

The Synthesis of Dicyanine A¹

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THE only available supply of the photosensitizing dye, dicyanine, before its preparation in this laboratory, was the German product, "Höchst dicyanine." A method of preparation described by O. Fischer⁴ is based on the action of potassium hydroxide on an α , γ -quinoline quaternary salt in alcohol. An improved method, developed by Mikeska, Haller, and Adams,³ is based on the action of sodium ethylate on the α , γ -quinoline quaternary salt in a medium of absolute alcohol. The yields of dye in both methods are so exceedingly low that unless a large quantity of intermediate is used and great care is taken in the preparation, no solid dye, or a product greatly contaminated with cyanine and tar, can be obtained.

In the preparation of dicyanine by the action of sodium ethylate on α , γ -quinoline intermediate (quaternary salt), at least two types of dyes are formed. One shows a maximum light absorption in the region of 6200 Å. (cyanine), and the other one in the region of 6700 Å. (dicyanine). The relative proportions of these dyes varied in different experiments in which the same intermediate was used. It was obvious that the presence in the original base of other quinolines, such as quinaldines, was not the only or even the principal cause for the formation of contaminating dyes. In order to determine their effect on the speed of reaction, relative tendency toward predominance of cyanine or dicyanine, tar formation, etc., it was therefore decided to test the influence of the following factors—kind of solvent used, concentration of OH-ion, type of alkali, catalysts, water, oxygen, time, and temperature.

No space will be taken for detailed description or for recording results of the numerous qualitative experiments made other than to call attention to the important features.

VARIATION OF SOLVENT

The first set of experiments involved the variation in the type of solvent. Of the solvents tried—methanol, ethyl alcohol, amyl alcohol, chloroform, pyridine, quinoline, acetone—only chloroform showed any marked effect on the reaction, either when used by itself or in alcoholic solution. Two distinct effects were obtained—the speed of reaction was greatly increased, and cyanine was formed almost to the exclusion of dicyanine. All the other solvents either were no better than, or were inferior to, alcohol, so that the next set of experiments was made with ethyl alcohol as the medium, to test the effect of different alkalis and salts giving an alkaline reaction on hydrolysis. Alcoholic solutions of the following were tried—sodium acetate, potassium acetate, sodium hydroxide, potassium hydroxide, potassium sulfide, and sodium sulfide. Striking results were observed with sodium sulfide. The

In a previous paper,² in which attention was called to the fact that there is no American commercial source of dicyanine dyes, an improved method was described for the preparation of 2,4-dimethyl-6-ethoxyquinoline, one of the principal bases for dicyanine A.

In this paper is described a study of the conditions affecting the synthesis of dicyanine A and an improved process of preparation which yields at least twelve times as much dicyanine A per unit weight of intermediate as that obtainable by the Mikeska-Haller-Adams method.³

The process depends on the action of sodium sulfide on α , γ -quinoline intermediates in alcoholic solution, in the presence of small amounts of chloroform.

Dicyanine A, prepared by the method given here, was tested by the Bureau of Standards and found to be an efficient sensitizer.

speed of reaction was markedly increased and the presence of three types of dyes was observed spectroscopically—the two previously described and a third showing a maximum in the region of 7200 Å. Of these, dicyanine (6700 Å.) predominated. As 95 per cent alcohol seemed to be somewhat superior to absolute alcohol for this work, and as heat hastened the reaction without apparently introducing injurious

factors, as a basis for further study 95 per cent alcohol was used as the medium and sodium sulfide as the alkaline salt, and heat was applied to the reaction.

The first few quantitative experiments (recorded as b, H₁ and H₂ in Table I) showed that the yield of dicyanine was from two to three times as large as that obtained with sodium ethylate,³ and their quality as observed spectroscopically was about the same. At this point the general plan of study that had been outlined was suddenly interrupted. Accidentally, recovered alcohol was used in some of the experiments instead of the pure 95 per cent alcohol. As recorded in Experiments K₁ and K₂, the yield of dicyanine was decidedly increased. Since the number of impurities known to be present in the recovered alcohol used was rather large, it was some time before it was experimentally proved that this increase was due to a small amount of chloroform. This was somewhat startling, in view of the early experiments which showed clearly that chloroform inhibited the formation of dicyanine to the extent that cyanine was the predominating product. That this was true only when sodium ethylate was used is clearly shown in Experiments G, E, F, C, D, and A, Table I. The yield of dye obtained by the use of sodium sulfide and chloroform was over twelve times that obtained by the Mikeska-Haller-Adams method.

TABLE I—COMPARISON OF DICYANINE YIELDS WHEN SODIUM ETHYLATE IS USED, AND WHEN SODIUM SULFIDE ALONE AND SODIUM SULFIDE WITH CHCl₃ IS USED

Inter-mediate ^a	Alcoholic Solution of Na ₂ S Cc.	Sodium Ethylate	Chloroform Cc.	Time Hrs.	Temperature °C.	Yield Dye G.	Quality
b	1	25	..	1	60-70	0.085	Good
H ₁	2	45	..	2	65-70	0.090	
H ₂	2	45	..	2	65-70	0.090	
K ₁	2	45(recovered alcohol)	..	2	65-70	0.375	
K ₂	2	45(recovered alcohol)	..	1/2	65-70	0.400	
G	1	25	..	1	65-70	0.165	
E	1	25	..	1	65-70	0.050	
F	1	25	..	1	65-70	0.175	
C	1	25	..	20	20-25 (room temp.)	0.360	
D	4	100	..	1/2	60-70	1.250	
A	1	..	Equiv. of 0.0345 g. Na in 25 cc. alcohol	1/2	60-70	None	Solution almost all cyanine

Average obtained by Mikeska-Haller-Adams method: 0.025 g./g. intermediate.

^a The term "intermediate" used in this and subsequent tables refers to 2,4-dimethyl-6-ethoxyquinoline ethiodide.

¹ Presented before the Division of Dye Chemistry at the 64th Meeting of the American Chemical Society, Pittsburgh, Pa., September 4 to 8, 1922.

² THIS JOURNAL, 14 (1922), 704.

³ J. Am. Chem. Soc., 42 (1920), 2392.

⁴ Fischer, Bauer, Scherbe, and Müller, J. prakt. Chem., 98 (1918), 204.

The investigation, therefore, resolved itself into a determination of the optimum conditions for the preparation of dicyanine by the action of alcoholic sodium sulfide and chloroform on the quinoline intermediate.

The general method used in all of the experiments was as follows:

An alcoholic solution of sodium sulfide of the desired concentration was prepared by boiling a weighed amount of $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ in 95 per cent alcohol for 2 min. After the hot solution was cooled to the reaction temperature it was filtered, a given volume was poured into an Erlenmeyer flask, and the 2,4-dimethyl-6-ethoxyquinoline ethiodide was dissolved in it. A given volume of chloroform was then added quickly, and the whole was warmed in a thermostatic bath for the time and at the temperature indicated with each experiment. The reaction mixture was then cooled and filtered by suction, and the precipitate was washed, first with 10 cc. of 95 per cent alcohol for each 1 g. of ethiodide used, then with 15 to 20 cc. of U. S. P. ether to remove the alcohol, and finally with enough water (usually from 20 to 50 cc.) to remove all salts, including sodium sulfide. The crystals of dicyanine were then washed with 5 cc. of 95 per cent alcohol to remove the water, and with from 15 to 20 cc. of U. S. P. ether to remove the alcohol, and the air-dried crystals were weighed. The absorption spectra were determined on a 1 in 200,000 alcoholic solution, using a Hilger spectrocope with the Nutting photometer.

The absorption maxima are stated in terms of specific coefficient of extinction, E , where $E = -\log \frac{(I_c)}{(I)}$.

In the concentration of sample used in the experiments (1 to 200,000), the values of the maxima, E , obtained are functions which vary directly with the concentrations of dicyanine and cyanine, respectively, and represent approximately accurate data on the relative content of dyes contained in the samples analyzed.

Photosensitizing tests were made in the Bureau of Standards in accordance with their usual methods.

The preparation of definite concentrations of alcoholic sodium sulfide offered some difficulty. Care was taken, however, to use the same alcoholic sulfide solution for any given set of experiments where variables were introduced other than sulfide concentration. Where sulfide itself varied, the other conditions were made empirically uniform for the experiments of that set. Titration of aliquots of the alcohol-sodium sulfide solution, after dilution with water, were made with 0.5 N HCl , using methyl orange as indicator. These served as checks for the preparation of subsequent experiments where similar concentrations of sodium sulfide in alcohol were desired.

EXPERIMENTS TO DETERMINE PROPORTION OF CHLOROFORM

The following experiments were made to determine the optimum proportion of chloroform to be used in the reaction:

TABLE II—VARIATION IN AMOUNT OF CHLOROFORM
Uniform Conditions: 1 g. intermediate, 25 cc. Solution A^a heated 1 hr. at 50° C.

No.	Chloroform Cc.	Yield Dye G.	ABSORPTION SPECTRUM MAXIMA AT		—AFTER PURIFICATION— ABSORPTION SPECTRUM MAXIMA AT	
			6720 Å. (Dicyanine)	6200 Å. (Cyanine)	Yield G.	6720 Å. (Dicyanine)
1	1	0.320	0.175
2	2	0.290	1.01	0.62	0.175	1.40
3	3	0.235	0.95	0.55	0.155	1.20
4	4	0.195	0.140
5	5	0.150	0.110
16 ^b	0.5	0.255	1.12	0.55
17	0.75	0.265	1.16	0.62
18	1.0	0.280	1.04	0.5
19	1.25	0.305	1.06	0.66
20	1.5	0.315	0.98	0.48
21	2.0	0.285	1.16	0.64

^a 20 g. $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ boiled in 200 cc. of 95 per cent alcohol for 2 min. Filtrate = Na_2S , Solution A.

^b New solution of sodium sulfide used in Nos. 16 to 21, inclusive.

^c Schook, *Met. Chem. Eng.*, 11 (1913), 494.

The products obtained from Experiments 1 to 5, inclusive, were subjected to further purification by boiling in chloroform and filtering, with the view to concentrating the dicyanine in the insoluble portion and removing most of the more soluble cyanine. As evidenced by spectroscopic examination (Experiments 2 and 3), much higher concentration of dicyanine with respect to cyanine was obtained, but, contrary to expectations, the sensitization test by the Bureau of Standards (Example 2, Table VIII) showed the purified product to be somewhat less effective, as compared with unpurified dicyanine. Crystals obtained from the chloroform-soluble portion (No. 3, soluble portion, Table VIII) gave no better results photographically. The relative concentration of dicyanine with respect to cyanine (determined spectroscopically) is apparently not an absolute criterion of its effectiveness as a sensitizer. This is borne out by further experiments such as Nos. 7 (Table II), 54, and 55 (Table VI). All these proved to be good sensitizers, though they contained relatively less dicyanine and more cyanine than No. 2, Table II.

VARIATION OF SODIUM SULFIDE

As the best proportion appeared to be about 1.5 cc. of CHCl_3 to 1 g. of ethiodide, the next set of experiments were carried out using that concentration of chloroform, and varying the concentration of the sodium sulfide. The results are shown in Table III.

TABLE III—VARIATION IN CONCENTRATION OF ALCOHOLIC SODIUM SULFIDE SOLUTION

No.	Uniform Conditions: 1 g. intermediate, 25 cc. alcoholic sodium sulfide, ^a 1.5 cc. CHCl_3 , heated 1 hr. at 50° C.		Yield Dye G.	Physical Appearance	ABSORPTION SPECTRUM MAXIMA AT	
	$\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ Used per 30 Cc. G.	30 Cc. G.			6720 Å. (Dicyanine)	6200 Å. (Cyanine)
25	1	0.070	1.24	0.44
26	2	0.150	1.25	0.62
27	3	0.185	1.15	0.62
28	4	0.240	1.24	0.60
29	5	0.315	1.25	0.72
30	6	0.325	1.25	0.72
31	7	0.350	1.22	0.47
32	9	0.390	Difficult to filter	1.25	0.68
33 ^b	10	0.260	Dark dull	1.28	0.62
34	12	0.255	Dark dull	0.90	0.60
35	15	0.348	Dark dull	1.00	0.58

^a Sodium sulfide solutions were prepared by boiling $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ in 30 cc. of 95 per cent alcohol for 2 min., cooling and filtering.

^b Second layer of aqueous sulfide separated in Nos. 33, 34, and 35.

The proportion of chloroform and sodium sulfide, as determined by the results in Tables II and III, was 1.5 cc. of CHCl_3 and that concentration of sodium sulfide obtained from boiling 25 g. of $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ in 100 cc. of 95 per cent alcohol (approximate average Nos. 31 and 32). These gave the best average results, considering both yield and quality of the dye, and were based on the use of 1 g. of the intermediate.

VARIATION OF INTERMEDIATE

In the next set of experiments the concentration of ethiodide intermediate in the alcohol was varied, while the ratio of chloroform to ethiodide was maintained approximately the same. The results are indicated in Table IV.

TABLE IV—VARIATION IN CONCENTRATION OF INTERMEDIATE WITH RESPECT TO SULFIDE-ALCOHOL SOLUTION

Uniform Conditions: Each experiment, 25 cc. of Solution C,^a proportion of CHCl_3 to intermediate = 1.5 cc., 1 g.; time = 1 hr.; temperature = 50° C.

No.	Inter- mediate G.	CHCl_3 Cc.	Yield Dye G.	Yield per G. Inter- mediate G.	Physical Appearance	ABSORPTION SPECTRUM MAXIMA AT	
						6720 Å. (Dicyanine)	6200 Å. (Cyanine)
36	0.5000	0.75	0.100	0.200	Bright green crystals	1.18	0.55
37	1.0000	1.5	0.320	0.320	Bright green crystals	1.08	0.52
38	2.0000	3.0	0.595	0.300	Bright green crystals	1.20	0.65
39	3.0000	4.5	0.970	0.325	Bright green crystals	1.05	1.00

^a Sodium sulfide solution, C = 25 g. $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ per 100 cc. of 95 per cent alcohol and filtering.

Taking into consideration both the yield and quality of the dicyanine product, it appeared that a variation from the original concentration of 1 g. of ethiodide to 25 cc. of alcohol afforded no advantage.

VARIATION OF TEMPERATURE

The next set of experiments was conducted under the most favorable conditions established in Tables II, III, and IV, with respect to concentration of reagents, while the temperature was varied from 40° to 80° C. The results are indicated in Table V.

TABLE V—VARIATION IN TEMPERATURE

Uniform Conditions: 1 g. of intermediate, 1.5 cc. of CHCl_3 , 25 cc. of Solution D,^a period 1 hr.

No.	Temperature ° C.	Yield Dye G.	Physical Appearance	ABSORPTION SPECTRUM MAXIMA AT	
				6720 Å. (Dicyanine)	6200 Å. (Cyanine)
40	40	0.330	Good	1.08	0.70
45	60	0.290	Good	1.06	0.50
46	B. p. (approx. 80° C.)	0.310	Very dull	0.84	0.55
48	40	0.310	Good bright	0.95	0.60
49	50	0.315	Good bright	1.25	0.65
50	60	0.280	Good bright	1.20	0.55
47 ^b	Room temp.	0.215	Bright	1.02	0.75

^a Alcoholic sodium sulfide solution, D = 25 g. of $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ per 100 cc. of 95 per cent alcohol.

^b Allowed to stand 20 hrs. as yield was too small in 1 hr.

No advantage was gained by using a temperature below or above 50° C. where short periods of time were involved.

VARIATION OF TIME

The following experiments were then carried out, using the optimum conditions derived from the foregoing experiments, while the time of reaction was varied.

TABLE VI—VARIATION IN TIME

Uniform Conditions: 1 g. of intermediate, 25 cc. of Solution E,^a 1.5 cc. of CHCl_3 , temp. = 50° C.

No.	Time Hrs.	Yield Dye G.	Appearance	ABSORPTION SPECTRUM MAXIMA AT	
				6720 Å. (Dicyanine)	6200 Å. (Cyanine)
51	1/2	0.305	Bright green	1.28	0.60
52	3/4	0.315	Dark green	1.10	0.60
53	1	0.325	Dark green	1.02	0.60
54	1 1/2	0.325	Bright green	1.00	0.42
55	2	0.300	Dark green ^b	1.05	0.40
116 ^c	3	0.370	Dark green
117 ^c	3	0.435	Dark green
118 ^d	2 1/2	1.600	Dark green	1.1	0.62
110 ^e	1/2	0.250	Dark green	1.25	0.52
111 ^e	2	0.360	Dark green	0.85	0.62

^a Sodium sulfide solution, E = 25 g. of $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ per 100 cc. of 95 per cent alcohol.

^b Washed with ether; ether-soluble matter considerable.

^c Solution F = new sodium sulfide solution used in Nos. 116 and 117.

^d Expt. 118, used 4 g. of intermediate, 100 cc. of sodium sulfide solution.

^e New solution of Na_2S .

As evident from Table VI, the slight increase in yield obtained by prolonging the heating to several hours was not worth while because of the inferiority of the product thus obtained. The highest concentration of dicyanine was given in Experiment 51, where the period of heating was 1/2 hr. Experiments 110 and 111 showed the same tendency.

It was already evident from a few sporadic experiments (No. 47, Table VII) that good results could be obtained by allowing the reaction mixture to stand for a day at room temperature. As shown by the experiments in Table VII, a greater yield of dye may be obtained thus, while a variation in the chloroform concentration (within reasonable range) appears to have little effect.

TABLE VII—EXPERIMENTS OVER LONG PERIOD OF TIME AT ROOM TEMPERATURE WITH VARIATION IN CHCl_3

Uniform Conditions: 1 g. of intermediate, 25 cc. of sodium sulfide,^a temp. = room temperature, period 22 hrs.

No.	Alcoholic Na_2S Soln. Cc.	CHCl_3 Cc.	Yield Dye G.	Appearance	ABSORPTION SPECTRUM MAXIMA AT	
					6720 Å. (Dicyanine)	6200 Å. (Cyanine)
104	25 H ₁ ^a	1	0.450	Bright green	1.12	0.78
105	25 H ₁	1 1/2	0.450	Bright green	1.02	0.75
106	25 H ₁	2	0.430	Duller green	1.00	0.55
107	25 H ₂ ^a	1	0.350	Bright green	0.70	0.64
108	25 H ₂	1 1/2	0.350	Dull green	1.10	0.85
109	25 H ₂	2	0.370	Bright green	1.11	0.85
7	25 Soln. A	2	0.355	0.90	0.54
3a	Special Soln. 25	2	0.300	1.15	0.68
5a	Special Soln. 25	...	0.085	1.20	0.60

^a Sodium sulfide solution, H = 50 g. of $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$ per 200 cc. of 95 per cent alcohol; designated, H₁ when hot solution was used; designated H₂ when cold solution was used.

Although the investigation was largely confined to dicyanine A IV, experiments were made with dicyanine IV and A VI, using the corresponding intermediates. The foregoing method was found applicable to these, although the yields were not as good as that obtained with A IV.

SENSITIZATION TESTS

As the reports obtained from the Bureau of Standards on the practical performance of the dyes are very comprehensive, only such data are recorded (Table VIII) as will bring out important features.

ACKNOWLEDGMENT

The author wishes to express thanks to Dr. W. F. Meggers and Mrs. F. J. Stimson, of the Bureau of Standards, for their valuable coöperation.

TABLE VIII—SENSITIZATION TESTS MADE BY THE BUREAU OF STANDARDS

No.	DESCRIPTION	Solubility	Quality as Sensitizers	Speed	Behavior up to—	
					7500 Å.	Beyond 7500 Å. to 9000 Å.
4	Sample prepared by old method		Equivalent to Höchst			
2	No. 2, Table II, after purification with CHCl_3	Not readily soluble	Fairly good sensitizer	Not as good as No. 3		
3	Obtained from CHCl_3 soluble portion of No. 3, Table II					
7	Table VII		Very satisfactory }	3 times as fast as No. 4	As good as Höchst	As good as Höchst
3a	Table VII					
5a	Table VII					
16	Table II			2 times as fast as No. 4		
				2 1/2 times as fast as No. 4		
51	Table VI		Same as No. 16			Not quite as good as Höchst
54	Table VI					
55	Table VI					
118	Table VI		Between Nos. 54 and 55 (up to 7500 Å.)		Less than No. 55	Quite as good as Höchst (No. 7 somewhat superior in monochromatic work)