Compounds Related to Acridine. IV.[1,2] The Condensation of 9-Ethylacridine and *p*-Nitrosodimethylaniline

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(Received July 23, 1965)

Recently[3] we found that the condensation of the acridine with an active methyl group and the aromatic nitroso compound, under the influence of a catalytic amount of hydrochloric acid (HA), afforded as condensation products an anil and a nitrone in fairly good yields compared with the yield when an alkaline catalyst is used.

Since, however, no informationn has been available regarding the condensation of the ethyl group and the aromatic nitroso compound, it appeared of interest to investigate whether 9-ethylacridine (I) can be condensed with *p*-nitrosodimethylaniline (II).

Results and Discussion

The condensation of I and II did not take place in the presence of potassium carbonate, but a small amount of *p*, *p*′-bis(dimethylamino)azoxybenzene (III), m. p. 240—241°C (lit.[4] 241—242°C) was formed.

However, the presence of HA as a catalyst in

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[1] Preliminary communication: This Bulletin, **37**, 436 (1964).

[2] Part III: O. Tsuge and M. Nishinohara, **38**, 2034 (1965).

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

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

place of an alkaline catalyst afforded condensation products (IV) as reddish crystals, m. p. about 260°C (decomp.).

The effect of different amounts of HA on the yield of IV was investigated; the results are shown in Table I. The maximum yield of IV was obtained when the molar ratio of HA to I was about 1.1 (0.2 ml. in Table I); a fairly large amount of HA was needed, in contrast with the case of the condensation of the 9-methylacridine and II. Also, acridone was not formed, even if the amount of HA was increased.

TABLE I. THE EFFECT OF DIFFERENTS OF HA ON THE YIELD OF CONDENSATION PRODUCTS (IV)*

HCl ml.	Yield g.	HCl ml.	Yield g.
0.01	trace	0.3	1.05
0.03	trace	0.4	0.70
0.1	0.96	0.8	0.01
0.2	1.28		

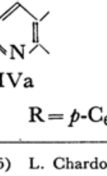
* Mixtures of I (1.0 g.), II (1.4 g.) and the specified amounts of HA in ethanol (20 ml.) were refluxed for 3 hr.

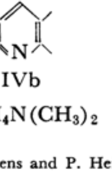
The hydrolysis of IV with 12% aqueous hydrochloric acid afforded acridine-9-carboxaldehyde (V), m. p. 147°C (lit.[5] 147°C), in a high yield. On the other hand, the treatment of IV with cold 10% aqueous sulfuric acid gave orange prisms (VI), m. p. 208°C (decomp.). The elemental analytical data of VI were in agreement with the formula $C_{23}H_{19}O_2N_3$, whose infrared spectrum exhibited the sharp bands at 1662 and 1604 cm^{-1} ascribed to the carbonyl group and the C=N bond respectively. Also, the qualitative test for the formyl group by the Tollens reagent was positive.

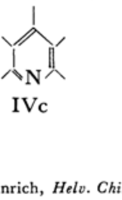
Furthermore, VI was oxidized with silver oxide to give *N*-(*p*-dimethylaminophenyl)-*α*-(9-acridyl)-nitrone (VII),[3] m. p. 243°C (decomp.), which was then easily hydrolyzed with dilute hydrochloric acid to V. VI was also easily hydrolyzed with the dilute acid to give V.

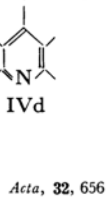
These observations indicate that VI is 9-acridylglyoxal-*α*-*N*-(*p*-dimethylaminophenyl)nitrone.

In view of the fact that V and VI were obtained by the hydrolysis of IV, it seems most reasonable to assume that IV is either one of the compounds (IVa—IVd) whose structrues correspond with those of the condensation products of one mole of I and two moles of II, or a mixture of them.


IVa


IVb


IVc


IVd

R = p-$C_6H_4N(CH_3)_2$

The condensation of VI and *p*-aminodimethylaniline afforded 9-acridylglyoxal-*α*-*N*-(dimethylaminophenyl)nitrone-*β*-*N*-(*p*-dimethylaminophenyl)anil (IVb), which was identified by an elemental analysis, as reddish-brown prisms, m. p. 265°C (decomp.). The infrared spectrum of IVb in KBr is given in Fig. 1.

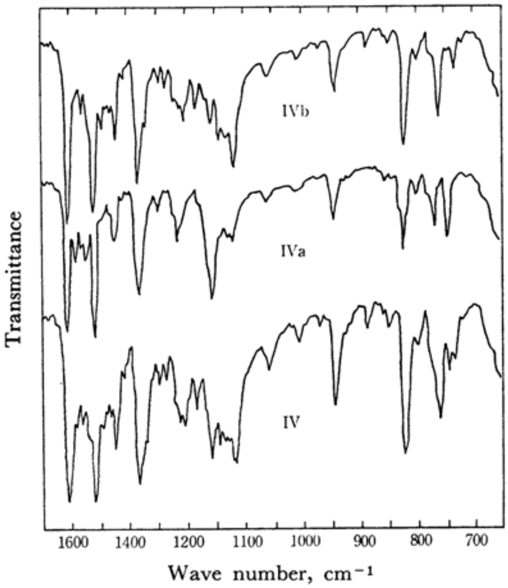


Fig. 1. Infrared spectra of IV, IVa and IVb in KBr.

On the other hand, 9-acridylglyoxal-*α*, *β*-*N*-(*p*-dimethylaminophenyl)dianil (IVa) was obtained as red prisms, m. p. 283°C (decomp.), by several fractional recrystallizations of IV from pyridine, or by the deoxygenation of IVb with triethyl phosphite. The infrared spectrum of IVa is also shown in Fig. 1.

On the basis of the infrared spectrum of IV, which revealed all the distinctive bands of IVa and IVb to be as shown in Fig. 1, and of the elemental analysis of IV,[6] it may be supposed that IV is a mixture of IVa and IVb only.

Moreover, it seems most reasonable to conclude that the hydrolysis of IV to V proceeds successively through the course depicted in Chart 1: IVa→VIII→IX→V; IVb→VI→VII→V, although 9-acridylglyoxal-*α*-*N*-(*p*-dimethylaminophenyl)anil (VIII) and acridine-9-carboxaldehyde *N*-(*p*-dimethylaminophenyl)anil (IX) could not be isolated.

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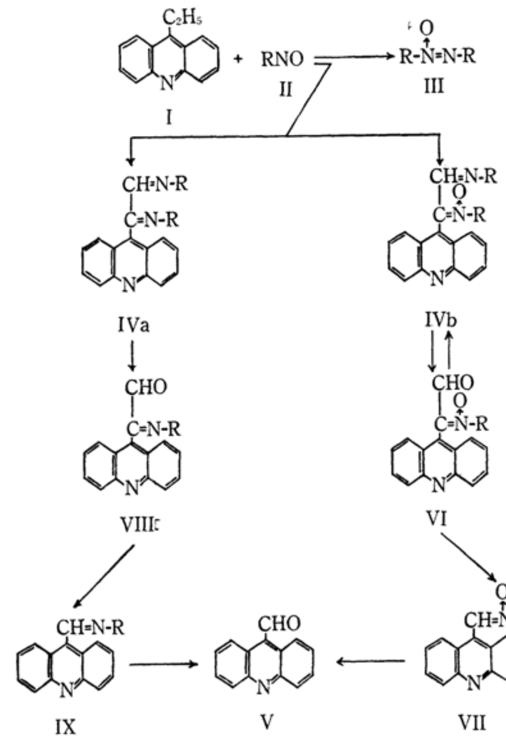
[5] L. Chardonnens and P. Heinrich, *Helv. Chim. Acta*, **32**, 656 (1949).

[6] As will be shown in the Experimental section, the elemental analysis of IV showed the intermediate values between those of IVa and IVb (or IVc), but these values were considerably different from those of IVd (C, 73.93; H, 5.80; N, 13.91%).



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

Chart 1

It is known that anil and nitrone compounds are difficult to separate. As the α, β-dianil (IVa) and α-nitrone-β-anil (IVb) have similarities in their chemical structures and properties, the separation was very difficult.

Although no chracteristic bands between IVa and IVb were observed in their infrared spectra, as is shown in Fig. 2, the quantitative estimation of IVa and IVb in IV was established by using of the ratio method,⁷⁾ which was carried out by the measurement of the absorbances A_1 and A_2 for the bands at 1120 and 1592 cm^{-1} respectively.

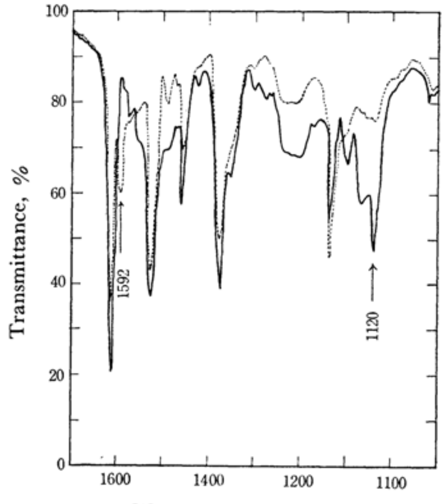


Fig. 2. Infrared spectra of IVa and IVb in chloroform.
······ IVa, —— IVb

Thus, samples of a mixture consisting of specified amounts of IVa and IVb were prepared and the absorbances A_1 and A_2 were measured according to the baseline method. The calibration curves plotting the relationship between A_1/A_2 or A_2/A_1 and the concentration (wt.%) of IVb are shown in Fig. 3.

According to the calibration curves thus obtained, the effect of reaction conditions on the yields of IVa and of IVb was examined. The results are given in Tables II and III.

When the molar ratio of HA to I was about 1.1 (Table III), the main product was the α-nitrone-β-anil IVb, whose yield was increased with an increment in the nitroso compound II. While the

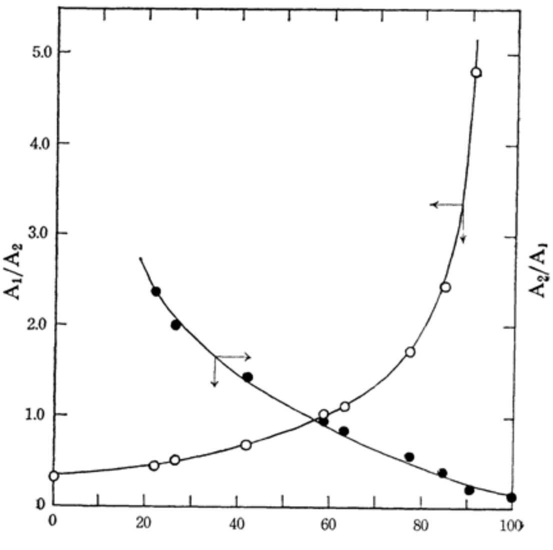


Fig. 3. Calibration curves.

Table II. Effect of HA*

HA ml.	Product				
	A_1/A_2	IVb in IV wt.%	Yield		
			IV g.	IVa %	IVb %
0.03	2.04	80.5	0.15	2.6	10.4
0.1	2.11	81.5	0.65	10.6	45.3
0.2	0.80	49	0.35	15.8	14.7

* Mixtures of I (0.50 g.), II (0.70 g.) and the specified amounts of HA in ethanol (7 ml.) were refluxed for 3 hr.

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7) S. Takagi, "Experiment and Calculation of Quantitative Analyses" (in Japanese), Vol. III, Kyoritsu, Tokyo (1961), p. 91.

TABLE III. EFFECT OF II*1

II*2	Product				
	A_1/A_2	IVb in IV wt.%	Yield		
			IV g.	IVa %	IVb %
1	0.64	39	2.25	13.5	8.3
2	2.11	81.5	0.65	10.6	45.3
3	2.19	82	0.76	12.1	53.3
4	2.43	83	0.95	14.5	67.4

*1 Mixtures of I (0.50 g.), the specified amounts of II, and HA (0.1 ml.) in ethanol (7 ml.) were refluxed for 3 hr.

*2 Moles per mole I.

yield of α, β-dianil IVa was little affected by II, it was low. In particular, it is interest that IVa and IVb were formed, even when an equimolar amount of II was used.

Experimental[8]

9-Ethylacridine (I) was prepared by the condensation of diphenylamine and propionic acid in the presence of anhydrous zinc chloride, m. p. 116°C.[9]

The Reaction of I with *p*-Nitrosodimethylaniline (II).—To a solution of 1.0 g. of I and 1.4 g. of II in 20 ml. of ethanol, 0.20 ml. of HA was added.[10] After having been refluxed for 3 hr., the mixture was allowed to stand overnight. Filtration gave 1.28 g. of reddishbrown crystals (IV), m. p. 260—262°C (decomp.).

Found: C, 77.51, 77.74; H, 6.04, 6.10; N, 14.11, 14.36%.

Several fractional recrystallizations of IV from pyridine afforded a small amount of 9-acridylglyoxal-α, β-*N*-(*p*-dimethylaminophenyl) dianil (IVa) as red prisms, m. p. 283°C (decomp.).

Found: C, 78.87; H, 6.19; N, 14.65. Calcd. for $C_{31}H_{29}N_5$: C, 78.95; H, 6.20; N, 14.85%.

The results of other reactions under varying conditions are shown in Tables I, II and III.

The Hydrolysis of IV. — *With Dilute Hydrochoric Acid.*—A mixture of 2.0 g. of IV in 7.5 ml. of 12% aqueous hydrochloric acid was heated on a water bath for several minutes. After the mixture had cooled, the precipitated crystals were filtered and washed with the saturated sodium chloride aqueous solution - dilute hydrochloric acid mixture. The insoluble crystals were dissolved in a large amount of hot water and then filtered. To the filtrate, a sodium acetate aqueous solution was then added to give yellow crystals. Filtration gave 0.95 g. of yellow crystals, m. p. 141—143°C. Recrystallization from the petroleum benzine - benzene mixture afforded yellow needles, m. p. 146—147°C. This compound was proved, by the admixed m. p. determination and its infrared spectrum, to be identical with an authentic sample of acridine-9-carboxaldehyde (V), m. p. 147°C.[4]

With Cold 10% Aqueous Sulfuric Acid.—Ten milliliters of 10% sulfuric acid was added to 0.5 g. of IV under ice-cooling. Immediately, the reaction mixture was filtered by suction to give yellow crystals, which, upon being washed with aqueous ammonia, afforded 0.12 g. of orange crystals, m. p. 204°C (decomp.). Recrystallization from benzene gave 9-acridylglyoxal-α-*N*-(*p*-dimethylaminophenyl) nitrone (VI) as orange needles, m. p. 208°C (decomp.).

Found: C, 74.85; H, 5.18; N, 11.13. Calcd. for $C_{23}H_{19}O_2N_3$: C, 74.78; H, 5.18; N, 11.37%. IR (KBr): $\nu_{C=O}$ 1662 cm^{-1}.

The Oxidation of VI with Silver Oxide.—A mixture of 0.26 g. of VI in 170 ml. of the Tollens reagent was heated on a water bath for 4 hr. During the heating, the reaction mixture resulted in the precipitation of silver and yellow brown crystals. After it had been cooled, the mixture was extracted with chloroform. The chloroform solution was then evaporated in vacuo to give 0.10 g. of reddish-brown crystals, m. p. 239°C (decomp.). Recrystallization from chlorobenzene afforded reddish-brown prisms, m. p. 243°C (decomp.). This compound was proved, by a study of its infrared spectrum, to be identical with the *N*-(*p*-dimethylaminophenyl)-α-(9-acridyl)-nitrone (VII)[3] obtained from the condensation of 9-methylacridine and II.

9-Acridylglyoxal-α-*N*-(*p*-dimethylaminophenyl)-nitrone-β-*N*-(*p*-dimethylaminophenyl) anil (IVb).—A mixture of 0.1 g. of VI, 0.2 g. of *p*-aminodimethylaniline and 1 drop of acetic acid in 5 ml. of ethanol was refluxed for 2 hr. After the mixture had cooled, filtration afforded 0.12 g. (93%) of IVb as red crysals, m. p. 265°C (decomp.). Recrystallization from benzene gave red prisms, m. p. 265°C (decomp.).

Found: C, 76.67; H, 6.24; N, 14.10. Calcd. for $C_{31}H_{29}ON_5$: C, 76.36; H, 6.00; N, 14.36%.

The Reaction of IVb with Triethyl Phosphite.—A mixture of 0.5 g. of IVb and 2.0 g. of triethyl phosphite[11] was gently refluxed under a nitrogen atmosphere on an oil bath (160—165°C) for 20 hr. After the mixture had stood overnight, the precipitated crystals were filtered and then washed with ethanol to give 0.38 g. (80%) of red crystals, m. p. 279°C (decomp.). Recrystallization from pyridine gave red prisms, m. p. 283°C (decomp.), these were proved, by a study of their infrared spectrum, to be identical with the IVa obtained by the fractional recrystallization of IV from pyridine.

The Spectroscopic Determination of IVa and IVb in IV.—The infrared absorption measurements were made with a Koken IR-S double beam spectrophotometer with a sodium chloride prism.

Chloroform solutions containing IVa and IVb, in which the weight percentages of IVb were 0, 22.2, 26.3, 41.6, 58.8, 63.1, 77.4, 84.6, 90.2 and 100% respectively, were prepared. The absorbances A_1 and A_2 for the bands at 1120 and 1592 cm^{-1} respectively were measured by the baseline method. The absorbances A_1 and A_2 in the order of the above concentrations of IVb were as follows. A_1: 0.064, 0.083, 0.085, 0.091, 0.135, 0.143, 0.166, 0.196, 0.207 and 0.238. A_2: 0.199, 0.192, 0.170, 0.161, 0.133, 0.127, 0.096, 0.080, 0.043 and 0.038.

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[8] All melting points are uncorrected.

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

[10] HA used as a catalyst in this experiment: d^{27} 1.1748.

[11] "Organic Syntheses," **31**, 111 (1951).

The calibration curves obtained by the ratio method are shown in Fig. 3.

The authors wish to express their gratitude to the Kaisei Aid Association for providing the funds for this investigation. They indebted to the staff of the Analytical Service Centre of this university for the microanalyses.

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