136. *Preparation of Unsymmetrical Carbocyanines.*

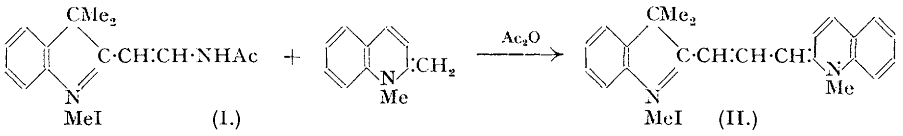
By J. D. Kendall and J. R. Majer.

The quaternary alkyl *p*-toluenesulphonates of a number of heterocyclic bases containing reactive methyl or methylene groups have been condensed with esters of trithio-orthoformic acid in acid anhydride solution to give compounds which contain the group $>C:CH\cdot SR$ (R = alkyl or aralkyl). These compounds react in the presence of bases, with compounds containing a reactive methyl or methylene group to yield cyanine dyes.

The first unsymmetrical carbocyanines were prepared by the action of an alkali and an oxidising agent on quaternary salts of 2 : 4-dimethylquinoline or its substitution products (D.R.-P. 155,541). The blue dyes were called " dicyanines ", and their preparation was investigated by later workers (Wise and Adams, *Amer. J. Eng. Chem.*, 1918, **10**, 801; Mikesko, Haller, and Adams, *J. Amer. Chem. Soc.*, 1920, **42**, 2392; O. Fischer, *J. pr. Chem.*, 1918, **98**, 209), but it was not until 1924 that Mills and Odams showed that dicyanines were derivatives of 2 : 4′-carbocyanine (*J.*, 1924, 1916). Mills and Odams prepared the parent 1 : 1′-diethyl-2 : 4′-carbocyanine iodide by treating a mixture of lepidine and quinaldine ethonitrates with di-*o*-formylmethylaminodiphenyl disulphide and pyridine and separating the dicyanine from its congeners.

These methods were applicable only to quinoline derivatives, and the central methine group was believed to be provided by the breakdown of one of the quaternary salts. Later methods were directed to the condensation of derivatives of formic acid with two different quaternary salts in a step-wise fashion, the formic acid derivative providing a central methine group for the unsymmetrical carbocyanine dye.

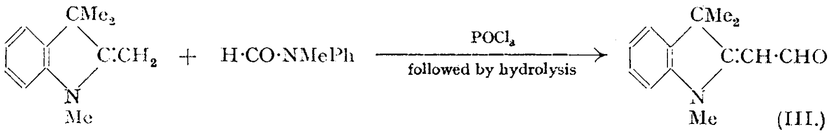
The first of these methods (Soc. Chem. Ind. Basle, B.P. 334,706, 1928) suggested the use of formiminoethyl ether hydrochloride. This was condensed with Fischer's base in acetic acid–acetic anhydride followed by treatment with aqueous potassium iodide. The resulting intermediate 1 : 3 : 3-trimethyl-2-2′-acetamidovinylindolenine iodide (I) was boiled with *N*-methyl-2-methylene-2 : 3-dihydroquinoline in acetic anhydride to yield the unsymmetrical carbocyanine (II). Similar intermediates were prepared later from formamide or thioformamide (Knott, Kodak, B.P. 577,549).



(I.) (II.)

Piggott and Rodd found that related intermediates of this type and carbocyanine dyes could be prepared by the use of diaryl formamidines (I.C.I., B.P.P. 344,409; 354,898); the intermediates, which contained 2-arylamino- or -acetarylamido-vinyl groups, also reacted with indoles and formed dyes with pyrazolones (B.P.P. 353,863, 366,904). Knott found that this type of intermediate could also be prepared from *iso*formanilide (*J.*, 1946, 120).

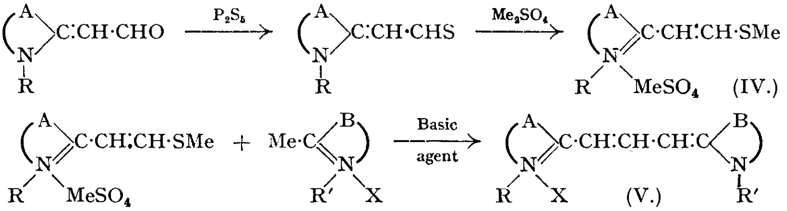
Other formic acid derivatives, *e.g.*, *N*-methylformanilide were found to yield reactive intermediates by first reacting in phosphorus oxychloride solution with α-methyleneindoline bases of the type of Fischer's base and subsequent alkaline hydrolysis (I.G., B.P. 438,278). By this method heterocyclic aldehydes were formed, *e.g.*, 1 : 3 : 3-trimethyl-2-formylmethyleneindole (III).



(III.)

These aldehydes likewise yielded carbocyanines on condensation with methylene bases in phosphorus oxychloride solution (I.G., B.P. 438,603) or with quaternary salts in pyridine solution (I.G., B.P. 442,160).

Corresponding ω-aldehydes containing the thiazole ring were prepared later by Kodak (B.P. 466,245) and used in the synthesis of unsymmetrical carbocyanines (B.P. 466,246) and merocyanines (B.P. 466,244). Other workers attempted to increase the reactivity of the aldehydes by converting them into their semicarbazones and thiosemicarbazones (I.G., B.P. 510,242), and into methylthio-compounds (IV) by heating them with phosphorus pentasulphide to give thioaldehydes which were then converted into quaternary salts with methyl sulphate (Kumetat and Riester, U.S.P. 2,349,179). Like the corresponding compounds with α-thioether groupings (Kendall, B.P. 424,559) these intermediates, which contained the vinylogous 2-methylthiovinyl groupings, were very reactive and of great value in the preparation of the unsymmetrical carbocyanines (V) (Kumetat and Riester, U.S.P. 2,354,524). Their method of preparation *via* the aldehydes, however, was not simple and the yields were poor.



(IV.)

(V.)

(A and B = remainders of heterocyclic rings)

(Resonance extreme)

In an attempt to obtain a simpler method of synthesis attention was directed to the preparation by Kimura of symmetrical carbocyanines and neocyanines from quaternary salts of heterocyclic nitrogen bases with α-methyl groups and ethyl trithio-orthoformate in acetic anhydride–pyridine solution (*Chem. Zentr.*, 1937, II, 4187). It appeared possible that, if this reaction proceeded *via* the intermediate formation of the 2-ethylthiovinyl compounds, these might be isolated under appropriate conditions. The formation of a 2-ethylthiovinyl compound was confirmed when 2-methylbenzthiazole methiodide was boiled with ethyl trithio-orthoformate in acetic anhydride. The main product was, however, a trinuclear dye of the neocyanine type as noted by Kimura, but this was contaminated with some of the 2-2′-ethylthiovinylbenzthiazole methiodide. If 2-methylbenzthiazole metho-*p*-toluenesulphonate was used instead of the methiodide, the neocyanine colour, which formed initially on heating, rapidly disappeared and, on addition of potassium iodide solution, the required 2-2′-ethylthiovinylbenzthiazole methiodide was precipitated in good yield substantially free from the neocyanine and carbocyanine.

The reason for the difference in behaviour of the two quaternary salts is puzzling but not without parallel in cyanine dye chemistry. Thus although 2-methyl-β-naphthothiazole ethiodide will not react with ethyl orthoacetate in pyridine (Hamer, *J.*, 1929, 2598), the etho-*p*-toluenesulphonate gives the *meso*-methylcarbocyanine dye under similar conditions (Brooker, B.P. 378,870). The solubility of the quaternary salt is not the sole factor, and the chemistry of the reactions is being investigated further.

By using 2 : 3 : 3-trimethylindolenine methiodide the 3 : 3-dimethyl-2-2′-ethylthiovinylindolenine methiodide was obtained and separated directly, as the cyanine dye formed at the same time was very soluble in acetic anhydride. 2-Ethylthiovinyl derivatives of all the heterocyclic bases employed could be isolated as the alkyl *p*-toluenesulphonates on removal of the acetic anhydride either by hydrolysis or distillation, and the resultant product could be crystallised or precipitated as a less soluble salt by solution in ethanol and addition of an alkali halide solution.

The reaction was effected using other trithio-orthoformate esters such as methyl and benzyl tritho-orthoformate, but the intermediates obtained were less soluble and in the latter case somewhat less reactive. Ten of these reactive intermediates were prepared and converted into carbocyanines in pyridine or ethanol solution with the addition of triethylamine. For direct preparation of carbocyanine dyes it was unnecessary to isolate from the acetic anhydride solution the intermediate which gave the dye on addition of the requisite quaternary salt and triethylamine. Symmetrical carbocyanines were likewise obtained with ease, but since so many have been described previously their preparations have been omitted from the present communication. Two merocyanines were also prepared by condensations with 1-phenyl-3-methyl-5-pyrazolone and *N*-ethylrhodanine in pyridine solution.

EXPERIMENTAL.

Preparation of 2-Alkythiovinyl Compounds.—Ethyl trithio-orthoformate was prepared by the method of Holmberg (*Ber.*, 1907, **40**, 1740).

Quinaldine (14·3 g.) was fused with methyl *p*-toluenesulphonate (18·6 g.) for 1 hour at 100°. The product was dissolved in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (22 c.c.) and the solution boiled for 30 minutes. When the original green colour had faded to a dull yellow the acetic anhydride was removed under reduced pressure and the residue crystallised from methanol–ether. 2-2′-*Ethylthiovinylquinoline metho*-p-*toluenesulphonate* (12·2 g.) was obtained as yellow needles, m. p. 102° (Found : S, 15·8. $C_{21}H_{23}O_3NS_2$ requires S, 16·0%).

2-2′-*Ethylthiovinylbenzthiazole metho*-p-*toluenesulphonate* was prepared similarly from 2-methylbenzthiazole (7·5 g.), methyl *p*-toluenesulphonate (9·3 g.), acetic anhydride (50 c.c.), and ethyl trithio-orthoformate (11 c.c.). The crude product was crystallised from ethanol–ether to give straw-coloured needles, m. p. 171° (decomp.) (Found : S, 24·05. $C_{19}H_{21}O_3NS_3$ requires S, 23·65%).

2-2′-*Ethylthio-1′-methylvinylbenzthiazole methiodide* was prepared by fusing 2-ethylbenzthiazole (16·3 g.) with methyl *p*-toluenesulphonate (18·6 g.) for 3 hours at 130—140°. The quaternary salt was dissolved in acetic anhydride (100 c.c.) containing ethyl trithio-orthoformate (22 c.c.), and the solution boiled until the colour had faded (30 minutes) and poured into hot potassium iodide solution (100 c.c. of 20%). The dark precipitate was crystallised from methanol to give dark brown crystals (9 g.), m. p. 168° (decomp.) (Found : S, 17·4. $C_{13}H_{16}NIS_2$ requires S, 17%).

2-2′-*Ethylthiovinylbenzthiazole methiodide* was prepared in a similar way from 2-methylbenzthiazole (14·9 g.), methyl *p*-toluenesulphonate (18·6 g.), acetic anhydride (100 c.c.), and ethyl trithio-orthoformate (22 c.c.). After crystallisation from methanol it was obtained as steel-blue needles (20 g.), m. p. 194° (decomp.) (Found : S, 17·4. $C_{12}H_{14}NIS_2$ requires S, 17·65%).

2-2′-*Ethylthiovinylquinoline methiodide* was prepared from quinaldine (7·1 g.), methyl *p*-toluenesulphonate (9·3 g.), acetic anhydride (50 c.c.), and ethyl trithio-orthoformate (11 c.c.). The crude product was crystallised from methanol to yield brown crystals (11·3 g.), m. p. 178° (Found : I, 35·4. $C_{14}H_{16}NIS$ requires 35·5%).

2-2′-*Ethylthiovinylbenzoxazole methiodide* was prepared from 2-methylbenzoxazole (6·6 g.), methyl *p*-toluenesulphonate (9·3 g.), acetic anhydride (40 c.c.), and ethyl trithio-orthoformate (11 c.c.). On pouring into hot potassium iodide solution a tar was first precipitated. After decantation from the tar the aqueous solution was cooled to 0° ; a brown solid then crystallised. This was obtained as metallic brown needles from methanol, m. p. 193° (decomp.). A further crop was obtained by basifying the filtrate with sodium carbonate solution. The total yield was 6 g. (Found : S, 9·1. $C_{12}H_{14}ONIS$ requires S, 9·2%).

2-2′-*Ethylthiovinylbenzthiazole ethiodide* was prepared from 2-methylbenzthiazole (7·5 g.), ethyl *p*-toluenesulphonate (10·0 g.), acetic anhydride (50 c.c.), and ethyl trithio-orthoformate (11 c.c.). It was obtained from methanol as brown crystals (6 g.), m. p. 195° (decomp.) (Found : I, 33·4; S, 16·8. $C_{13}H_{16}NIS_2$ requires I, 33·7; S, 17%).

Benzyl Trithio-orthoformate.—Ethyl formate (9·5 c.c.) was mixed with benzylthiol (28·5 c.c.) and the mixture saturated with hydrogen chloride. The white solid which was deposited (29·7 g., 97%) was collected and dried in a vacuum ; m. p. 103°.

2-2′-*Benzylthiovinylbenzthiazole methiodide* was prepared by fusing 2-methylbenzthiazole (1·49 g.) with methyl *p*-toluenesulphonate (1·86 g.) for 1 hour at 100° ; benzyl trithio-orthoformate (4·2 g.) and acetic anhydride (15 c.c.) were added and the mixture boiled for 30 minutes. Acetic anhydride was removed under reduced pressure and the residue dissolved in ethanol (20 c.c.) and poured into aqueous potassium iodide (20 c.c. of a 10% solution). The oily solid precipitate was crystallised from methanol to yield brown crystals (2 g.), m. p. 163° (Found : S, 15·05. $C_{17}H_{16}NIS_2$ requires 15·05%).

Methyl Trithio-orthoformate.—Methylthiol and dry hydrogen chloride were passed simultaneously into ethyl formate (200 c.c.) until saturation occurred. The mixture was then poured on ice and the upper layer separated. The aqueous layer was extracted with ether, and the oil and ether extracts were bulked, washed with sodium carbonate solution and water, and dried (K_2CO_3). The ether was removed and the residue distilled, yielding a colourless oil (50 g.), b. p. 106—108°/10 mm.

2-2′-*Methylthiovinylbenzthiazole methiodide* was prepared from 2 methylbenzthiazole (3·0 g.), methyl *p*-toluenesulphonate (3·72 g.), acetic anhydride (30 c.c.), and methyl trithio-orthoformate (3·0 c.c.). It was obtained from ethanol as dark brown crystals, m. p. 190° (decomp.) (Found : I, 36·4; S, 18·0. $C_{11}H_{12}NIS_2$ requires I, 36·4; S, 18·4%).

1 : 1′-*Diethyl*-2 : 4′-*carbocyanine Iodide* ([1-*Ethyl*-2-*quinoline*][1-*ethyl*-4-*quinoline*]*trimethincyanine Iodide*).—Quinaldine (1·43 g.) was fused with ethyl *p*-toluenesulphonate (2·00 g.) for 3 hours at 140—150°. The product was dissolved in acetic anhydride (15 c.c.) containing ethyl trithio-orthoformate (2 c.c.), and the solution refluxed for 30 minutes. Lepidine ethiodide (2·98 g.) and triethylamine (1·4 c.c.) were added, and the heating continued for a further 20 minutes; a deep blue colour had then appeared. The green crystals which separated on cooling were collected and crystallised from methanol to yield the *iodide* as grass-green needles, m. p. 255° (Found : I, 26·4. $C_{25}H_{25}N_2I$ requires I, 26·5%).

3 : 3′ : 8-*Trimethylthiacarbocyanine Iodide* (*Bis*-[3-*methylbenzthiazole*]-α-*methyltrimethincyanine Iodide*).—2-Ethylbenzthiazole (1·63 g.) was fused with methyl *p*-toluenesulphonate (1·86 g.) for 1 hour at 100°. 2-2′-Ethylthiovinylbenzthiazole methiodide (2·87 g.) and pyridine (15 c.c.) were added and the mixture refluxed for 15 minutes; a purple colour had then developed. On dilution with water a green *dye* separated; this was collected and crystallised from methanol to yield green crystals with a gold reflex (3·8 g.), m. p. 258° (Found : I, 26·4. $C_{20}H_{19}N_2IS_2$ requires I, 26·6%).

3 : 3′-*Diethyloxaselenacarbocyanine Iodide* ([3-*Ethylbenzoxazole*][3-*ethylbenzselenazole*]*trimethincyanine Iodide*).—2-Methylbenzselenazole (2·00 g.) was fused with ethyl *p*-toluenesulphonate (2·00 g.) for 3 hours at 140—150°. The product was dissolved in acetic anhydride (15 c.c.) containing ethyl trithio-orthoformate (2·2 c.c.) and refluxed for 30 minutes. 2-Methylbenzoxazole ethiodide (2·75 g.) and triethylamine (1·4 c.c.) were added and the heating continued for 15 minutes. The crystals which separated

from the red solution on cooling were collected and crystallised from methanol to yield the *iodide* as deep purple needles with metallic reflex (1·0 g.), m. p. 240° (Found : I, 24·3. $C_{21}H_{21}ON_2ISe$ requires I, 24·2%).

3 : 6′-*Dimethyl*-1′-*ethylthiaquino*-2 : 2′-*carbocyanine iodide* ([3-*methylbenzthiazole*][6-*methyl*-1-*ethyl*-2-*quinoline*]*trimethincyanine iodide*) was prepared similarly from 2-methylbenzthiazole (1·49 g.), methyl *p*-toluenesulphonate (1·86 g.), ethyl trithio-orthoformate (2 c.c.), and *p*-toluquinaldine ethiodide (3·13 g.). It was obtained from methanol as green flaky crystals, m. p. 278° (decomp.) (Found : S, 6·8. $C_{22}H_{27}N_2IS$ requires S, 6·8%).

3′-*Methyl*-3-*ethyloxathiacarbocyanine Iodide* ([3-*Ethylbenzoxazole*][3-*methylbenzthiazole*]*trimethincyanine Iodide*).—2-Methylbenzthiazole (1·49 g.) and methyl *p*-toluenesulphonate (1·86 g.) were heated at 100° for 1 hour. The product was dissolved in acetic anhydride (15 c.c.) containing ethyl trithio-orthoformate (2 c.c.) and refluxed for 30 minutes. 2-Methylbenzoxazole ethiodide (2·89 g.) and triethylamine (1·4 c.c.) were added and the heating continued for 20 minutes. The pink solution was diluted with ethanol and the precipitated red crystals were collected and crystallised from methanol to yield the *iodide* as purple crystals, m. p. 242° (decomp.) (Found : I, 27·0; S, 6·9. $C_{20}H_{19}ON_2IS$ requires I, 27·4; S, 6·9%).

3 : 3′-*Diethyloxathiacarbocyanine iodide* ([3-*ethylbenzoxazole*][3-*ethylbenzthiazole*]*trimethincyanine iodide*) was prepared similarly from 2-methylbenzoxazole (4·0 g.), ethyl *p*-toluenesulphonate (6·0 g.), ethyl trithio-orthoformate (6 c.c.), and 2 methylbenzthiazole ethiodide (9·0 g.). It was obtained as dark blue needles, m. p. 243° (decomp.) (Found : I, 26·7. $C_{21}H_{21}ON_2IS$ requires I, 26·8%).

3 : 3′-*Dimethyloxathiacarbocyanine Iodide* ([3-*Methylbenzoxazole*][3-*methylbenzthiazole*]*trimethincyanine Iodide*).—2-Methylbenzoxazole methiodide (5·3 g.) and 2-2′-ethylthiovinylbenzthiazole methiodide (7·26 g.) were refluxed in pyridine (40 c.c.) for 1 hour. The *dye* which separated on dilution with water was collected and crystallised from methanol to yield 5·2 g. of fluffy red needles, m. p. 254° (decomp.) (Found : I, 28·0. $C_{19}H_{17}ON_2IS$ requires I, 28·3%).

3 : 3′-*Dimethylthiathiazolinocarbocyanine Iodide* ([3-*Methylthiazoline*][3-*methylbenzthiazole*]*trimethincyanine Iodide*).—2-Methylthiazoline (1·00 g.) was fused with methyl *p*-toluenesulphonate (1·86 g.) for 1 hour at 100°. The product was dissolved in acetic anhydride (10 c.c.) and ethyl trithio-orthoformate (2·2 c.c.), and the mixture refluxed for 30 minutes. 2-Methylbenzthiazole methiodide (2·85 g.) and triethylamine (1·4 c.c.) were added and the mixture refluxed for 10 minutes; a thick precipitate had then formed. The *dye* was filtered off and crystallised from methanol to yield dark red crystals with a bright green reflex (1·5 g.), m. p. 278° (decomp.) (Found : I, 30·3. $C_{15}H_{17}N_2IS_2$ requires I, 30·5%).

1-*Phenyl*-3 : 1′ : 3′ : 3′-*tetramethyl*-2′-*ethylideneindolylidene*-5-*pyrazolone*.—1-Phenyl-3-methyl-5-pyrazolone (1·74 g.) and 1 : 3 : 3-trimethyl-2-2′-ethylthiovinylindolenium iodide (3·73 g.) were dissolved in dry pyridine (25 c.c.) and the mixture boiled for 15 minutes. The *dye* precipitated on dilution with water was collected and crystallised from methanol to yield red needles (2·9 g.), m. p. 183° (Found : C, 77·3; H, 6·3. $C_{23}H_{23}ON_3$ requires C, 77·2; H, 6·4%).

2-*Keto*-4-*thio*-3′-*methyl*-3-*ethyl*-5 : 2′-*ethylidenebenzthiazolylidenetetrahydrothiazole* was prepared similarly from *N*-ethylrhodanic acid (0·8 g.), 2-2′-ethylthiovinylbenzthiazole methiodide (1·81 g.), and pyridine (10 c.c.). It was obtained from methanol as red needles, m. p. 280° (Found : C, 54·2; H, 4·0; S, 29·0. $C_{15}H_{14}ON_2S_3$ requires C, 53·9; H, 4·2; S, 28·75%).

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