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213. Tsutomu Momose, Yosuke Ohkura, and Kazumasa Hirauchi :

Color Reaction Mechanism of Anthrone with Sugars. (2). Some Reaction Products of Furfural with Anthrone (Organic Analysis. XLVII*[1]).

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In a previous paper[1] of this series, the mechanism of the color reaction of anthrone with sugars was partly clarified by isolating one of the main dyes in a crystalline form, which was forwarded as 1,2,5- or 1,3,5-trianthronylidenepentane. In this reaction, other dyes might be formed which were due to the formation of furfural compounds by strong sulfuric acid, but those could not be separated successfully. On the other hand, Yamamoto[2] stated that a condensation product of one mole of anthrone with two moles of furfural was devided from the reaction mixture, and recently, Sawamura and Koyama[3] obtained furfurideneanthrone when the color reaction was carried out in a chilled condition. This paper presents another reaction mechanism of anthrone with furfural, isolating a precursor of the coloring matter in a crystalline form.

Isolation of the Dye

Anthrone was heated with the same weight of furfural in 70 v/v % sulfuric acid in a boiling water bath for several minutes. The intensely colored mixture was poured into ice water, the separated substance was collected, and extracted with hot benzene. A large amount of insoluble substance remained still gave a blue color with sulfuric acid, but this could not be treated successfully.

Chromatographic separation of the extract on alumina with benzene as eluant gave three main fractions which were devided by their adsorption colors on alumina. The first fraction, which showed a yellow band on alumina and a red coloration with sulfuric acid, seemed to be a mixture of several substances, and was difficult to separate.

The largest fraction, the second, which showed a blue band on alumina, left violet needles with golden metallic luster of m.p. 275° (decomp.) (Dye I) in relatively high yield when the solvent was condensed. Dye I was sparingly soluble in organic solvents and partially decomposed when it was refluxed with a polar solvent such as ethanol or acetic acid. The dye initially gave a blue violet color with sulfuric acid, which had the absorption maximum at 530 mμ, and then the color gradually turned to blue with increasing intensity, shifting the maximum to a longer wave length region. These absorption curves were shown in Fig. 1. The changed dye precipitated with water from the acid could not be purified by recrystallization or even by chromatography. On the other hand, the reaction mixture of anthrone with furfural in sulfuric acid had the maximum at 650 mμ as shown in Fig. 2. This fact indicated that Dye I was not a main coloring matter itself, but one of the precursors.

The third fraction showed a brown band on alumina, and left a small amount of red brown needles of m.p. 255° (decomp.) when the solvent was evaporated. This dye gave a dark blue color with sulfuric acid, but it was difficult to separate its enough quantity for further study.

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*[1] Part XLVI : Anal. Chem., **35**, 1751 (1963).

*[2] Katakasu, Fukuoka (百瀬 勉, 大倉洋甫, 平内三政).

[1] T. Momose, Y. Ueda, K. Sawada, A. Sugi : This Bulletin, **5**, 31 (1957).

[2] K. Yamamoto : Folia Pharmacol. Japan., **52**, 602 (1956); *Idem* : Osaka City Med. J., **4**, 213 (1958).

[3] R. Sawamura, T. Koyama : This Bulletin, **11**, 274 (1963).

The alumina column still held a large quantity of dark brown matter at the top, which showed a blue color by sulfuric acid, and could not be eluted with usual organic solvents, suggesting that other dyes might be present in the resin.

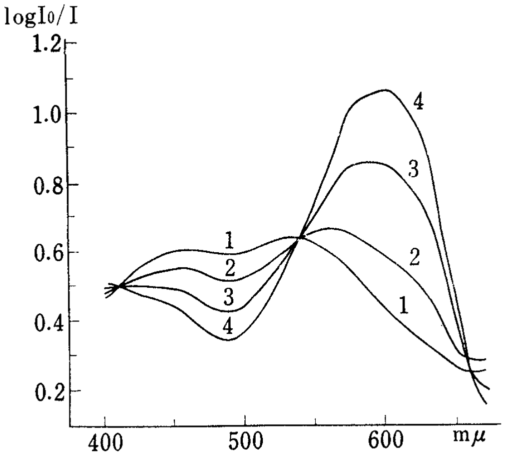


Fig. 1. Absorption Curves of Dye I

5.5 mg. of dye I was dissolved in 100 ml. of 70 v/v % H_2SO_4 and the curves were measured.

1: Immediately 2: After 30 min.
3: After 40 min. 4: After 90 min.

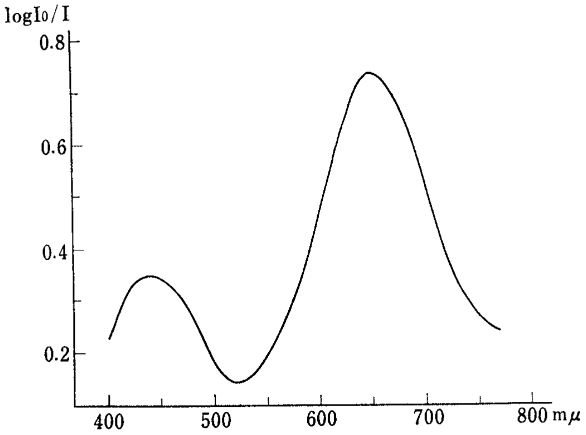


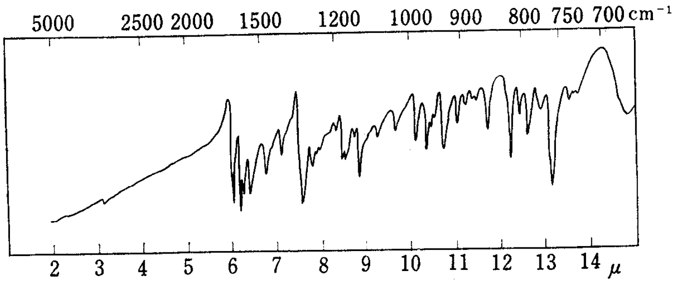
Fig. 2. Absorption Curve of the Reaction Mixture of Anthrone with Furfural

25 μg. of furfural was heated with 1.0 mg. of anthrone at 100° for 5 min. in 11 ml. of 70 v/v % H_2SO_4, and allowed to stand for 30 min. at about 5°.

Structure of the Dye and Reaction Mechanism

The molecular weight of Dye I determined by the Beckmann method was 566. The data of elementary analysis agreed with the formula $C_{38}H_{22}O_4$. The infrared spectrum of the dye was shown in Fig. 3-a, and had a carbonyl band at 1653 cm^{-1} which might be caused by anthronylidene residue. Seven bands at 3125, 1582, 1553, 1035, 930, 878,

a, Dye I



b, Dye II

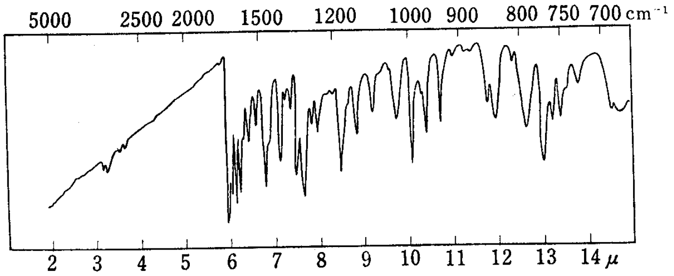


Fig. 3. Infrared Spectra of the Dyes (KBr Pellet)

and 762 cm^{-1} indicated that the dye might have 2-substituted furan ring,[4~8] and furthermore, the absorption band at 990 cm^{-1} suggested that the molecule might have 2,5-disubstituted furan ring.[4] Benzene solution of the dye had a violet color, and its visible light absorption spectrum was shown in Fig. 4.

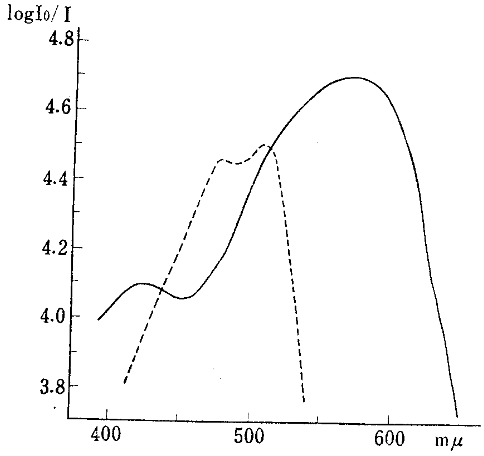
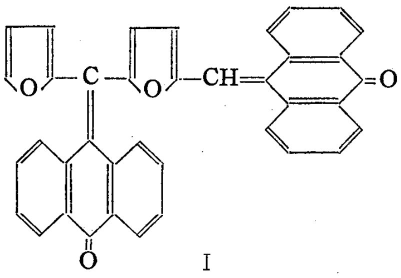


Fig. 4. Absorption Spectra of the Dyes in Benzene
—— Dye I
--- Dye II

The above data indicated that Dye I might be a condensation product of two moles of anthrone with two moles of furfural, and a probable structure of the dye might be written as I.



I

This assumed structure might be confirmed by the fact that the same dye was synthesized as in the following.

Anthrone was warmed with a large excess of furfural in phosphoric acid, poured into water, and the brown substance that separated was extracted with benzene. Chromatographic separation of the extract on alumina gave three fractions. The main fraction, the third, left red brown needles of m.p. 237° (decomp.) (Dye II) when the solvent was concentrated. From the data of analysis and molecular weight determination, the new dye agreed with the formula $C_{24}H_{14}O_4$, and gave its mono-2,4-dinitrophenylhydrazone as deep violet prisms of m.p. 285° (decomp.).

Dye II might be a ketone and gave neither color reaction of aldehyde with Tollens reagent nor with sodium pentacyanoammine ferroate in the presence of hydrogen sulfide.[9] The infrared spectrum of the dye showed two bands at 1678 and 1656 cm^{-1}, which might be caused by conjugated carbonyl groups. The spectrum also suggested the existence of 2- and 2,5-disubstituted furan rings in the molecule by the absorption

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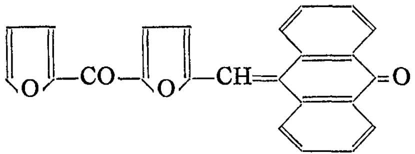
4) K. Takano : Nippon Kagaku Zasshi, **82**, 372 (1961).
5) M. Yamaguchi : Japan Analyst, **7**, 210 (1957).
6) L.H. Jones, *et al.* : Anal. Chem., **28**, 191 (1956).
7) A.H. Cross, *et al.* : J. appl. Chem., **7**, 562 (1957).
8) L.H. Rogers, D. Williams : J. Am. Chem. Soc., **80**, 2169 (1938).
9) F. Feigl, V. Anger, R. Zappert : Mikrochemie, **15**, 192 (1934).

bands at 3135, 1587, 1555, 1031, 934, 878, 768, and 992 cm^{-1} as shown in Fig. 3-b. On the other hand, it was known that furfural might condense with its formyl group to 5-position of another molecule in the resinification in acidic medium.[10] Therefore, Dye II might have the structure of II. The visible light absorption spectrum of Dye II is shown in Fig. 4.



II

The condensation of anthrone to Dye II in sulfuric acid gave violet needles of m.p. 275° (decomp.), which were identified as Dye I by the melting point of admixture and infrared spectrum.

It is important to note that Dye I was also obtained from the reaction mixture of anthrone with xylose in sulfuric acid. This fact clearly explained that furfural was formed in the color reaction.

Experimental

Isolation of Dye I——To a solution of 20 g. of anthrone in 600 ml. of 70 v/v % H_2SO_4, 20 g. of furfural was added with stirring and heated in a boiling water bath for 7 min. The mixture was cooled in a running H_2O and poured into ice H_2O. The separated substance was collected and washed with H_2O. After drying in a vacuum desiccator, it was refluxed with benzene, and filtered while hot. The filtrate was concentrated, poured onto a neutralized and moderately activated alumina column, and eluted with benzene. The second fraction gave crystals when the solvent was concentrated. Recrystallization from a large volume of benzene gave violet needles of golden metallic luster, m.p. 275°(decomp.) (Dye I). Yield, 400 mg. *Anal.* Calcd. for $C_{38}H_{22}O_4$: C, 84.11; H, 4.08; mol. wt., 543. Found : C, 84.05; H, 4.09; mol. wt., 566.

In the case of xylose, 10 g. of it was dissolved in 30 ml. of H_2O, and 10 g. of anthrone dissolved in 300 ml. of 80 v/v % H_2SO_4 was added under cooling. The mixture was heated in a boiling water bath for 10 min., treated as above, and chromatographed. The fraction which showed a blueband on alumina gave crude crystals when the solvent was concentrated. They were washed with a large volume of benzene and dissolved in the same solvent with refluxing, and then purified by chromatography to give violet needles of golden metallic luster, m.p. 275°(decomp.), which were identified as Dye I by the melting point of admixture and IR spectrum. Yield, 50 mg.

Isolation of Dye II——To a solution of 10 g. of anthrone in 40 ml. of furfural, 150 ml. of 85% H_3PO_4 was added with small portions with stirring. The mixture was kept at 50° for 30 min., and poured into H_2O. The separated substance was treated as above, and chromatographed. The third fraction gave crystals when the solvent was concentrated. Recrystallization from benzene gave red brown needles, m.p. 237°(decomp.) (Dye II). Yield, 50 mg. *Anal.* Calcd. for $C_{24}H_{14}O_4$: C, 78.68; H, 3.85; mol. wt., 366. Found : C, 78.42; H, 4.04; mol. wt., 362.

2,4-Dinitrophenylhydrazone of Dye II was prepared by usual method in the presence of H_3PO_4, and recrystallization from nitrobenzene gave deep violet prisms with golden metallic luster, m.p. 285° (decomp.). *Anal.* Calcd. for $C_{30}H_{18}O_7N_4$: C, 65.93; H, 3.32; N, 10.25. Found : C, 65.50; H, 3.52; N, 10.04.

Preparation of Dye I from Dye II——To a solution of 100 mg. of anthrone in 20 ml. of 70 v/v% H_2SO_4, 40 mg. of Dye II in 7 ml. of 70 v/v % H_2SO_4 was added and heated for 10 min. at 60~70°. The mixture was poured into ice H_2O, the separated violet substance was collected and washed with H_2O. After drying, the substance was disssolved in benzene with refluxing, poured onto alumina column, and eluted with benzene. The blue band on alumina gave crystals when the eluate was concentrated. Recrystallization from benzene gave violet needles with golden metallic luster, m.p. 275°(decomp.), which were identified as Dye I.

Absorption Spectra——The visible spectra were measured by a Beckmann DK-2 ratio recording spectrophotometer in a glass cell of 10 mm. optical length. The IR spectra were measured by a Koken DS-301 IR spectrophotometer in KBr pellet about 1 mm. thickness.

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[10] A.P. Dunlop, F.N. Peters, "The Furans" p. 398 (1953) Reinhold Publishing Corp.

The authors express their gratitude to Dr. Yo Ueda for his kind suggestion on the IR spectral analysis. They are indebted to Mr. M. Shido and Miss S. Indo for the microanalyses, and also to Messrs. H. Matsui and K. Hikita and Miss Y. Soeda for the spectral measurements.

Summary

A crystalline dye was separated from the reaction mixture of anthrone with furfural or xylose in sulfuric acid, and its probable structure was presented. The same dye was also yielded by condensing anthrone to another dye which was separated from the reaction mixture of the same reagents in phosphoric acid.

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214. **Akira Takamizawa, Kentaro Hirai, Yoshio Hamashima, and Hisao Sato**: Studies on the Pyrimidine Derivatives. XXIV.[*1] Syntheses of Several Thiol-type Thiamine Derivatives and their Primary Screening Tests.

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The synthesis of O-chlorocarbonylthiamine (II) by the action of phosgene on thiamine hydrochloride (I), and its conversion into O-alkoxycarbonylthiamine (III) or O-carbamoylthiamine (IV) were recently reported from this laboratory.1) S-Ethoxycarbonylthiamine (CET) (V), S-butoxycarbonylthiamine (CBT) (VI) and O,S-bis(ethoxycarbonyl)thiamine (DCET) (VII)2) exhibit a thiamine acitvity to approximately the same extent as thiamine hydrochloride (I), and when administered orally, they are highly absorbed and maintain their thiamine levels for a longer period than thiamine hydrochloride.3) Of these compounds, VII is most stable.4) Thiamine propyl disulfide (VIII) is also known for its good intestinal absorption. We were also interested in studying the reaction of VIII with phosgene and also the biological activity of its O-substituted derivatives.

VIII reacted in chloroform solution with phogene to give O-chlorocarbonylthiamine propyl disulfide (IX) as a syrupy product. IX, on treatment with ethanol, yielded O-ethoxycarbonylthiamine propyl disulfide (X) as a hydrochloride, m.p. 149~151°. As X could not be obtained by the action of ethyl chloroformate on VIII, it is evident that X was produced through IX in this reaction.

X was also obtained by the action of sodium propyl thiosulfate (Bunte's salt[*3]) on S-ethoxycarbonylthiamine (V) in alkaline solution. O-Dimethylcarbamoylthiamine propyl

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[*1] Part XXIII : Ann. Rep. Shionogi Research Lab., **12**, 48 (1962).

[*2] Sagisu, Fukushima-ku, Osaka (高見沢 映, 平井健太郎, 浜島好男, 佐藤久夫).

[*3] Organic thiosulfate (XXVII). cf. H. Bunte : Ber. **7**, 646 (1874).

1) A. Takamizawa, K. Hirai, Y. Hamashima : This Bulletin, **11**, 882 (1963).

2) A. Takamizawa, K. Hirai : *Ibid.*, **10**, 1102 (1962).

3) *a*) T. Minesita, M. Morita, T. Iwata : Ann. Rep. Shionogi Research Lab., **12**, 6 (1962). *b*) Vitamin B_1 New Deriv. Research sub Comm., Japan : Vitamins, **25**, 516 (1962).

4) R. Yamamoto, T. Kubota, K. Inazu : Ann. Rep. Shionogi Research Lab., **12**, 17 (1962).