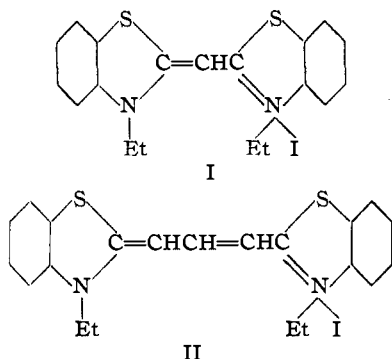


[COMMUNICATION NO. 542 FROM THE KODAK RESEARCH LABORATORIES]

Studies in the Cyanine Dye Series. I. A New Method of Preparing Certain Carbo-cyanines

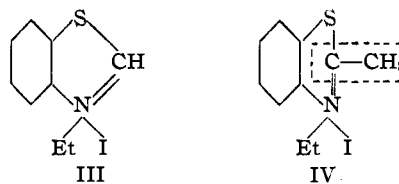
BY LESLIE G. S. BROOKER AND FRANK L. WHITE

Cyanine dyes derived from benzothiazole were first prepared by Hofmann,¹ but many years elapsed before the constitution of the compounds was elucidated. This was accomplished by Mills,² who showed that when a mixture of benzothiazole ethiodide and 1-methylbenzothiazole ethiodide was heated in pyridine solution for several hours at 100°, a mixture of dyes was produced. A yellow dye formed in a preponderating amount was proved to have structure I, whilst a purplish-red dye formed simultaneously had structure II. Mills applied the names "thiocyanine" and "carbothiocyanine" to compounds I and II, respectively, and compound II was later known as "thiocarbocyanine,"³ but it is now generally recognized that the forms "thiacyanine" and "thiacarbocyanine" are more in accordance with international nomenclature.

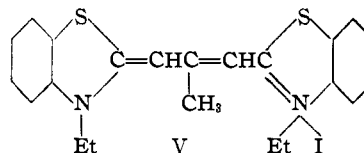


Mills² proved that, in the reaction which he studied, both the benzothiazole nuclei of the thiocarbocyanine (II) were derived from the quaternary salt containing the 1-methyl group. He therefore concluded that part of the benzothiazole quaternary salt (III) underwent decomposition and furnished a methenyl group which became the central methenyl group of the trimethenyl chain of the thiocarbocyanine dye (II).

We have now found that, contrary to the observation of Mills, a purplish-red dye is formed when 1-methylbenzothiazole ethiodide (IV) is heated alone in pyridine. This dye is visually



indistinguishable from II in solution but differs from it structurally in that it contains a methyl group attached to the central carbon atom of the three-carbon chain. In the formation of this dye, 2,2'-diethyl-8-methylthiacarbocyanine iodide (V), the =CMe— group at the center of the dye mole-



cule must be provided by decomposition of a portion of the quaternary salt as indicated by the dotted line in IV.

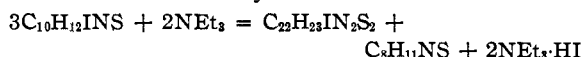
The best general method for the preparation of carbocyanine dyes involves the use of ethyl orthoformate in conjunction with anhydrous pyridine as solvent,³ and Hamer⁴ first prepared V by a modification of this synthesis in which ethyl orthoacetate replaced ethyl orthoformate. The identity of the products obtained by this method and by our new method has been established by a comparison of their melting points and mixed melting point which were all identical, and by an examination of their optical and photographic properties which were also identical, whereas these characteristics of the dye produced by the new method differed from those of 2,2'-diethylthiacarbocyanine iodide.

The yield of V obtained by heating 1-methylbenzothiazole ethiodide in pyridine for several hours is only 4%, but if the etho-*p*-toluenesulfonate of the base is used, the yield is increased to 14%. If, however, triethylamine or piperidine is used in addition to the pyridine, the yield is much higher, a 56% yield being obtained when the ethiodide of the base (3 mols) is boiled in pyridine with triethylamine (3 mols). The period of reaction is at the same time materially decreased.

(1) Hofmann, *Ber.*, **20**, 2262 (1887).(2) Mills, *J. Chem. Soc.*, **121**, 455 (1922).(3) Hamer, *ibid.*, 2796 (1927).(4) Hamer, *J. Chem. Soc.*, 3160 (1928).

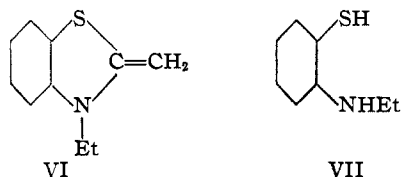
In the present synthesis which dispenses with the use of ethyl orthoacetate, only one dye product, the 8-methylthiacarbocyanine (V), is obtained. Careful examination has failed to reveal the presence of a thiacyanocyanine unsubstituted in the 8-position, whilst the presence of a quaternary salt of benzothiazole itself is necessary for the production of a thiacyanocyanine (I). In the case of the experiment which furnished the 56% yield, 91% of the crude dye was accounted for, in several crops, as pure 8-methyl dye, and each crop agreed fully in its properties with the authentic 8-methyl dye.

Where triethylamine is used, the reaction may be written tentatively



According to this, two molecules of base are necessary for every three molecules of quaternary salt undergoing the reaction and the percentage yields of dye have been calculated on this basis. In some experiments, however, the yields are improved by taking an excess of base over that indicated by the equation.

It is probable from the work of Mills and Raper⁵ and of Clark⁶ that the methylene base 2-ethyl-1-methylenebenzothiazoline (VI) is formed by the action of pyridine, or of other base, employed on 1-methylbenzothiazole ethiodide.



Ethylaminothiophenol (VII) is a probable by-product of our reaction, but no attempt has been made to identify it in the reaction mixture.

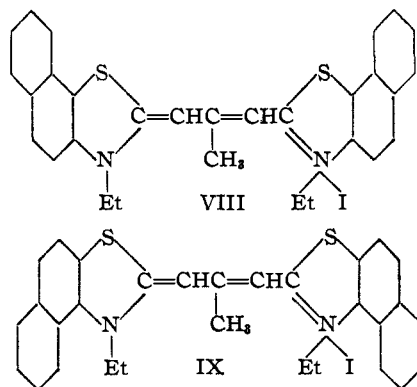
König and Meier⁷ noted the formation of a purplish-red coloration when a methylene base of similar structure to VI, 1-methyl-2-methylenebenzothiazoline, was exposed to light and air. The change was accelerated by heat and when the product was treated with alcoholic hydrobromic acid a small quantity of a dye was obtained, the absorption of which was said to agree with that of 2,2'-dimethylthiacarbocyanine iodide within the limits of experimental error, but the possibility of the dye being an 8-methyl derivative was also mentioned.

(5) Mills and Raper, *J. Chem. Soc.*, **127**, 2466 (1925).

(6) Clark, *ibid.*, 2313 (1928).

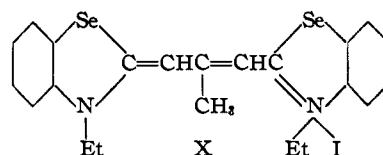
(7) König and Meier, *J. prakt. Chem.*, **109**, 324 (1925).

By employing quaternary salts of the methyl-naphthothiazoles which have been applied to cyanine dye formation by one of us,⁸ the two isomeric 8-methyl-dibenzothiacarbocyanines VIII and IX were produced by the new method.



The first of these, 2,2'-diethyl-8-methyl-5,6,5',6'-dibenzothiacarbocyanine iodide (VIII), was prepared using 1-methyl- α -naphthothiazole ethiodide and ethyl orthoacetate by Hamer,⁸ who found that 2,2'-diethyl-8-methyl-3,4,3',4'-dibenzothiacarbocyanine iodide (IX) could not be prepared by the same method from 2-methyl- β -naphthothiazole ethiodide. However, the dye (IX) is obtained if the etho-*p*-toluenesulfonate of the base is employed⁹ with subsequent conversion of the *p*-toluenesulfonate of the dye to the corresponding iodide. In the present work, however, the bromide corresponding to IX rather than the iodide has been prepared by both methods on account of the low solubility of the iodide.

The method of preparation from the quaternary salt without the intervention of ethyl orthoacetate was also successful with 1-methylbenzoselenazole ethiodide, the dye 2,2'-diethyl-8-methyl-selenacarbocyanine iodide (X) being obtained.



This dye likewise could be obtained by the interaction of 1-methylbenzoselenazole etho-*p*-toluenesulfonate and ethyl orthoacetate with subsequent conversion to the iodide.¹⁰

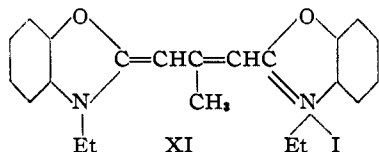
An attempt to prepare 2,2'-diethyl-8-methyl-oxacarbocyanine iodide by Hamer's modification

(8) Brooker, U. S. Patents 1,846,300, 1,846,301, 1,861,836; see also Hamer, *J. Chem. Soc.*, 2598 (1929).

(9) Brooker, U. S. Patent 1,846,301.

(10) Cf. Kodak Ltd., British Patent 390,406.

of her general method was unsuccessful,⁴ but this dye (XI) has been prepared by the interaction of 1-methylbenzoxazole ethiodide, ethyl orthoacetate



and triethylamine in pyridine solution.¹¹ This dye was also prepared from the quaternary salt in the absence of ethyl orthoacetate, the best results being obtained when triethylamine was used as condensing agent in conjunction with *n*-propyl alcohol as solvent.

In every case the 8-methyl dye made by the new method was compared with the dye made by the use of ethyl orthoacetate and their identity established using the means adopted in the case of 2,2'-diethyl-8-methylthiacarbocyanine iodide. Comparisons were also made with the corresponding dyes unsubstituted in the 8-position, but these were always distinctly different in their properties.

The absorption curves were determined for methyl alcoholic solutions of the dyes using a Hüfner spectrophotometer and a Schultz cell. They were also determined using a König-Martens instrument. We wish to express our thanks to Mr. E. Richardson and Dr. L. A. Jones for carrying out this work. It is an interesting generalization that in every case examined except one the maximum absorption of an 8-methyl dye lies nearer to the blue end of the spectrum than that of the corresponding carbocyanine unsubstituted in the trimethenyl chain. This difference reaches a maximum value of 200 Å. in the case of the dibenzothiacarbocyanines. The exception is provided by the oxacarbocyanines in which case the 8-methyl dye (XI) has its maximum absorption 60 Å. nearer the red end of the spectrum than has the corresponding unsubstituted dye.

The dyes were compared photographically by incorporating solutions containing optimum quantities with the emulsion just before coating. The emulsion used was of medium speed and was chosen to give high contrast. The plates were given a moderate exposure in a wedge spectrograph and were processed simultaneously, uniform conditions being maintained as far as possible. Details of the sensitizing effects given below were obtained directly from the resulting

spectrograms. Our thanks are due to several colleagues in the laboratory for this work and also to Dr. L. T. Hallett, who carried out the analyses.

Experimental

The pyridine used in the following experiments was dried over fused barium oxide and freshly distilled before use. The triethylamine was a practical grade of material, dried first by standing over solid potassium hydroxide, and then by refluxing with fused barium oxide for three hours. It was then fractionated and the cut, b. p. 86–90°, used. All the melting points recorded below were taken by immersing the melting point tube in the bath at about 25° below the point at which change was first seen to occur in a preliminary determination. Correction was made for the emergent column.

2,2'-Diethyl-8-methylthiacarbocyanine Iodide.—1-Methylbenzothiazole ethiodide (9.15 g., 3 mols) was refluxed in pyridine (30 cc.) with triethylamine (3.03 g., 3 mols) for one-half hour. Dye began to crystallize out during the reaction. After cooling, ether (200 cc.) was added to complete the separation, and the residue was washed with hot water and treated with acetone to remove tarry impurities. The yield (2.82 g.) was 56% of the theoretical, being 51% after two recrystallizations from methyl alcohol (three crops).

The dye in each crop consisted of coppery crystals identical in appearance with authentic 2,2'-diethyl-8-methylthiacarbocyanine iodide obtained by the method of Hamer.⁴ The melting point of the first crop of crystals was determined side by side with that of the authentic dye. Both specimens melted simultaneously at 286–287° dec. and mixing the two did not depress the melting point (Hamer⁴ gives m. p. about 290° with decomposition from about 280°). On the other hand, 2,2'-diethylthiacarbocyanine iodide melts at 270–271° dec. (Mills² gives m. p. 269° dec.; Hamer⁴ gives 264–265° dec.) and admixture of this with the first crop of dye made by the new method produced a marked depression. The second and third crops were only slightly less pure than the first crop, since they melted not more than 3° below the latter. A similar series of mixed melting point determinations on these crops indicated that they too consisted of the 8-methyl dye.

Iodine determinations on the three crops gave figures in good agreement with the required value for the 8-methyl dye.

Anal. Calcd. for C₂₂H₂₈IN₂S₂: I, 25.07. Found: first crop, I, 25.06; second crop, I, 25.02; third crop, I, 25.07 (calcd. for C₂₁H₂₁IN₂S₂: I, 25.78).

The absorption curves of the three crops had maxima at 5430 Å., in good agreement with that of the absorption curve of the authentic 8-methyl dye (Hamer⁴ gives 5400 Å. in ethyl alcohol). The absorption curve of a solution of 2,2'-diethylthiacarbocyanine iodide has its maximum at 5575 Å. (Mills² gives 5590 Å. and Hamer⁴ gives 5600 Å. for ethyl alcohol solutions.)

The sensitizing spectra of the three crops of dye made by the new method were likewise identical with the spectrum of the authentic 8-methyl dye, and differed appreci-

(11) Brooker, U. S. Patent 1,962,124.

ably from that of 2,2'-diethylthiacarbocyanine iodide. The 8-methyl dye is a stronger photographic sensitizer than the unsubstituted dye and in particular the gap between the regions of ordinary and extra sensitivity is much less with the former.

When 1-methylbenzothiazole ethiodide (9.15 g., 3 mols) was refluxed with pyridine (70 cc.) for six hours, and the dye isolated using the method given above, the yield was low (weight 0.19 g., 4%).

1-Methylbenzothiazole etho-*p*-toluenesulfonate was prepared by heating 1-methylbenzothiazole (8.95 g., 1 mol) and ethyl *p*-toluenesulfonate (12 g., 1 mol) at 100° for six days. The product was dissolved in hot methyl alcohol (7 cc.) and precipitated in crystalline form by adding acetone (16 cc.) with stirring and cooling; wt. 13 g.; colorless crystals, m. p. 163.5–164.5°.

Anal. Calcd. for $C_{17}H_{19}NO_2S_2$: N, 4.01. Found: N, 4.13.

A second crop was obtained by concentrating the mother liquors followed by addition of acetone; total wt. 18.5 g. (88%).

When this salt (10.5 g., 3 mols) was refluxed with pyridine (15 cc.) for three hours and the dye precipitated with ether, dissolved in methyl alcohol (25 cc.) and converted into the iodide using a hot solution of potassium iodide (5 g.) in water (50 cc.), the yield of crude dye after treating with acetone was 0.71 g. (14%). In this and in the preceding preparation of the dye the identity of the products with authentic 8-methyl dye was established as in the first case.

2,2'-8-Trimethylthiacarbocyanine Iodide.—1-Methylbenzothiazole methiodide (8.73 g., 3 mols) was refluxed in pyridine (35 cc.) with triethylamine (3.03 g., 3 mols) for three hours. Dye separated during the reaction and was isolated as was the 2,2'-diethyl-8-methyl compound. The yield (1.81 g.) was 38%, being 32% after two recrystallizations from methyl alcohol (three crops). Melting point determinations carried out as already described indicated that the product was identical with the authentic dye, m. p. 299° dec. (Hamer⁴ gives m. p. about 298° dec.) whereas 2,2'-dimethylthiacarbocyanine iodide has m. p. 287° dec. (König and Meier⁷ give m. p. 254°, Hamer⁴ gives m. p. 280° dec.). The first crop of the twice recrystallized dye was analyzed.

Anal. Calcd. for $C_{20}H_{19}IN_2S_2$: I, 26.55. Found: I, 26.32 (calcd. for $C_{19}H_{17}IN_2S_2$: I, 27.34).

The absorption of the dye made by the new method agreed with that of an authentic specimen. Each had a maximum at 5380 Å. (Hamer⁴ gives 5400 Å. in ethyl alcohol). The absorption maximum for 2,2'-dimethylthiacarbocyanine iodide is at 5550 Å. (König and Meier⁷ give 5580 Å. in ethyl alcohol).

The dye made by the new method agreed fully in its sensitizing action with an authentic specimen. Both specimens gave broad bands with maxima at about 5300 and 5950 Å. The dye is considerably more powerful than 2,2'-dimethylthiacarbocyanine iodide.

2,2'-Diethyl-8-methyl-5,6,5',6'-dibenzothiacarbocyanine Iodide.—1-Methyl- α -naphthothiazole etho-*p*-toluenesulfonate was prepared by heating equimolecular proportions of 1-methyl- α -naphthothiazole and ethyl-*p*-toluenesulfonate at 120–130° for forty-five hours. The

product was ground with acetone, dissolved in hot methyl alcohol and precipitated by adding an equal volume of acetone with chilling (yield 77%; with a second crop the total yield was 96%); minute colorless crystals of m. p. 200–206° with softening from 190°.

Anal. Calcd. for $C_{21}H_{21}NO_2S_2$: C, 63.11; H, 5.30. Found: C, 62.60; H, 5.16.

The above salt (12 g., 3 mols) was refluxed in pyridine (20 cc.) with triethylamine (2.02 g., 2 mols) for fifteen minutes. The dye was precipitated by the addition of ether (150 cc.) and the residue dissolved in hot methyl alcohol (30 cc.) and precipitated as the iodide by adding a hot solution of potassium iodide (5 g.) in water (50 cc.). The dye was washed with hot water (75 cc.) and treated with acetone (75 cc.) to remove tarry impurities. The yield (0.46 g.) was 7.5%, being 6.6% after two recrystallizations from methyl alcohol (two crops); m. p. 297° dec. (Hamer⁸ gives about 298° dec.). A specimen of 2,2'-diethyl-5,6,5',6'-dibenzothiacarbocyanine iodide had m. p. 295° dec. (Hamer⁸ gives 294° dec.).

Anal. Calcd. for $C_{30}H_{27}IN_2S_2$: I, 20.93. Found: I, 20.67. Calcd. for $C_{29}H_{25}IN_2S_2$: I, 21.43.

The absorption of the dye made by the new method agrees with that of the authentic dye. The maximum is at 5725 Å. (Hamer⁸ gives 5750 Å. in ethyl alcohol). The maximum absorption of 2,2'-diethyl-5,6,5',6'-dibenzothiacarbocyanine iodide, however, is at 5925 Å. (Hamer⁸ gives 6000 Å. in ethyl alcohol). The sensitizing action of the 8-methyl dye made by the new method agreed exactly with that of an authentic specimen, and was markedly different from that of the corresponding dye unsubstituted in the three-carbon chain. The sensitizing band of the latter stretches considerably further toward the red end of the spectrum, the maximum effect being at about 6400 Å., whilst the maximum of the 8-methyl dye is at about 6175 Å. In both cases there is an ill-defined secondary maximum nearer the blue.

2,2'-Diethyl-8-methyl-3,4,3',4'-dibenzothiacarbocyanine Bromide.—2-Methyl- β -naphthothiazole etho-*p*-toluenesulfonate was prepared by heating equimolecular proportions of 2-methyl- β -naphthothiazole and ethyl *p*-toluenesulfonate at 115–120° for three weeks, crystallization being induced in the mass by rubbing the walls of the flask after about the seventh day. The crude salt formed a somewhat yellowish solid mass and it was purified by grinding with ether and washing with acetone. The salt forms a cream-colored crystalline powder, very soluble in water and the lower alcohols, sparingly soluble in acetone, and insoluble in ether. It was used without further purification; m. p. 151–154° with softening from 140°.

Anal. Calcd. for $C_{21}H_{21}NO_2S_2$: C, 63.11; H, 5.30. Found: C, 62.35; H, 5.28.

The salt (8.0 g., 2 mols) was boiled under reflux for one hour with ethyl orthoacetate (4.85 g., 3 mols) and pyridine (25 cc.). The dye was precipitated by the addition of ether (150 cc.) and the tarry residue dissolved in hot methyl alcohol (100 cc.) and precipitated as the bromide by adding a hot solution of potassium bromide (5 g.) in water (100 cc.). The dye was washed with warm water (100 cc.) and treated with acetone (50 cc.) to remove im-

purities. The yield was 36%, being 27% after recrystallization from methyl alcohol (140 cc. per g.). It was obtained as minute dark greenish crystals, m. p. 240° dec.

Anal. Calcd. for $C_{30}H_{27}BrN_2S_2$: Br, 14.29. Found: Br, 14.32.

The dye has a maximum absorption at 5750 Å. with a secondary band having its head at about 5350 Å. It is a very powerful sensitizer with a sharp maximum at about 6600 Å. and with a broad secondary maximum at about 5500 Å.

The dye was also prepared as follows. 2-Methyl- β -naphthothiazole etho-*p*-toluenesulfonate (12 g., 3 mols) was refluxed in pyridine (15 cc.) with triethylamine (2.02 g., 2 mols) for ten minutes. The dye was isolated as the bromide using a similar procedure to the above. The yield (0.34 g.) was 6%, being 3% after two recrystallizations from methyl alcohol.

Anal. Found: Br, 14.34.

The melting point, absorption and sensitizing effect of the dye made by this method agreed fully with the results obtained for the authentic specimen, whereas the absorption curve of 2,2'-diethyl-3,4,3',4'-dibenzothiacarbocyanine bromide has a maximum at 5950 Å. (Hamer⁸ gives 6000 Å. for the iodide in ethyl alcohol) and the 8-methyl dye is a more powerful sensitizer than the unsubstituted dye, which has principal and secondary sensitizing maxima at 6400 and 5600 Å., respectively. The 2,2'-diethyl-3,4,3',4'-dibenzothiacarbocyanine bromide was prepared by refluxing 2-methyl- β -naphthothiazole etho-*p*-toluenesulfonate (4 g., 2 mols) with ethyl orthoformate (2.23 g., 3 mols) and pyridine (10 cc.) for one hour, the dye being then converted into the bromide; yield 84%, being 66% after recrystallization from methyl alcohol (250 cc. per g.). The dye forms minute greenish-bronze crystals, m. p. 268° dec.

Anal. Calcd. for $C_{29}H_{25}BrN_2S_2$: Br, 14.66. Found: Br, 14.67.

2,2'-Diethyl-8-methylselenacarbocyanine Iodide.—1-Methylbenzoselenazole (3.9 g., 2 mols) and ethyl *p*-toluenesulfonate (4 g., 2 mols) were heated at 100° for fifty hours. The crude quaternary salt was used without purification, being refluxed with ethyl orthoacetate (3.2 g., 2 mols) in pyridine (20 cc.) for twenty minutes. The dye was precipitated with ether and after conversion to the iodide was obtained in a yield of 36%. Recrystallized from methyl alcohol (550 cc. per g.) the yield was 23%. The dye forms coppery crystals, m. p. 296° dec.

Anal. Calcd. for $C_{22}H_{23}IN_2Se_2$: I, 21.13. Found: I, 21.04.

The dye has an absorption maximum at 5525 Å., there being evidence of a weak second band nearer the blue at about 5200 Å. The dye is a powerful sensitizer with two well-defined maxima at 6100 and 5350 Å., respectively, of which the former is the stronger.

When 1-methylbenzoselenazole ethiodide (5.3 g., 3 mols) was refluxed for one-half hour with triethylamine (1.5 g., 3 mols) in pyridine (15 cc.) the dye, isolated as above, was obtained in a yield of 32%, being 23% after two recrystallizations (two crops).

Anal. Found: I, 21.20.

The appearance of this dye was identical with that of the

specimen prepared using the ortho ester and their identity was confirmed by the means already detailed.

The maximum absorption of 2,2'-diethylselenacarbocyanine iodide ($C_{21}H_{21}IN_2Se_2$ requires I, 21.64) was at 5675 Å. (Clark¹² gives 5700 Å. in ethyl alcohol.) This dye is not such a powerful sensitizer as the 8-methyl dye.

2,2' - Diethyl - 8 - methyloxacarbocyanine Iodide.—1-Methylbenzoxazole ethiodide (8.7 g., 2 mols) was heated under reflux with ethyl orthoacetate (9.7 g., 4 mols), triethylamine (1.5 g., 1 mol) and pyridine (30 cc.) for fifteen minutes. The dye was precipitated with ether, and after washing with water followed by acetone was obtained in a yield of 12%, being 10% after recrystallization from methyl alcohol (60 cc. per g.). The dye forms red prisms with a blue reflex, m. p. 274° dec.

Anal. Calcd. for $C_{22}H_{23}IN_2O_2$: I, 26.77. Found: I, 26.57.

The dye has its maximum absorption at 4885 Å. and there is a secondary maximum at about 4650 Å. The dye sensitizes with its maximum effect at 5100 Å. It was also obtained by boiling 1-methylbenzoxazole ethiodide (4.34 g., 3 mols) with triethylamine (1.52 g., 3 mols) in *n*-propyl alcohol (10 cc.) for one and one-half hours. After precipitation with ether and washing with water followed by treatment with acetone, the dye was obtained in a yield of 6%, being 5% after recrystallization (two crops). The dye was identical in its properties with the authentic specimen described above.

Anal. Found: I, 26.68.

2,2'-Diethyloxacarbocyanine iodide, on the other hand, has its maximum absorption at 4825 Å. and melts at 285° dec. (Hamer⁸ gives 4850 Å. in ethyl alcohol and m. p. 277-279° dec.). This dye ($C_{21}H_{21}IN_2O_2$) requires: I, 27.58.

Summary

1. A new method for the preparation of certain carbocyanine dyes containing the chain $=CHC-Me=CH-$ consists in heating, in a basic medium, a quaternary salt of a heterocyclic ammonium base containing a reactive methyl group. Part of the salt undergoes decomposition yielding the $=CMe-$ group which forms the central part of the resulting dye molecule.

2. The reaction has been applied to salts of 1-methylbenzothiazole, 1-methylbenzoselenazole and 1-methylbenzoxazole, as well as to salts of the methylnaphthothiazoles.

3. Optical and photographic properties of certain new dyes are given. In every case studied, except that of the oxacarbocyanines, the absorption maximum in methyl alcohol of a carbocyanine dye containing an 8-methyl group lies nearer to the blue end of the spectrum than does that of the corresponding unsubstituted dye.

ROCHESTER, N. Y.

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(12) Clark, *J. Chem. Soc.*, 216 (1933).