[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

RESEARCHES ON THIAZINES. III. THE SYNTHESIS OF CYANINE DYES OF THE *PERI*-NAPHTHOMETATHIAZINE SERIES*†

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Cyanine dyes containing the thiazole nucleus are well known and many of them are useful photographic sensitizers. Analogous dyes carrying the thiazine nucleus, however, have not been described. It was, therefore, the object of this research to synthesize such dyes from the 2-methyl-*peri*-naphthometathiazine (I) of Bogert and Bartlett,[1] in order to contribute to the elucidation of the problem of the relation between chemical constitution and photosensitizing properties. One reason for the choice of this particular thiazine was that the isomeric cyanines from methyl-*alpha*- and *beta*-naphthothiazoles (II and III) were already known and could thus be used for comparison.

The thiazine (I) was treated with both methyl and ethyl iodides. With the former, the reaction proceeded normally, with formation of the methiodide (IV); but with ethyl iodide it followed an abnormal course, which yielded the hydriodide as the main product, with but small amounts of the desired ethiodide.

From the methiodide (IV), a thiazinocarbocyanine (VII) was obtained by the action of ethyl orthoformate in pyridine solution. The ethiodide, which could not be isolated, yielded the corresponding thiazinocarbocyanine only when treated with ethyl orthoformate and potassium acetate in acetic anhydride solution. Condensed with *p*-dimethylaminobenzaldehyde, in absolute ethanol solution, the methiodide and hydriodide (IV) gave the *p*-dimethylaminostyryl derivatives (VI).

Digestion of the methiodide (IV), in alcoholic solution, with silver chlo-

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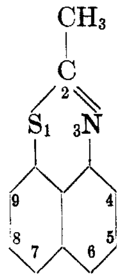
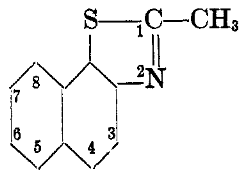
* Based upon the dissertation submitted by Mr. Joy, May, 1934, for the Ph.D. degree, under the Faculty of Pure Science, Columbia University, New York, N. Y., to which the reader is referred for further experimental details and literature citations.—M. T. B.

† Presented in abstract before the Division of Dye Chemistry, at the Washington Meeting of the American Chemical Society, March 27, 1933.

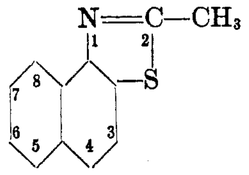
[1] BOGERT AND BARTLETT, *J. Am. Chem. Soc.*, **53**, 4046 (1931).



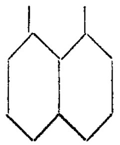
I

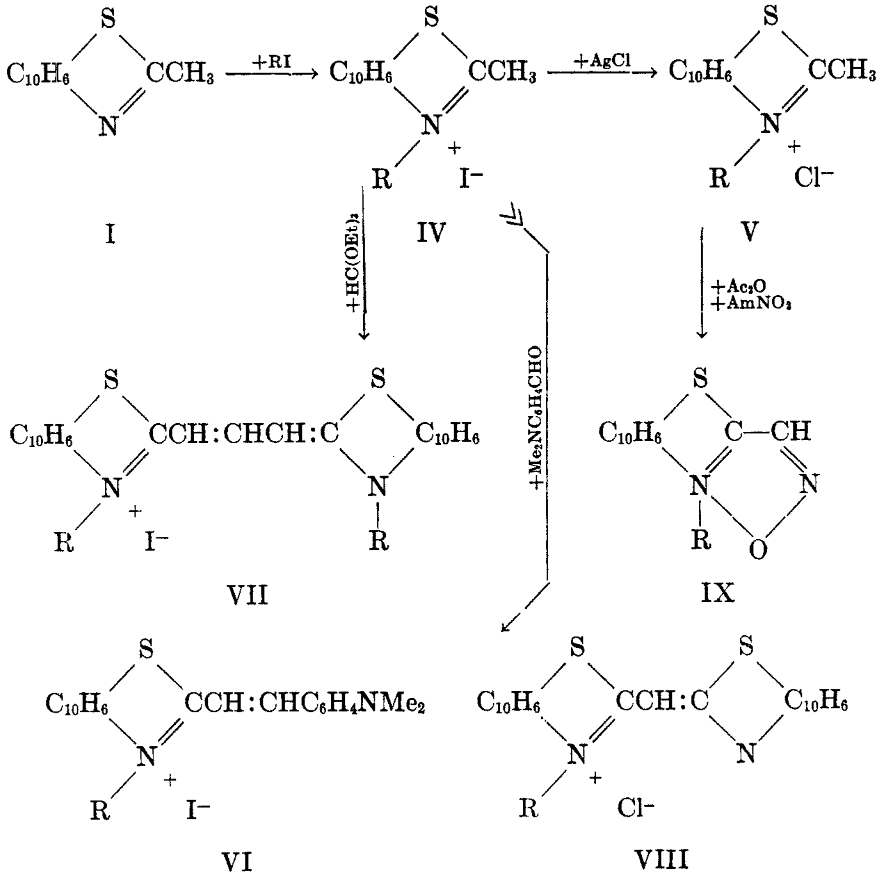


II (*alpha-*)



III (*beta-*)

In the following structural formulae, $C_{10}H_6$ =  and R = H, Me or Et.



ride, changed it to the corresponding methochloride which, when heated in acetic anhydride solution with amyl nitrite, following the method used by Fisher and Hamer[2] for the preparation of thiocyanines, did not yield the expected dye (VIII), but bright yellow needles with a metallic lustre, which melted with decomposition at 236°, and on analysis gave figures corresponding to the empirical formula, $C_{13}H_{10}N_2OS$. Of the several constitutions which might be suggested for this product, we think that the furazan structure (IX) is the most probable. The hydriodide (IV) formed a similar compound.

The process of Beattie, Heilbron, and Irving[3] applied to the thiazine methiodide (IV), yielded what appeared to be the expected thiazinodicarbocyanine, but which we were unable to obtain analytically pure.

The various dyes secured were tested for both absorption spectra and photosensitizing properties, since the sensitization maximum lies in the vicinity of the absorption maximum and usually somewhat farther towards the red, this displacement often amounting to about 200 Å. The details are given in the experimental part. The results did not indicate any outstanding photosensitizing action for the *peri*-naphthometathiazine nucleus. Further, these thiazinocarbocyanines showed only a single absorption maximum, whereas the analogous carbocyanines of the thiazole series show two.

It is hoped to determine also whether these dyes possess any selective bacteriostatic or bactericidal properties.

The nomenclature and numbering used throughout this paper are those of *Chemical Abstracts.*

Acknowledgments.—We are indebted to Professor H. W. Webb and Dr. L. J. Hayner, of the Columbia University Department of Physics, for assistance in the preliminary examination of certain of the dyes. The sensitization tests and absorption spectra of the styryls (VI) and the sensitization tests of the thiazinocarbocyanines (VII) were determined by the Eastman Kodak Co. laboratories, through the courtesy of Dr. C. E. K. Mees, Vice President; the absorption spectra of the thiazinocarbocyanines, by Dr. R. S. Este, of the Electrical Testing Laboratories, New York City.

EXPERIMENTAL

Unless otherwise stated, all melting points recorded are "corrected." Those below 150°, were taken while the temperature was being raised at the rate of 3° per minute; those above 150°, at 8° per minute.

1,8-Nitronaphthalenesulfonyl chloride.—The method used by Bogert and Bartlett[1] was simplified and improved as follows.

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[2] Fisher and Hamer, *J. Chem. Soc.*, **1930**, 2502.

[3] Beattie, Heilbron, and Irving, *ibid.*, **1932**, 260.

To 1000 g. of technical sodium 1-naphthalenesulfonate, dried at 120°, there was added 600 g. of phosphorus pentachloride, and the mixture was heated cautiously at 100°, with occasional stirring, until it became homogeneous (about 30 minutes) when it was poured upon cracked ice with rapid mechanical stirring. The crude sulfonyl chloride was collected by filtration, ground with ice, to hydrolyze any remaining phosphorus halides, and dried on porous plates; m.p., 42°; yield, 920 g., or 93%. Crystallized five times from ligroïn, it melted at 66–67°, as reported by Bogert and Bartlett.

To 300 cc. of nitric acid (sp. gr., 1.5), there was added with stirring 200 g. of the crude 1-naphthalenesulfonyl chloride (m.p., 42°) suspended in 80 cc. of acetic anhydride, at a temperature of 0–12°. After all the chloride had been added the stirring was continued for ten minutes. The solution was then poured upon cracked ice with vigorous mechanical stirring which was continued for about 45 minutes. The nitrated sulfonyl chloride was removed, triturated with ether, to remove gummy impurities, and dried; yield, 150 g. This crude product was dissolved in rather more than three times its weight of warm benzene, the solution was filtered and the 1,8-nitronaphthalenesulfonyl chloride was precipitated from the filtrate by the addition of two volumes of gasolene; yield, 38 g.; m.p. 154°. A single recrystallization from benzene and gasolene, raised this m.p. to 161–162°, which is that recorded in the literature.

*2-Methyl-*peri*-naphthometathiazine* (I).—The chlorostannate of *peri*-aminonaphthylmercaptan, prepared as reported by Bogert and Bartlett, was used, instead of the tin chloride addition product, for cyclization to the thiazine, and the yield was improved by the addition of metallic tin, whose reducing action inhibited disulfide formation. The thiazine was obtained nearly pure and in high yield, by making use of its selective solubility in petroleum ether.

In detail, this improved technic was as follows. After dissolving 50 g. of fused sodium acetate in 500 cc. of boiling glacial acetic acid and adding 20 g. of tin, 50 g. of *peri*-aminonaphthylmercaptan chlorostannate was introduced in one lot with vigorous stirring. When all lumps had been broken up, 65 g. of acetic anhydride was poured into the hot solution, and the mixture was allowed to cool to room temperature. It was then neutralized with ammonium hydroxide solution; the yellow precipitate was filtered out, dried, and extracted with petroleum ether in the extraction apparatus described by Bogert and Conklin.[4] Evaporation of the petroleum ether extract, left 21 g., or a yield of 57%, of the naphthothiazine, m.p. 93°, sufficiently pure for the preparation of the alkyl halides described beyond. Recrystallized from acetone, the m.p. was raised to 96.5–97.5°, the figure found by Bogert and Bartlett.

Methiodide (IV).—A mixture of 30 g. of the thiazine (I), 25.6 g. of methyl iodide, and 0.05 g. of hydroquinone, was heated for 12 hours at 100° in a sealed tube. The hard brown product was extracted with cold chloroform, to remove unidentified dark, gummy impurities. It then melted at 190° and was sufficiently pure for use in subsequent condensations; yield, 32 g., or 62%. Omission of the hydroquinone, reduced the yield to 54%. The crude methiodide, when crystallized rapidly from absolute ethanol, formed short yellow needles, which were slightly soluble in water. Introduced into the bath at 197°, they shrank at 204°, and melted gradually with decomposition at 222–230°.

Anal. Calc'd for $C_{13}H_{12}INS$: C, 45.75; H, 3.55; I, 37.21.
Found: C, 45.77; H, 3.57; I, 36.71.

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[4] Bogert and Conklin, *J. Am. Chem. Soc.*, **55**, 1705 (1933).

The methiodides of the isomeric naphthothiazoles (II and III) have been described by Hamer[5] as nearly colorless, and as crystallizable from 95% ethanol, whereas our product suffered considerable decomposition when an attempt was made to crystallize it from that solvent.

Hydriodide and Ethiodide.—A mixture of 20 g. of the thiazine (I) with 8.1 cc. (1.2 moles) of ethyl iodide was heated for 24 hours at 100° in a sealed tube. The viscous brown product, containing some crystals, was extracted with cold chloroform, and there remained 14 g., or 39%, of a yellow-brown crystalline solid. From the chloroform extract, there was recovered, by extraction with hydrochloric acid, 7 g. of the original thiazine.

The crystalline solid, insoluble in chloroform, was believed at first to be the desired ethiodide, inasmuch as a small quantity of 3,3′-diethyl-*peri*-naphthothiazinocarbocyanine iodide (VII) was obtained from it by the usual reaction; but further crystallizations from absolute ethanol, together with analyses, proved that it consisted chiefly of the hydriodide, apparently formed by the breakdown of the ethyl iodide. Introduced into the bath at 255°, it decomposed at 259°. Treated with ammonium hydroxide solution, it gave a product which was identical in m.p. and mixed m.p. with the original thiazine.

Anal. Calc'd for $C_{12}H_{10}INS$: C, 44.03; H, 3.08; I, 38.81.
Found: C, 44.22; H, 3.17; I, 39.48.

As further proof of this identification, a benzene solution of the original thiazine (I) was treated with dry hydrogen iodide. A yellow hydriodide was obtained, in practically 100% yield which, when heated alone or mixed with the hydriodide formed in the ethyl iodide reaction, decomposed at the same temperature as the latter. Further, the two products exhibited exactly the same behavior when reacted with *p*-dimethylaminobenzaldehyde.

It is worth noting that Hamer[5] obtained less than 1% of *beta*-naphthothiazole ethiodide by the use of ethyl iodide, but a 31% yield when she employed ethyl *p*-toluenesulfonate and potassium iodide. Our attempts to utilize the latter method for the preparation of the thiazine ethiodide, however, were unsuccessful, as too much tar was formed.

Methochloride.—A solution of 5 g. of the methiodide (IV) in 250 cc. of alcohol was boiled for 45 minutes with an excess of freshly prepared and well washed silver chloride. The silver iodide was filtered out and the filtrate concentrated rapidly to a small volume. As it cooled, the methochloride separated in yellow needles, free from iodine, melting with decomposition at 230°; yield, 2 g., or 55%. Rapidly recrystallized from absolute ethanol, the decomposition point was raised to 234–235° when the crystals were introduced into the bath at 227°.

Anal. Calc'd for $C_{13}H_{12}ClNS$: C, 62.51; H, 4.85; Cl, 14.20.
Found: C, 62.18; H, 4.80; Cl, 14.67.

Hydrochloride.—Prepared from the corresponding hydriodide by the method used above for the methochloride, the crude product separated in yellow needles which melted with decomposition at 230°; yield, 2.9 g., or 78%. This decomposition point was raised to 233–234° (introduced into bath at 225°) by rapid recrystallization from absolute ethanol.

Anal. Calc'd for $C_{14}H_{14}ClNS$: Cl, 15.05. Found: Cl, 14.99.

*Reactions of 2-Methyl-*peri*-naphthometathiazine Methochloride and Hydrochloride with Acetic Anhydride and Amyl Nitrite.*—This was an attempt to apply to the *peri*-

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[5] HAMER, *J. Chem. Soc.*, **1929**, 2598.

naphthometathiazine group the thiocyanine reaction of Fisher and Hamer.[5] A mixture of 0.5 g. of the thiazine methochloride with 15 cc. of acetic anhydride was heated to 80°, and 0.23 g. of amyl nitrite (b.p., 96–106°) was added with stirring. A gas was evolved and the mixture turned an intense yellow. It was allowed to cool to 65°, and was then thoroughly chilled. The precipitate was removed, washed with ethyl acetate, and dried; yield of crude crystals, 0.3 g., or 58%, m.p. 230°. Recrystallized from absolute alcohol, the product was obtained in bright yellow needles, with a metallic lustre, which decomposed at 236° when introduced into the bath at 226°.

This compound was not the expected dye of thiocyanine type (VIII), but was halogen-free, and insoluble in either dilute sodium hydroxide or dilute hydrochloric acid.

Anal. Calc'd for $C_{13}H_{10}N_2OS$: C, 64.45; H, 4.16; N, 11.57; S, 12.23.
Found: C, 64.36; H, 4.08; N, 12.10; S, 12.22.

When the thiazine hydrochloride was used instead of the methochloride, in this reaction, the results were entirely similar, the crystalline product having the empirical formula $(C_{12}H_8N_2OS)_n$; yield, 62%. It decomposed at 237–238° when inserted in the bath at 228°.

Anal. Calc'd for $C_{12}H_8N_2OS$: C, 63.13; H, 3.53.
Found: C, 62.79; H, 3.65.

It is our belief that these products were *peri*-naphthometathiazinofurazans (IX), but not enough material was available for further study.

*3,3'-Dimethyl-*peri*-naphthometathiazinocarbocyanine Iodide* (VII).—The carbocyanine method of Hamer[6] was used for the preparation of this compound. A mixture of 2 g. of the thiazine methiodide (IV), 2 cc. of ethyl orthoformate and 10 cc. of dry pyridine, was heated just below the boiling point. An intense purplish red color developed immediately and at the end of 5 minutes long green needles separated in large amount. When these were filtered out and the filtrate was heated again, another crop of crystals resulted, and this treatment was repeated as long as additional crops were obtained. This piecemeal separation of the product was necessary, because when the crystals were heated for any length of time in the reaction mixture, they suffered some decomposition. The speed of the reaction was surprising, the total time required to throw out all the crystals, even in this stepwise manner, was only about 15 minutes; whereas in most other similar cases recorded in the literature, the reaction has required from 1 to 6 hours for completion.

The various lots of crystals were combined, and washed thoroughly with cold alcohol and then with ethyl acetate; yield, 0.7 g., or 43%; melting with decomposition at 221°; insoluble in water, slightly soluble in alcohol. The product dyed silk a purplish red. Recrystallized from chloroform, in the extractor mentioned previously, it was obtained in dark green needles, of metallic lustre, which melted with decomposition at 222° when introduced into the bath at 214°. These crystals carried chloroform of crystallization, which was held so tenaciously that the crystals lost but little weight when heated for 45 minutes *in vacuo* at 110–120°. The formation of stable solvates of cyanine dyes has been noted by others also. For analysis the compound was heated for an hour at 80°.

Anal. Calc'd for $C_{27}H_{21}IN_2S_2 \cdot CHCl_3$: C, 49.16; H, 3.24; N, 4.10; Ag halide, 97.23.
Found: C, 49.73; H, 3.35; N, 4.56; Ag halide, 91.40.

The analysis of such solvates is generally unsatisfactory. It is manifest that the loss of even a small quantity of the chloroform would throw the silver halide deter-

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[6] HAMER, *ibid.*, **1927**, 2796.

mination far out, since each molecule of the former gives three of the latter. The halide determination, however, does indicate the presence of chloroform.

The dye had no sensitizing power, and its single absorption maximum was found to lie at 5350 Å. In the case of carbocyanines of other types, it often happens that the *N*-methyl dyes have a much feebler sensitizing action than the corresponding ethyl derivatives. The *N*-methyl carbocyanines prepared from the *alpha-* and *beta*-naphthothiazoles are likewise but weak sensitizers, and the chief absorption maxima for both lie at about 6000 Å. This shift towards the blue in the case of the naphthothiazine dye was unexpected, because of the fact that the thiazine methiodide is yellow, while the thiazole methiodides are nearly colorless. Mills[7] has expressed the opinion that, since quinoline methiodides are yellow, and benzothiazole methiodides nearly colorless, it was to be expected that cyanine dyes containing the quinoline nucleus should have absorption maxima lying farther towards the red than those of the corresponding dyes containing a benzothiazole nucleus.

3,3'-Diethyl-peri-*naphthometathiazinocarbocyanine Iodide.*—On heating the mixture of hydriodide and ethiodide obtained by the action of ethyl iodide upon the thiazine (I), with ethyl orthoformate and pyridine (or acetic anhydride), a decided purplish red color developed, but no crystals separated. The dye was finally secured as follows.

A solution of 0.08 g. of anhydrous potassium acetate and 0.5 cc. of ethyl orthoformate in 4.5 cc. of acetic anhydride was heated to boiling. The heating was then discontinued and there was stirred in quickly 0.5 g. of the crude product resulting from the interaction of ethyl iodide and the thiazine (I). The color of the solution changed immediately to an intense reddish purple and, after a minute or two, when the temperature of the mixture had fallen to 120°, it was chilled, two volumes of ethyl acetate were added, and the crystals which separated were removed. The combined crops of crystals from seven such runs were ground up carefully with water and further purified by treatment with 15 cc. of boiling methanol; yield, 0.25 g. The product formed lustrous green needles, which melted at 243° with decomposition when introduced into the bath at 235°. Its formation from the crude reaction product of ethyl iodide and the thiazine proves clearly the presence therein of the thiazine ethiodide (IV). It dyed silk a reddish purple, similar to that produced by the above-mentioned methyl homolog. Its absorption spectrum also resembled the latter, its single absorption maximum being at 5400 Å, with a slight shift towards the red, as has been noted by other investigators in analogous cases. The fact that the absorption spectra of these two dyes showed but a single maximum was surprising, since most carbocyanines exhibit two such maxima.

Further, the dye possessed no sensitizing action whatever, although the analogous *N*-ethyl dyes containing the closely related naphthothiazole nuclei are powerful sensitizers.

From chloroform, this compound, like its methyl homolog, separated with solvent of crystallization.

Anal. Calc'd for $C_{29}H_{25}IN_2S_2CH\cdot{}_2Cl_3$: C, 50.61, H, 3.68.
Found: C, 51.50; H, 3.76.

In as much as solvates do not always crystallize with exactly one molecule of the solvent, these analytical results are submitted as fairly satisfactory.

2-p-*Dimethylaminostyryl*-peri-*naphthometathiazine Methiodide* (VI).—A mixture of 1 g. of the thiazine methiodide (IV) and 0.42 g. (1.2 moles) of *p*-dimethylamino-

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[7] Mills, *ibid.*, **121**, 455 (1922).

benzaldehyde, in absolute ethanol (or acetic anhydride) solution, was boiled for ten minutes. An intense reddish purple color appeared almost immediately, soon followed by a separation of purple needles. After standing for an hour at room temperature, the mixture was filtered, the crystals washed with absolute ethanol, then with ethyl acetate, and dried; yield, 0.87 g., or 63%; m.p. 228°. These crystals were purified for analysis by recrystallization by extraction from methanol. Introduced into the bath at 230°, the crystals melted with decomposition at 235°.

Anal. Calc'd for $C_{22}H_{21}IN_2S$: C, 55.92; H, 4.48; N, 5.93.
Found: C, 55.39; H, 4.62; N, 6.13.

The compound was soluble in chloroform or acetone. It did not dye silk. As a sensitizer, it proved to be of a weak benzothiazole type. Its broad absorption band showed a single poorly defined maximum at about 4700 Å. Both *alpha-* and *beta*-naphthothiazole ethiodides form *p*-dimethylaminostyryl derivatives with fairly powerful sensitizing action.

In carrying out the above reaction, the addition of a few drops of piperidine completely inhibited the condensation. This was unexpected, because in other cases piperidine has been found to be a useful catalyst in promoting aldol formation.

The researches of Mills and Raper[8] have shown that in the formation of these styryls, the methiodide first loses hydrogen iodide, giving a methylene base which then condenses with the aldehyde to an allene base, with which the hydrogen iodide then recombines.

*2-*p*-Dimethylaminostyryl-*peri*-naphthometathiazine Hydriodide*, prepared like the above methiodide, from the corresponding thiazine hydriodide, also formed purple needles which, in the crude state, melted with decomposition at 239°; yield, 1.1 g., or 79%. Purified as described for the methiodide, and introduced into the bath at 238°, it darkened and emitted vapors at 243°, melting with decomposition and swelling at 250°. Like the methiodide it was devoid of tinctorial properties, but proved to be a feeble sensitizer of benzothiazole type. Its broad absorption band possessed a single poorly defined maximum at about 4500 Å.

Anal. Calc'd for $C_{24}H_{25}IN_2S$: C, 55.00; H, 4.18; N, 6.11.
Found: C, 54.94; H, 4.50; N, 5.96.

*3,3′-Dimethyl-12-chloro-*peri*-naphthometathiazinodicarbocyanine Iodide.*—The dicarbocyanine method of Beattie, Heilbron and Irving[3] was tried.

Mucochloric acid, prepared as described by them, was converted into the *alpha*-chloro-*beta*-anilinoacraldehyde anil hydrochloride, $C_6H_5NHCH\text{: }CClCH\text{:}NC_6H_5$, by the method of Dieckmann and Platz.[9]

A mixture of 0.22 g. of this anil hydrochloride, 0.15 g. of anhydrous potassium acetate and 10 cc. of acetic anhydride, was heated to boiling. The heating was then stopped and 0.5 g. of the thiazine methiodide (IV) was added immediately with stirring. The mixture turned an intense blue. When it had cooled to 120°, it was chilled and an equal volume of ethyl acetate added. The dark crystals were removed and freed from acetic anhydride by washing with ethyl acetate. The product from four such runs was washed thoroughly with water and extracted with boiling methanol until the filtrate was blue. This left a residue of 0.55 g., equivalent to a yield of 30%. Introduced into the bath at 211°, it melted with decomposition at 221°. It dyed silk blue. It was so difficultly soluble in all solvents tried that we were unable to purify it satisfactorily, and the analytic results, therefore, differed by several per cent from the figures calculated.

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[8] MILLS AND RAPER, *ibid.*, **127**, 2466 (1925).

[9] DIECKMANN AND PLATZ, *Ber.*, **37**, 4638 (1904).

Since its solutions were blue, while those of the monocarbocyanine iodide (VII) were reddish purple, it seems that the increase of two methine groups in the side chain has caused the expected shift of the absorption towards the red.

*Attempts to Prepare other Dyes from 2-Methyl-*peri*-naphthometathiazine*

Pseudocyanine.—The thiazine methiodide (IV) failed to condense with 2-iodoquinoline methiodide in absolute ethanol solution, in the presence of sodium hydroxide. No cyanine color developed and no crystals separated. This failure was foreshadowed by the sensitivity to piperidine of the thiazine methiodide in the *p*-dimethylaminostyryl condensation, as noted already.

Other types.—Attempts to produce a desensitizer, by condensing thiazine methiodide with *p*-nitrosodimethylaniline in absolute ethanol, with or without piperidine as catalyst, resulted only in tars. A similar lack of success attended our experiments for the production of a tricarbocyanine by the methods of Hamer and Fisher.[10]

SUMMARY

1. 2-Methyl-*peri*-naphthometathiazine has been converted into quaternary halides and these, in turn, into cyanine dyes.

2. In photosensitizing power, these thiazine dyes appear to be much weaker than the corresponding naphthothiazole or benzothiazole derivatives.

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[10] Hamer and Fisher, *J. Chem. Soc.*, **1933**, 189.