence of HCl as a catalyst afforded the 1 : 2 adduct (VIIIa) ($C_{31}H_{29}O_2N_5$) as red prisms.

The effects of different amounts of HCl as a catalyst on the yield of VIIIa were also investigated; the results are shown in Table 2.

TABLE 2. CONDITIONS AND YIELDS OF VIIIa IN THE REACTION OF VI WITH VIIa[a)]

VI:VIIa mole ratio	HCl (m*l*)	Yield of VIIIa (%)
1:1	0.1	29
1:2	0.05	38
1:2	0.1	43
1:2	0.1	47[b)]
1:2	0.1	41[c)]
1:2	0.2	29
1:2	0.35	16

a) Reactions of VI (1.0 g) with specified amounts of VIIa and HCl (d^{27} 1.1748) were conducted in ethanol (15 m*l*) at room temperature for 2 hr.
b) Reaction temperature: 0°C.
c) Reaction time: 12 hr.

A similar reaction of VI with *p*-nitrosodiethylaniline (VIIb) gave the corresponding 1 : 2 adduct (VIIIb) as red needles. However, nitrosobenzene, *p*-methyl- or *p*-chloronitrosobenzene did not give the corresponding adduct under similar conditions; resinous materials were obtained exclusively in each case.

On the basis of the chemical transformations to the known compounds shown in Scheme 2, and on the basis of the spectroscopic evidence, the 1 : 2 adduct was established to be 1-(9-acridinyl)-1,2-bis(*p*-dialkylaminophenylimino)ethane N^1,N^2-dioxide (VIII).

The hydrolysis of VIIIa with 12% aqueous HCl afforded acridine-9-carbaldehyde (IX)[2)] in a 73% yield. When VIIIa was treated with cold 10% aqueous sulfuric acid, (9-acridinyl)formylmethylene-*p*-dimethylaminoaniline *N*-oxide (X),[3)] which was then subjected to decarbonylation to form (9-acridinylmethylene)-*p*-dimethylaminoaniline *N*-oxide (XI),[2)] was obtained in a 57% yield.

Furthermore, VIIIa was deoxygenated with triethyl phosphite to afford 1-(9-acridinyl)-1,2-bis(*p*-dimethylaminophenylimino)ethane (XII).[3)]

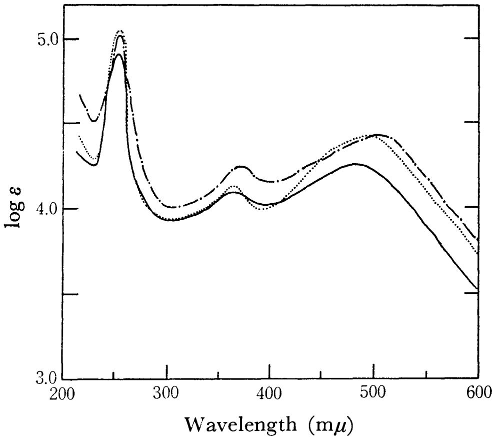
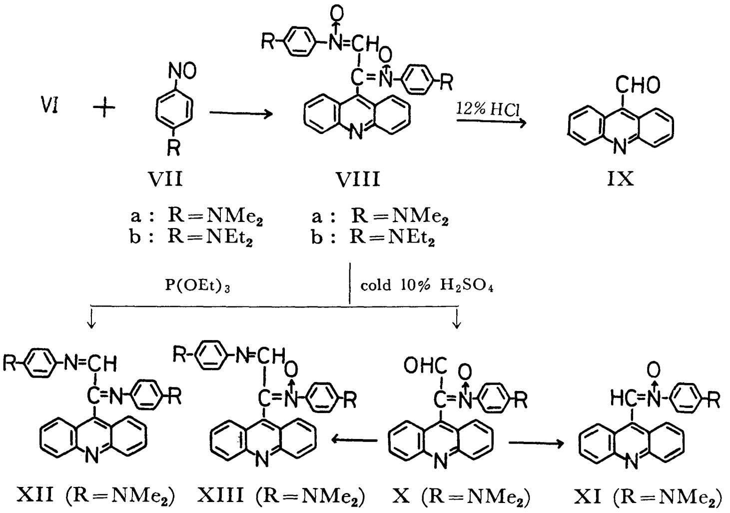


Fig. 1. Ultraviolet spectra in ethanol, VIIIa (——); VIIIb (—·—·); XIII (······).



Scheme 2

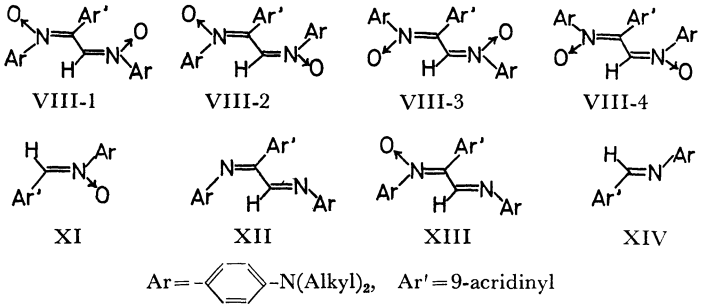


Fig. 2.

The condensation of X and *p*-dimethylaminoaniline gave 1-(9-acridinyl)-1,2-bis(*p*-dimethylaminophenylimino)ethane *N*^{1}-oxide (XIII).[3]

The spectral data of VIII are also compatible with the proposed structure. The ultraviolet (Fig. 1) and infrared spectra are very similar to those of XIII. The NMR spectrum of VIIIb in CDCl$_3$ showed signals at τ 9.12 and 8.78 (each 6H, methyl-protons, triplet), at τ 6.95 and 6.65 (each 4H, methylene-protons, quartet), at τ 1.7—4.2 (16H, aromatic protons), and at τ 0.87 (1H, methine proton).

Four geometrical isomers resulting from the *syn*- and *anti*-configurations are, then, possible for the structure of VIII (Fig. 2). An inspection of the Dreiding models for VIII indicates that there is an appreciable interaction between the acridine and phenyl rings in VIII-2—VIII-4, but not in VIII-1. Consequently, it may be thought that VIII-1 is the most favorable configuration for VIII.

Similar inspections of the Dreiding models for XI, XII, XIII, and (9-acridinylmethylene)-*p*-dimethylaminoaniline (XIV) indicate that the most favorable configurations for the above compounds are those shown in Fig. 2.

The NMR spectra in CDCl$_3$ showed the methine proton at τ 0.30, 0.33, 0.32, and 0.30 in XI, XII, XIII, and XIV respectively. Presumably, the appearance of the methine proton at an abnormally low field might be understood in terms of the deshielding effect of aromatic rings.[5] All the ultraviolet spectra of the compounds VIII and XI—XIV exhibited absorptions compatible with a long conjugated system.

The proposed configurations for the above compounds are supported by the above observations as well as by the inspections of the Dreiding models.

Experimental

All the melting points are uncorrected. The infrared spectra were measured in KBr disks, while the NMR spectra were determined at 60 MHz with a Hitachi R-20 spectrometer, using tetramethylsilane as the internal reference. The mass spectra were obtained on a Hitachi RMS-4 spectrometer at an electrode voltage of 70 eV.

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[5] J. F. King and T. Durst (*Can. J. Chem.*, **40**, 882 (1962)) have reported that the methine proton of benzylidenaniline appears at τ 1.65 in the NMR spectrum (carbon tetrachloride).

9-(1,2-Dibromoethyl)acridine (I). Into a solution of 2.0 g of 9-vinylacridine[1] in 20 m*l* of dry benzene, 1.6 g of bromine was added with stirring at 0°C. After the reaction mixture had then been stirred at room temperature for 20 min, filtration gave 3.45 g (quantitatively) of orange crystals. Recrystallization from ethanol afforded 9-(1,2-dibromoethyl)acridine(I) as orange prisms; mp 156—157°C (decomp.).

Found: C, 49.58; H, 2.72; N, 3.49%. Calcd for $C_{15}H_{11}NBr_2$: C, 49.31; H, 3.01; N, 3.84%.

The mass spectrum was also compatible with the dibromide I: parent peaks (M^+) at *m/e* 367, 365 and 363 (intensity 1 : 2 : 1); $(M\text{-}Br)^+$ at *m/e* 286 and 284 (intensity 1 : 1); $(M\text{-}2Br)^+$ at *m/e* 205 (base peak).

***trans*-1-(9-Acridinyl)-2-bromoethylene (II).** After a mixture of 1.5 g of the dibromide I in 5 m*l* of triethylamine had been refluxed for 4 hr, it was allowed to stand overnight, thus giving 1.15 g (97%) of yellow crystals. Recrystallization from benzene gave *trans*-1-(9-acridinyl)-2-bromoethylene (II) as pale yellow needles; mp 349—350°C (decomp.).

Found: C, 63.22; H, 3.21; N, 4.62%. Calcd for $C_{15}H_{10}NBr$: C, 63.38; H, 3.52; N, 4.92%. Infrared spectrum: 950 cm^{-1}. NMR spectrum in trifluoroacetic acid: τ 2.7 and 1.9 (each 1H, olefinic proton, doublet, $J=14$ Hz), 1.2—2.1 (8H, aromatic protons, multiplet).

1-(9-Acridinyl)-2-phenylethane (III). A solution of 3.0 g of the dibromide I and phenyllithium, which had been prepared from 7.5 g of bromobenzene and 0.7 g of lithium in 30 m*l* of diethyl ether, was stirred at 0°C for 40 min. After the reaction mixture had then been decomposed with ice water, the resulting mixture was extracted twice with 50-m*l* portions of benzene. The benzene extract was evaporated *in vacuo* to leave yellow crystals (mp 82—90°C), which were then dissolved in benzene. The benzene solution was chromatographed on alumina, affording 1.3 g (57%) of 1-(9-acridinyl)-2-phenylethane (III) as pale yellow needles; mp 100.5—101.5°C.

Found: C, 89.19; H, 6.14; N, 4.88%. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94%. Mass spectrum: *m/e* 283 (M^+), 192 [$(M\text{-}C_7H_7)^+$]. NMR spectrum in carbon tetrachloride: τ 6.9—7.2 and 6.05—6.45 (each 2H, methylene-protons, multiplet), 1.65—2.8 (13H, aromatic protons, multiplet).

General Method for the Reaction of the Dibromide I with Potassium Alkoxide. *i*) Into a solution of 3.0 g of the dibromide I in 40 m*l* of dioxane was stirred, drop by drop and at room temperature, a methanolic solution of potassium methoxide, prepared from 4.4 g of potassium and 50 m*l* of methanol. After the reaction mixture had then been refluxed for 1 hr, the solvent was evaporated *in vacuo* to leave a residue, which was then quenched with water. The resultant mixture was extracted with 100 m*l* of diethyl ether, after which the ether extract was evaporated to leave a brown oily material which, on the chromatography of the benzene solution on alumina, gave 2.0 g of pale yellow crystals (mp 98.5—100°C). Recrystallization from petroleum benzine (bp 45—60°C) gave 9-(1,2-dimethoxyethyl)acridine (IVa), mp 101.5—102.5°C, as pale yellow prisms.

Found: C, 76.78; H, 6.52; N, 5.21%. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24%. Mass spectrum: *m/e* 235 [$(M\text{-}CH_3OH)^+$], 220 [$(235-CH_3)^+$], 192 [$(220-CO)^+$]. NMR spectrum in carbon tetrachloride: τ 6.75 (6H, methyl-protons, singlet), 6.25 (2H, methylene-protons, doublet), 5.3 (1H, methine-proton, triplet), 1.65—2.65 (8H, aromatic protons, multiplet).

A similar reaction of the dibromide I with potassium ethoxide or *n*-propoxide gave the corresponding diether.

9-(1,2-Diethoxyethyl)acridine (IVb): mp 65—66°C; yellow prisms. Yield, 83%. Found: C, 77.08; H, 7.26; N, 4.83%. Calcd for $C_{19}H_{21}O_2N$: C, 77.26; H, 7.17; N, 4.74%.

9-(1,2-Di-*n*-propoxyethyl)acridine (IVc): mp 71—72°C; yellow prisms. Yield, 78%. Found: C, 78.13; H, 8.14; N, 4.58%. Calcd for $C_{21}H_{25}O_2N$: C, 77.98; H, 7.88; N, 4.33%.

ii) Into a solution of 5.0 g of the dibromide I in 50 m*l* of dioxane was stirred, drop by drop and at room temperature, a solution of potassium *t*-butoxide, prepared from 5.5 g of potassium and 250 m*l* of *t*-butyl alcohol. After the reaction mixture had then been refluxed for 1 hr, a treatment similar to that described in *i*) was carried out; *trans*-1-(9-acridinyl)-2-*t*-butoxyethylene (Vb), mp 141.5—142.5°C, was thus obtained as yellow prisms. Yield, 3.4 g (87%).

Found: C, 82.44; H, 6.94; N, 4.97%. Calcd for $C_{19}H_{19}ON$: C, 82.28; H, 6.91; N, 5.05%. Infrared spectrum: 945 cm^{-1}. Mass spectrum: *m/e* 277 (M^+). NMR spectrum in carbon tetrachloride: τ 8.57 (9H, methyl-protons, singlet), 1.5—3.4 (10H, olefinic and aromatic protons).

Reaction of the Dibromide I with Methanolic Potassium Hydroxide. *i*) A solution of 5.0 g of the dibromide I and 5.0 g of potassium hydroxide in a mixture of methanol (7 g) and dioxane (2.5 m*l*) was heated, while being stirred, at 65°C for 2 hr, and then cooled. After water had been added to it, the mixture was extracted three times with 25-m*l* portions of ether. The ether solution was dried over sodium sulfate, and the ether was distilled off, leaving a brown oily material. The benzene solution was chromatographed on alumina, affording 2.9 g (80%) of pale yellow crystals; mp 99—101°C. Recrystallization from petroleum benzine (bp 45—60°C) gave pale yellow prisms, mp 101.5—102.5°C, whose infrared spectrum was identical with that of the diether IVa.

ii) A solution of 5.0 g of the dibromide I and 5.0 g of potassium hydroxide in a mixture of methanol (4 g) and dioxane (10 m*l*) was heated, while being stirred, at 75—80°C for 2 hr. A treatment similar to that described in *i*) gave a reddish-brown oily material from the ether extract. The benzene solution was chromatographed on alumina to give 2.4 g (75%) of yellow crystals, mp 123—125°C, which, on recrystallization from petroleum benzine (bp 45—60°C), afforded *trans*-1-(9-acridinyl)-2-methoxyethylene (Va), mp 125—126°C, as yellow needles.

Found: C, 81.65; H, 5.49; N, 5.64%. Calcd for $C_{16}H_{13}ON$: C, 81.68; H, 5.52; N, 5.95%. Mass spectrum: *m/e* 235 (M^+), 220 [$(M\text{-}CH_3)^+$], 204 [$(M\text{-}OCH_3)^+$]. 192 [$(220-CO)^+$]. Infrared spectrum: 940 cm^{-1}.

iii) A solution of 5.0 g of the dibromide I and 5.0 g of potassium hydroxide in a mixture of methanol (1.0 g) and dioxane (2.5 m*l*) was heated, while being stirred, at 94—96°C for 20 min.

A similar treatment gave 1.5 g (55%) of brown crystals, mp 153—155°C (decomp.), from the ether extract. Recrystallization from benzene gave 9-ethynylacridine (VI), mp 157—158°C (decomp.), as yellow needles.

Found: C, 84.43; H, 4.70; N, 6.49%. Calcd for $C_{15}H_9N\cdot\frac{1}{2}H_2O$: C, 84.80; H, 4.71; N, 6.60%. Ultraviolet spectrum λ_{max}^{EtOH} mμ (log ε): 257 (5.3), 371 (4.1). Mass spectrum: *m/e* 203 (M^+).

The results of other reactions under varying conditions are shown in Table 1.

Reaction of the Acetylene VI with *p*-Nitrosodimethylaniline (VIIa). To a mixture of 0.3 g of the acetylene VI and 0.4 g of *p*-nitrosodimethylaniline (VIIa) in 5 m*l* of ethanol was added 0.03 m*l* of HCl at 0°C. The reaction mixture was then stirred at 0°C for 2 hr. Filtration gave 0.35 g (47%) of red crystals which, on recrystallization from pyridine, afforded 1-(9-acridinyl)-1,2-bis(*p*-dimethylaminophenylimino)-ethane N^1,N^2-dioxide (VIIIa), mp 217—218°C, as red prisms.

Found: C, 74.18; H, 5.91; N, 14.10%. Calcd for $C_{31}H_{29}O_2N_5$: C, 73.93; H, 5.80; N, 13.91%. Ultraviolet spectrum λ_{max}^{EtOH} mμ (log ε): 253 (4.9), 367 (4.1), 485 (4.3).

The results of other reactions under varying conditions are summarized in Table 2.

Reaction of the Acetylene VI with *p*-Nitrosodiethylaniline (VIIb). A similar reaction of 0.3 g of the acetylene VI with 0.53 g of *p*-nitrosodiethylaniline (VIIb) in the presence of HCl (0.03 m*l*) at 0°C for 2 hr gave the corresponding N^1,N^2-dioxide VIIIb, mp 190—191°C, as red needles. Yield, 0.41 g (50%).

Found: C, 75.54; H, 6.71; N, 12.16%. Calcd for $C_{35}H_{37}O_2N_5$: C, 75.10; H, 6.66; N, 12.31%. Ultraviolet spectrum λ_{max}^{EtOH} mμ (log ε): 254 (5.2), 368 (4.3), 505 (4.5).

Hydrolysis of the N^1,N^2-Dioxide VIIIa. *i*) A mixture of 0.2 g of the N^1,N^2-dioxide VIIIa in 2 m*l* of 12% aqueous HCl was heated at 90°C for 30 min, and then cooled. The precipitated crystals were collected and washed with ammonium hydroxide, giving 0.6 g (73%) of yellow crystals, mp 143—145°C. Recrystallization from a petroleum benzine-benzene mixture afforded yellow needles, mp 148°C. This compound was proved, by an admixed-mp determination and by a study of its infrared spectrum, to be identical with an authentic sample of acridine-9-carbaldehyde (IX), mp 147°C.[2)]

ii) After 10 m*l* of 10% sulfuric acid had been added to 0.5 g of VIIIa under ice cooling, it was allowed to stand at 0°C for 30 min. Filtration gave dark yellow crystals which, when washed with ammonium hydroxide, afforded 0.2 g (57%) of orange crystals. Recrystallization from benzene gave orange needles, mp 206—207°C (decomp.), which were proved, by a study of their infrared spectrum, to be identical with an authentic sample of (9-acridinyl)formylmethylene-*p*-dimethylaminoaniline *N*-oxide (X), mp 208°C (decomp.).[3)]

Decarbonylation of (9-Acridinyl)formylmethylene-*p*-dimethylaminoaniline *N*-Oxide (X). A suspension of 0.1 g of X and 1 drop of 20% aqueous sodium hydroxide in 5 m*l* of ethanol was refluxed for 3 hr. After the mixture had then been allowed to stand overnight, filtration gave 60 mg (67%) of red crystals. Recrystallization from pyridine gave red prisms, mp 243°C (decomp.). This compound was proved, by a study of its infrared spectrum, to be identical with (9-acridinylmethylene)-*p*-dimethylaminoaniline *N*-oxide (XI), mp 243°C (decomp.).[2)]

Reaction of the N^1,N^2-Dioxide VIIIa with Triethyl Phosphite. A mixture of 0.22 g of VIIIa and 2.0 g of triethyl phosphite was gently refluxed under a nitrogen atmosphere for 10 hr. After the mixture had then been allowed to stand overnight, the precipitated crystals were filtered off and then washed with ethanol to give 0.1 g (50%) of red crystals.

Recrystallization from pyridine gave red prisms, mp 282—283°C (decomp.). These were proved, by a study of their infrared spectrum, to be identical with an authentic sample of 1-(9-acridinyl)-1,2-bis(*p*-dimethylaminophenylimino)ethane (XII), mp 283°C (decomp.).[3)]

1-(9-Acridinyl)-1,2-bis(*p*-dimethylaminophenylimino)ethane N^1-Oxide (XIII). A mixture of 0.1 g of X, 0.2 g of *p*-dimethylaminoaniline, and 1 drop of acetic acid in 5 m*l* of ethanol was refluxed for 2 hr, and then cooled. Filtration gave 0.1 g (75%) of red crystals which, on recrystallization from benzene, afforded red prisms, mp 263—264°C (decomp.). This compound was proved, by a study of its infrared spectrum, to be identical with 1-(9-acridinyl)-1,2-bis-(*p*-dimethylaminophenylimino)ethane N^1-oxide (XIII), mp 265°C (decomp.).