# Compounds Related to Acridine. III.*[,1] The Formation of Acridone in the Reaction of 9-Methylacridine with *p*-Nitrosodimethylaniline

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In a previous paper[2] dealing with the condensations of the acridine with an active methyl group and of the aromatic nitroso compound, it was shown that the presence of a catalytic amount of hydrochloric acid (HA) revealed interesting features regarding the yields and the amounts of the anil and of the nitrone compound relative to those in the presence of the alkaline catalyst usually used in such reactions.

It was also reported there that in the reaction of 9-methylacridine (I) with *p*-nitrosodimethylaniline (II), a higher-melting substance, m. p. over 300°C, whose structure was not identified, came to be formed as the amount of HA increased, and that its maximum yield was obtained when equimolar amounts of I and of HA were used.

Since the structure of the higher-melting substance has now been clarified, further investigation was undertaken in order to elucidate the course of the formation of the compound.

## Results and Discussion

After the higher-melting substance obtained in the previous paper[2] was washed with hydrochloric acid, recrystallization from a large amount of benzene or sublimation afforded pale yellow prisms, m. p. 354°C. This compound was proved, by the admixed melting point and by the infrared spectrum, to be identical with acridone (III), which was prepared from 9-chloroacridine.[3]

It may be supposed that *N*-(*p*-dimethylaminophenyl)-$\alpha$-(9-acridyl)nitrone (IV), which is the main product when a catalytic amount of HA was used, and acridine-9-carboxaldehyde *N*-(*p*-dimethylaminophenyl)anil (V) could be formed at an initial stage of the reaction when a sufficient amount of HA was used.

It is well known that both IV and V are almost quantitatively hydrolyzed by dilute hydrochloric acid to afford acridine-9-carboxaldehyde (VI), and we found that the nitroso compound (II) was also formed in the hydrolysis of IV. The treatment of IV with an equimolar amount of HA in ethanol, however, afforded III, and the similar treatment of V resulted only in the formation of VI. Further, III was formed not only from IV but also

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[1] Part II: O. Tsuge and M. Nishinohara, *The Reports of the Research Institute of Science and Industry* (*Seisan Kagaku Kenkyusyo Hokoku*), *Kyushu University*, No. 37, 1 (1964).

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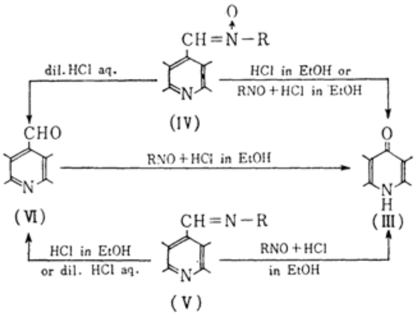
[2] O. Tsuge, M. Nishinohara and M. Tashiro, This Bulletin, **36**, 1477 (1963).

[3] R. C. Elderfield, "Heterocyclic Compounds," John Wiley & Sons, New York (1952), p. 505.



$R = p\text{-}C_6H_4N(CH_3)_2$

Chart 1

from V in the heating with II in the presence of HA, as is depicted in Chart 1.

These observations indicate that both II and HA play an important role in the formation of III. It could be postulated that both IV and V will be hydrolyzed to afford VI in the presence of sufficient amounts of HA, and that III is formed from VI by a secondary reaction. In fact, it was found that the treatment of VI with II in the presence of HA in ethanol gave III in a high yield, besides a small amount of *p, p'*-bis(dimethylamino)azoxybenzene (VII). However, III was not formed from VI when treated with II or with HA alone.

On the basis of the facts mentioned above, the possible courses of the formation of III from VI are shown in Chart 2. It has been established that acridine *N*-oxide (VIII) rearranges to III in the heating with acetic anhydride.[4] As VIII was not rearranged to III under the reaction conditions, the possibility that VIII, which might be formed through the courses a and /or b by the oxidative property of II, may be rearranged to III was excluded. It was also recognized that III was not formed from either acridine-9-carboxlic acid (XI) or acridine (X) under similar conditions.

Now, the replacement of the formyl group by the hydroxyl group by the action of a peroxide has been known as the Dakin hydroxylation reaction, which proceeds through the formate.[5] If III is formed through 9-acridyl formate (XI), as is shown in the course c, the treatment of VI with a peroxide should give III.

The treatment of VI with hydrogen peroxide in ethanol or with perbenzoic acid in chloroform really gave III with a good yield. Furthermore, the formate (XI) was isolated when the reaction of VI with hydrogen peroxide was quenched after a short while. Although XI could not be isolated

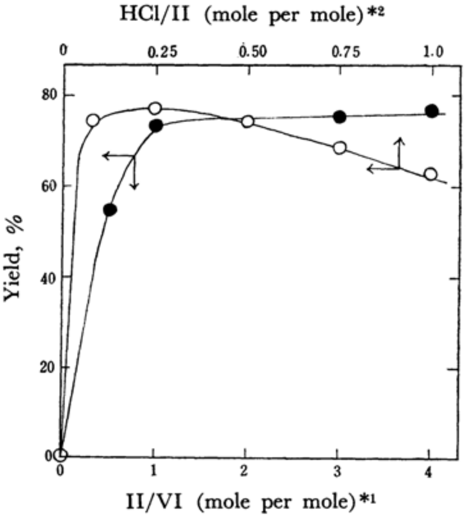


Fig. 1. Effects of hydrochloric acid and the nitroso compound (II) on the yield of acridone (III).

*1 Mixtures of the formyl compound VI (0.52 g.) and the specified amounts of II (II/HA=2) in ethanol (25 ml.) were refluxed for 3 hr.

*2 Mixtures of VI (0.52 g.), II (0.75 g.) and the specified amounts of HA in ethanol (25 ml.) were refluxed for 3 hr.

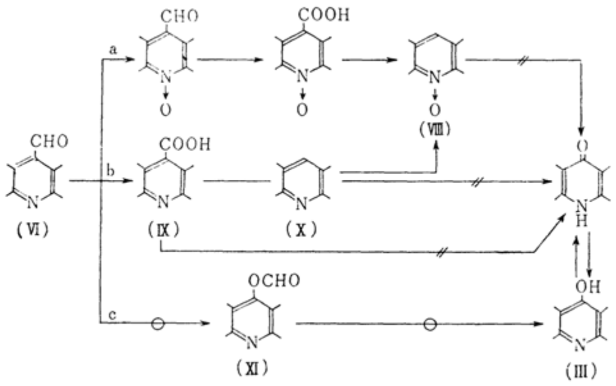


Chart 2

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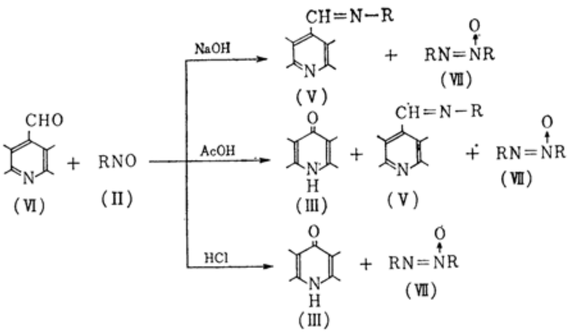
4) K. Kliegel and A. Fehrle, *Ber.*, **47**, 1629 (1914).

5) For example, 2-hydroxyphenyl formate was isolated in the reaction of salicylaldehyde with hydrogen peroxide. (A. v. Wacek and A. v. Bezard, *Ber.*, **74**, 845 (1941)).



R= $p$-$C_6H_4N(CH_3)_2$

Chart 3

in the reaction of VI with II in the presence of HA in ethanol, ethyl formate was identified by the gas chromatographic analysis of the distillate of the reaction mixture, as in the case of the reaction with hydrogen peroxide.

On the basis of these observations, it is reasonable to conclude that the formation of III from VI in the presence of II and HA proceeds through the course c.

The results of the effect of the amounts of II and of HA on the yield of III are shown in Fig. 1. It is notable that III was formed with a high yield even if an amount of II equimolar to VI and a catalytic amount of HA were used.

On the other hand, it was found that, in the treatment of VI with II in the presence of sodium hydroxide in ethanol, a small amount of the anil compound (V) was obtained, besides the azoxy compound (VII). Similar treatment in the presence of acetic acid in place of sodium hydroxide gave III, V and VII. The formation of V indicates that II was in part reduced to the corresponding amine in the reactions, since V can be formed only by the condensation of VI and the amine. Such a reduction of II to the amine would take place in the presence of HA. The above scheme is shown in Chart 3.

Further investigation of the oxidative property of II in the presence of HA will be published elsewhere in the near future.

## Experimental[6,7]

**The Reaction of 9-Methylacridine (I) with $p$-Nitrosodimethylaniline (II).**—A solution of 1.0 g. of I, 1.6 g. of II and 0.4 ml. of HA in 50 ml. of ethanol was refluxed for 2 hr. and then allowed to stand overnight. Filtration gave crystals which, on being washed with hot benzene (5 ml.×2), left 0.6 g. (35.4%) of the nitrone compound (IV) as reddish-brown prisms, m. p. 243°C (decomp.).[2] The benzene washings were then evaporated to give a small amount of the anil (V) as red prisms, m. p. 248°C.[2] The ethanol filtrate after the reaction was concentrated in vacuo, and then the residue was washed with concentrated hydrochloric acid to leave 0.46 g. of the higher-melting compound, m. p. over 300°C. Recrystallization from a large amount of benzene or sublimation gave pale yellow prisms, m. p. 354°C. This compound was proved, by the admixed melting point and by the infrared spectrum, to be identical with the acridone (III) which was obtained by the hydrolysis of 9-chloracridine.

Found: C, 79.93; H, 4.73; N, 7.05. Mol. wt. 191.[8] Calcd. for $C_{13}H_9ON$: C, 79.98; H, 4.65; N, 7.17%. Mol. wt. 195.2.

The results of other reactions under varying conditions have been reported in a previous paper.[2]

**The Formation of Acridone (III) from the Nitrone (IV) or Anil Compound (V).**—i) A mixture of 1.7 g. of IV and 0.4 ml. of HA in 50 ml. of ethanol was refluxed for 3 hr. After a large part of the ethanol had been evaporated in vacuo, the residue was washed with concentrated hydrochloric acid (5 ml.×2), aqueous ammonia, and then water to leave 0.38 g. (39%) of yellow crystals, m. p. 335—340°C. Recrystallization from a large amount of benzene gave yellow prisms, m. p. 354°C, whose infrared spectrum was superimposable on that of acridone.

The similar treatment of 0.8 g. of V and 0.2 ml. of HA in 30 ml. of ethanol afforded 0.37 g. (71%) of acridine-9-carboxaldehyde (VI), m. p. 147°C (lit.[9] 147°C).

ii) A mixture of 1.0 g. of IV, 1.0 g. of II and 0.3 ml. of HA in 30 ml. of ethanol was refluxed for 3 hr. and then cooled. Filtration gave 0.37 g. of brown crystals, m. p. 225—230°C, which, on recrystallization from benzene, afforded pale brown prisms, m. p. 240—241°C. This compound was proved by a study of its infrared spectrum to be identical with an authentic sample of $p,p'$-bis(dimethylamino)azoxybenzene (VII), m. p. 241—242°C.[10]

After the filtrate had been evaporated in vacuo, the residue was washed with hydrochloric acid, aqueous

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[6] All melting points are uncorrected.

[7] HA used in this experiment: $d^{27}$ 1.1748.

[8] Molecular weight was measured by the cryoscopic method, using dimethylsulfoxide (molecular depression constant=4.24) as the solvent.

[9] L. Chardonnens and P. Heinrich, *Helv. Chim. Acta*, **32**, 656 (1949).

[10] H. von Pechmann and W. Schmitz, *Ber.*, **31**, 295 (1898).

ammonia and then water to leave 0.34 g. (60%) of III.

A similar reaction of 0.5 g. of V with 0.5 g. of II in the presence of 0.15 ml. of HA in 20 ml. of ethanol afforded 0.18 g. (60%) of III and 0.18 g. of VII.

**The Reaciton of the Formyl Compound (VI) with II.**—*In the Presence of HA.*—A mixture of 0.52 g. of VI, 0.56 g. of II and 0.23 g. of the hydrochloride of II in 25 ml. of ethanol was refluxed for 3 hr., and then the ethanol was evaporated in vacuo. The residue was treated with hydrochloric acid, aqueous ammonia and water to give 0.37 g. (76%) of III, m. p. 350—353°C.

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

*In the Presence of Sodium Hydroxide.* — A mixture of 0.52 g. of VI, 0.75 g. of II and 0.50 g. of sodium hydroxide in 25 ml. of ethanol was refluxed for 3 hr. and then allowed to stand overnight. Filtration gave 0.12 g. of crystals, m. p. 195—230°C, which were found to be a mixture of V and VII by a study of the infrared spectrum. The recrystallization of the crystals from ethanol gave a small amount of V, m. p. 248°C. From the filtrate, III was not isolated.

*In the Presence of Acetic Acid.* — A mixture of 0.52 g. of VI, 0.75 g. of II and 0.5 ml. of glacial acetic acid in 30 ml. of ethanol was refluxed for 3 hr. Treatment similar to that described above gave 0.10 g. of reddish brown crystals, m. p. 200—225°C, which were found to be a mixture of V and VII by a study of the infrared spectrum. From the filtrate, 0.13 g. of II was obtained.

**The Reaction of the Formyl Compound (IV) with Hydrogen Peroxide.**—*i)* To a solution of 0.52 g. of VI in 25 ml. of ethanol there was added 0.5 ml. of 30% of hydrogen peroxide. The refluxing of the reaction mixture resulted in the precipitation of yellow crystals in several minutes: then it turned into a complete solution. After it had been refluxed for 2 hr., the ethanol was evaporated in vacuo. The residue was washed with hydrochloric acid, aqueous ammonia and then water to obtain 0.44 g. (90%), m. p. 247—250°C, of III.

*ii) The Isolation of the Formate (XI).*—After a mixture of 0.25 g. of VI and 0.25 ml. of hydrogen peroxide in 25 ml. of ethanol had been refluxed for 10 min., 0.13 g. of yellow crystals, m. p. 254°C (decomp.), was obtained by filtration. Recrystallization from ethanol then afforded yellow prisms, m. p. 254°C (decomp.).

Found: C, 74.98; H, 4.39; N, 6.22. Calcd. for $C_{14}H_9O_2N$ (XI): C, 75.34; H, 4.04; N, 6.27%.

**The Reaction of the Formyl Compound (VI) with Perbenzoic Acid.**—To 30 ml. of a chloroform solution of perbenzoic acid,[11] 2.0 g. of VI was added under ice-cooling. After the reaction mixture had been stirred under ice-cooling for 3 hr., filtration gave 0.90 g. of III. The filtrate was not examined further.

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[11] "Organic Syntheses," Coll. Vol. 1, 431 (1948).