150. *Quinoxaline Cyanines. Part I.*

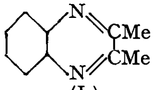
By A. H. Cook, J. Garner, and C. A. Perry.

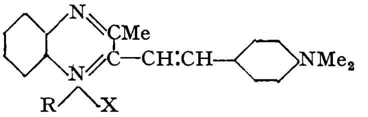
2 : 3-Dimethylquinoxaline methiodide has been converted into a symmetrical carbocyanine and into unsymmetrical carbocyanines where the second auxochromic nucleus is benzoxazole, dimethylindole, quinoline, or *p*-dimethylaminobenzene. By using similar or modified methods to effect dye formation at a low temperature a series of dyes has been obtained derived from 1-phenyl-2-methylene- and 1-phenyl-2-methylene-3-methyl-dihydroquinoxaline.

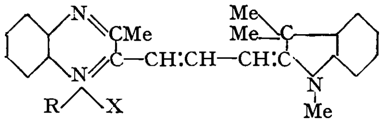
A strong bathochromic influence of the quinoxaline system is evident from the deep blue colour of the cyanines described.

The preparation of cyanine dyes from heterocyclic bases with reactive methyl groups or from their quaternary salts is well known. In addition to those derived from bases such as quinaldine and lepidine, cyanines derived from compounds containing other hetero-systems (oxazoles, thiazoles, imidazoles and quinazolines) have also been described. The only reference to the use of quinoxalines as the source of cyanines occurs in a recent patent (B.P. 506,720), though Kendall probably envisaged this possibility (*J. Soc. Dyers and Colourists*, 1936, **52**, 13) without specifically stating it. In the present paper it is shown that 2-methylquinoxalines possess the requisite activity for cyanine formation and a series of carbocyanines is described.

The starting point of these investigations was 2 : 3-dimethylquinoxaline (I). The methyl groups of this compound are known to be reactive, *e.g.*, towards benzaldehyde (Bennett and Willis, J., 1928, 1960), and were thus expected to form part of a cyanine chain. (I) yields only a monomethiodide (Bennett and Willis, *loc. cit.*), though in our experience this is formed only when anhydrous quinoxaline and not when the normal dihydrate is used. The monomethiodide readily formed cyanines, but before describing these it may be mentioned that no success attended attempts to extend the series by forming quaternary salts with ethyl or propyl iodide, benzyl chloride, *p*-nitrobenzyl chloride or 2 : 4-dinitrochlorobenzene even at the b. p. of the halides. Quaternisation of (I) and of other quinoxalines could nevertheless be achieved by heating with alkyl sulphonic esters, Grignard compounds, or particularly with alkyl sulphates.


(I.)

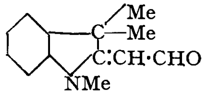

(II.)


(III.)

Quinoxalines not containing a methylene group in the 2-position failed to give colours by reactions similar to those described below, so there can be no doubt of the structure of the cyanines obtained.

(I) and methyl or ethyl sulphate react exothermally on gentle warming to give a low-melting, crystalline, water-soluble mono-metho- or -etho-sulphate accompanied by small amounts of green dyes. All of these quaternary salt preparations condensed to some extent with *p*-dimethylaminobenzaldehyde and other appropriate reactants, but as the resulting quinoxaline cyanines were usually unstable towards the hot reaction media, the usual cyanine preparative methods were inadmissible without modification; thus the preparation of these cyanines in quantity depended essentially on the discovery of conditions under which the condensations would proceed at room temperature. 2 : 3-Dimethylquinoxaline methiodide condensed only very slowly with *p*-dimethylaminobenzaldehyde in cold acetic anhydride, but in pyridine–acetic anhydride condensation was complete within 3—5 minutes with formation of the violet-blue dye (II; R = Me, X = acid radical). Similarly condensation of the methiodide with 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde (IV) afforded the violet-blue dye (III, R = Me) in remarkably high yield. These dyes could be obtained still more readily from the methosulphate without isolation of the intermediate salt. The *N*-ethyl analogues of (II) (R = Et) were likewise prepared, from crude ethosulphate.

To extend this series it was necessary (*a*) to prepare a 2-ω-methylene-aldehyde (V) or a derivative of equivalent reactivity and then to condense this with a second quaternary salt or (*b*) to condense the quaternary salts of 2 : 3-dimethylquinoxaline with a second aldehyde or equivalent derivative, *e.g.*, of the unknown aldehyde (VI) and others like it.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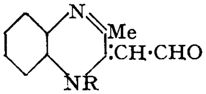
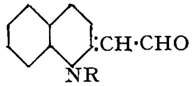
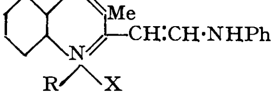
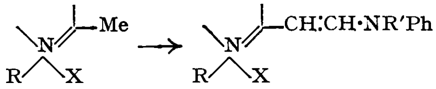

(V.)


(VI.)

Unfortunately the methiodide of (I) and the methylene base obtained from it with alkali were so sensitive that attempts to prepare (V) by introducing the aldehydo-group with methylformanilide and phosphorus oxychloride (cf. Vilsmeier and Haack, *Ber.*, 1927, **60**, 119) were unsuccessful; for the same reason, equally unsuccessful were attempts to prepare the anilinovinyl compound (inset) from the quaternary salt and diphenylformamidine (cf. B.P. 344,409).



Turning to (*b*), we first attempted to prepare aldehydes analogous to type (VI) (cf. B.P. 486,780) which are obtained by hydrolysing derivatives (VII, R′ = alkyl) with alkali. No difficulty was experienced in preparing compounds of type (VII) from methyldiphenylformamidine and quaternary salts of 2-methylbenz-



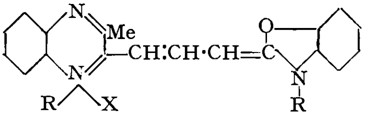
(VII.)

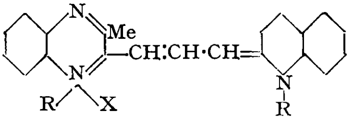
thiazole, 2-methylbenzoxazole or " Fischer's base," but, except for a small yield of 1-methyl-2-methylenebenzthiazolinealdehyde, no success attended attempts at hydrolysing the compounds.

It was interesting to find in this connexion that 1-phenyl-3-methyl-4-anilinomethylene-5-pyrazolone (Dains and Brown, *J. Amer. Chem. Soc.*, 1909, **31**, 1148) was not hydrolysed by alkali to the 4-aldehyde. On boiling for 3 hours with 4% aqueous-alcoholic hydrogen chloride it passed smoothly into bis-4 : 4′-1-phenyl-3-methyl-5-pyrazolonemethene. On the other hand 1-phenyl-3-methyl-4-methylanilinomethylene-5-pyrazolone was disrupted by boiling water into methylaniline and 1-phenyl-3-methyl-5-pyrazolone-4-aldehyde.

On attempting to condense compounds of type (VII, R = alkyl or H; the compounds where R = H are readily obtained from reactive quaternary salts and diphenylformamidine) with quinoxaline quaternary salts the instability of quinoxaline cyanines towards hot solvents was again encountered, so attempts in hot acetic anhydride failed. Eventually it became clear that transient appearance of the dyes was not conditioned by their instability towards acetic anhydride alone. They were stable towards boiling acetic anhydride or pyridine, but quickly disappeared in a mixture of the two. Under the normal preparative conditions in boiling acetic anhydride their instability was apparently due to mineral acid liberated during the reaction. So, on condensing quaternary salts of 2 : 3-dimethylquinoxaline with those of 2-anilinovinyl-benzoxazole or -quinoline derivatives in boiling acetic anhydride containing a large excess of sodium acetate the dyes (VIII) and (IX) were obtained.

(VIII.)

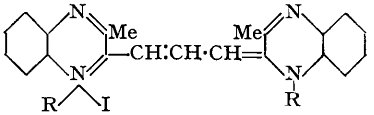


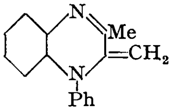


(IX.)

2 : 3-Dimethylquinoxaline methiodide failed to give significant yields of symmetrical dye on treatment with chloroform or chloral in caustic soda, ethyl orthoformate in acetic anhydride or pyridine, or with diphenylformamidine in hot acetic anhydride; all these methods gave coloured solutions, but in no case did they provide a practical route to the cyanine. Success was finally achieved by using sodium formate in acetic anhydride with strong cooling; 20—25% of the theoretical yield of (X, R = Me) was then obtained.

(X.)

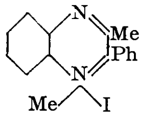




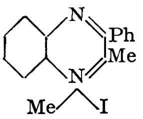
(XI.)

Analogues of the dyes already mentioned were obtained by first condensing *o*-aminodiphenylamine with diacetyl in alcoholic solution and precipitating the unstable methylene base (XI); in some instances no solvent was employed in preparing the quinoxaline and the crude product was used directly. (XI) and 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde yielded the analogue of (III) (R = Ph); in cold acetic anhydride moderate yields were obtained after 40 hours, but in acetic anhydride–pyridine excellent yields of crystalline dye were obtained after a few minutes. No condensation of (XI) with *p*-dimethylaminobenzaldehyde was observed in cold acetic anhydride even in presence of bases such as pyridine, piperidine, dimethylaniline or trimethylamine, or of acidic reagents. The condensation was, however, strongly catalysed by derivatives of boron such as the trifluoride or triacetate, particularly in presence of pyridine, but not by boric acid itself in presence of pyridine. The product was the analogue of (II) (R = Ph). Finally condensation of two molecular parts of (XI) with sodium formate in cold acetic anhydride containing acetyl chloride gave an excellent yield of the analogue of (X) (R = Ph).

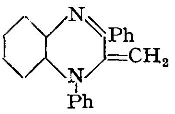
Lastly homologues of some of the dyes already mentioned were examined. 3-Phenyl-2-methylquinoxaline readily gave a monomethiodide; in the crude state this gave blue colours with appropriate aldehydes, but on purification this property was lost; it thus follows that the main constituent of the crude methiodide is (XII) and that the useful component (XIII) arises in only negligible quantity. When phenylmethylglyoxal was condensed with *o*-aminodiphenylamine to give what, from its reaction, could only be the unstable methylene



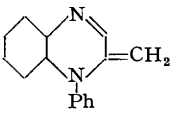
(XII.)



(XIII.



(XIV.)

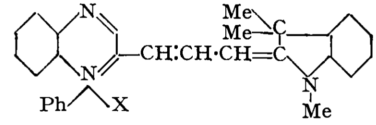


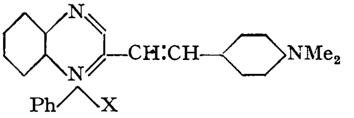
(XV.)

base (XIV), the resulting carbocyanines were oily and clearly not homogeneous. They appeared to have a stability not greatly superior to that of these dyes already mentioned and were not further examined.

Quinoxalines derived from methylglyoxal and *o*-phenylenediamines may also give two structurally isomeric quaternary salts, only one of which would be of value in the present connexion. Therefore, on the basis of experience gained with phenylmethylglyoxal, only the reaction between methylglyoxal and *o*-aminodiphenylamine was examined. In cold acetic anhydride the unstable methylene base (XV) was evidently formed, but no colour developed in presence of either *p*-dimethylaminobenzaldehyde or 1 : 3 : 3-trimethyl-2-methyleneindoline-ω-aldehyde even when bases were added. In the case of the indoline aldehyde, however, the carbocyanine (XVI) was rapidly formed in presence of boron trifluoride but not of phosphorus halides. With *p*-dimethylaminobenzaldehyde, (XVII) was obtained in presence of phosphorus oxychloride but not boron trifluoride.

(XVI.)





(XVII.)

Most of these cyanines are comparatively soluble in water and the colours are reversibly discharged by alkali. The colours of many fade in very dilute solution but are retained in presence of very dilute acid.

The most noteworthy feature of these compounds is their colour, which in most cases is an intense blue. Solutions absorb light very strongly in the red region of the visible spectrum, so the quinoxaline system exerts a much greater bathochromic influence than most if not all the auxochromic systems which have previously been used as the parents of cyanine dyes.

During the course of this work it was observed that quinoxaline quaternary salts or methylene bases gave brilliant and unusually intense blue colours with *p*-nitrosodimethylaniline in mixtures of pyridine with acetic anhydride. These colours are almost certainly due to " aza-cyanines " (substituted anils). They are exceedingly unstable, however, and the colours faded to dull brown within 2—3 hours; their further examination was therefore abandoned.

EXPERIMENTAL.

2-(1 : 3-*Dimethylquinoxaline*)-1-(4-*dimethylaminobenzene*)*dimethincyanine* (II, R = Me).—(*a*) Dimethylquinoxaline methiodide (1 g.) was warmed gently with pyridine (4 c.c.), and the solution cooled and treated with *p*-dimethylaminobenzaldehyde (0·5 g.) in acetic anhydride (4 c.c.). The solution became immediately deep purple and then deep blue. The dye was deposited on the tube after 3—5 minutes and after 15 minutes was collected and washed with ether (yield, 1·25 g.). It was moderately soluble in water and crystallised from alcohol in minute needles, m. p. 244° (Found: N, 9·7. $C_{20}H_{22}N_3I$ requires N, 9·7%). Light absorption (alcohol): Diffuse band 5710—6170 A., max. 5950 A.

(*b*) Anhydrous 2 : 3-dimethylquinoxaline (1 g.) was warmed with slightly more than 1 mol. of methyl sulphate. As soon as reaction commenced the flask was cooled. Much heat was evolved and the product became greenish-blue and solidified. (The methosulphate is low-melting and readily soluble in water but may be purified by washing with benzene, in which it is insoluble.) To the dark product, acetic anhydride (4 c.c.) and *p*-dimethylaminobenzaldehyde (0·5 g.) in pyridine (4 c.c.) were added. The solution was gently warmed to initiate reaction and then kept. When cold the *methosulphate* of the dye was collected and washed with ether (yield, 60%). It crystallised from alcohol in needles, m. p. 182—183° (Found: N, 10·0. $C_{21}H_{25}O_4N_3S$ requires N, 10·1%).

2-(3-*Methyl*-1-*ethylquinoxaline*)-1-(4-*dimethylaminobenzene*)*dimethincyanine* (II, R = Et) was obtained in a similar manner by using ethyl sulphate in place of methyl sulphate in the preceding preparation. The *ethosulphate* of the dye separated from alcohol in needles with a green sheen, m. p. 170—171° (yield, 60% of the theoretical) (Found: N, 9·2. $C_{23}H_{29}O_4N_3S$ requires N, 9·4%).

2-(1 : 3-*Dimethylquinoxaline*)-2-(1 : 3 : 3-*trimethylindoline*)*trimethincyanine* (III, R = Me).—1 : 3 : 3-Trimethyl-2-methyleneindoline-ω-aldehyde (0·67 g.) was dissolved in pyridine and acetic anhydride (2 c.c. of each) and shaken with 2 : 3-dimethylquinoxaline methiodide (1 g.) at room temperature. After 30 minutes water (8 c.c.) was added, and the dye collected. The green residue (1·5 g., m. p. 188°) crystallised from alcohol (20 c.c.) in needles with a green lustre, m. p. 189—190° (0·9 g.) (Found: N, 8·3; I, 26·3. $C_{21}H_{26}N_3I$ requires N, 8·7; I, 26·3%). Light absorption (alcohol): Max., 6150 A. The iodide was soluble in alcohol, more difficultly in water, to give brilliant blue solutions. Solutions in ethyl acetate were mauve. The same dye was obtained in equally good yield by method (*b*) above, through the methosulphate. The methosulphate of the dye was soluble in the reaction medium and after addition of water was salted out with potassium iodide.

2-(1 : 3-*Dimethylquinoxaline*)-2-(1-*methylquinoline*)*trimethincyanine* (IX, R = Me).—Quinaldine methiodide (6 g.) and diphenylformamidine (4 g.) were intimately mixed and heated at 120° until the melt became very stiff. The cooled melt was triturated with dilute hydrochloric acid, and the insoluble yellow powder crystallised from alcohol. 2-*Anilinovinylquinoline methiodide* separated in yellow needles, m. p. 256° (decomp.) (Found: N, 7·3. $C_{18}H_{17}N_2I$ requires N, 7·2%) (cf. B.P. 344,409).

N-Methyldiphenylformamidine (21 g.), intimately mixed with 2-methylbenzoxazole ethiodide (28·9 g.), was heated at 170° for 5 minutes. The cold product was triturated with dilute hydrochloric acid, and the residual brick-red ethiodide crystallised from ethanol. 2-*Methylanilinovinylbenzoxazole ethiodide* had m. p. 212° and the yield, as in similar reactions (below), was almost quantitative (Found: N, 7·1. $C_{17}H_{17}ON_2I$ requires N, 7·1%). 2-*Methylanilinovinylbenzthiazole methiodide*, obtained in a similar manner, crystallised in needles, m. p. 244°, from acetic acid (Found: N, 6·7; I, 31·2. $C_{17}H_{17}N_2IS$ requires N, 6·8; I, 31·1%). 2-*Methylanilinovinylquinoline methiodide* was obtained similarly, except that more moderate heating (120° for 10 minutes) was sufficient. It separated from alcohol in needles, m. p. 271° (Found: I, 32·0. $C_{19}H_{19}N_2I$ requires I, 31·6%).

Of the preceding three anilinovinyl compounds, only the benzthiazole derivative was successfully hydrolysed to the aldehyde. The methiodide (25 g.) was boiled for 15 minutes with sodium hydroxide (50 g.) in water (120 c.c.). The solid residue was extracted with benzene, and the solvent removed. 1-*Methyl*-2-*methylenebenzthiazoline*-ω-*aldehyde* separated in needles (2 g.), m. p. 99°, from alcohol (Found: N, 7·3. $C_{10}H_9ONS$ requires N, 7·3%) (cf. B.P. 486,780).

2 : 3-Dimethylquinoxaline methiodide (2 g.) was boiled for 10 minutes with acetic anhydride (10 c.c.), 2-anilinovinyl-

quinoline methiodide (2 g.), and anhydrous sodium acetate (3 g.). The solution was diluted with water, and the dye salted out with sodium chloride. It separated from aqueous alcohol as a dark violet, crystalline powder (0·7 g.), m. p. >360° (Found : N, 11·6. $C_{23}H_{22}N_3Cl$ requires N, 11·8%). Light absorption (alcohol) : Max. 5990, 5550 A.; I > II.

2-(1 : 3-*Dimethylquinoxaline*)-2-(1-*methylbenzoxazole*)*trimethincyanine* (VIII, R = Me).—2 : 3-Dimethylquinoxaline (2·9 g.) was quaternised with methyl sulphate (2 c.c.) as in previous examples, and the product added to a solution of 2-methylbenzoxazole methiodide (5 g.) and diphenylformamidine (3·6 g.) in acetic anhydride (20 c.c.) which had been previously boiled for 20 minutes. The whole was treated with anhydrous sodium acetate (7 g.) and boiled for 10 minutes. The solution was cooled and decomposed with water, and the dye salted out with potassium iodide. The *iodide* was crystallised repeatedly from dilute alcohol to give a dark greenish powder decomposing above 300° (Found : N, 8·9; I, 27·7. $C_{21}H_{20}ON_3I$ requires N, 9·2; I, 27·8%).

Bis-2-(1 : 3-*dimethylquinoxaline*)*trimethincyanine* (X, R = Me).—2 : 3-Dimethylquinoxaline methodide (2 g.) was stirred with acetic anhydride (20 c.c.), and sodium formate (1 g.) added with strong cooling in the early stages so that the temperature did not exceed 20—25°. After 30 hours the solution was diluted with water and aqueous potassium iodide, and the bronze-coloured dye (0·5 g.) crystallised from acetone to give needles with a bronze lustre, m. p. 204—205° (Found : N, 11·4. $C_{23}H_{23}N_4I$ requires N, 11·6%). The dye was only slightly soluble in alcohol or water and solutions were bright clear blue. Light absorption (alcohol) : Max. 6880, 6300 A.; I > II. If the temperature was allowed to rise during the condensation, the yield of dye was usually negligible; occasionally, however, a very small amount of another blue dye, practically insoluble in boiling alcohol and crystallising in needles only from pyridine, was obtained.

2-(1-*Phenyl*-3-*methylquinoxaline*)-1-(4-*dimethylaminobenzene*)*dimethincyanine* (II, R = Ph).—*o*-Aminodiphenylamine (3 g.) was condensed with diacetyl (1·5 c.c.) without a solvent. The pasty product was diluted with acetic anhydride (8 c.c.), and 2 c.c. of a 20% solution of boron trifluoride in acetic acid added, followed by pyridine (10 c.c.) in which was dissolved *p*-dimethylaminobenzaldehyde (2·5 g.). The solution became brilliant blue at once but was kept for 24 hours and then diluted with water (50 c.c.). Sodium chloride was added; the oily deposit solidified when warmed with saturated brine. The *chloride* was obtained by repeated crystallisation from 95% alcohol as a microcrystalline powder which slowly decomposed at about 320° without melting (Found : N, 10·1; Cl, 8·8. $C_{25}H_{24}N_3Cl$ requires N, 10·4; Cl, 8·9%). It gave indigo-blue solutions in alcohol and water. Light absorption (alcohol) : 6060—5720 A., max. 4890 A.

2-(1-*Phenyl*-3-*methylquinoxaline*)-2-(1 : 3 : 3-*trimethylindoline*)*trimethincyanine* (III, R = Ph).—*o*-Aminodiphenylamine (1 g.), dissolved in ether (10 c.c.), was condensed with diacetyl (0·5 c.c.); acetic anhydride (5 c.c.) was added, and ether removed under slight vacuum. 1 : 3 : 3-Trimethyl-2-methyleneindoline-ω-aldehyde (1·1 g.) was then added with pyridine (3 c.c.), and the whole kept overnight. Water (15 c.c.) was then added, and the green crystals, m. p. 152°, collected after 24 hours. This product (1·9 g.) was the *acetate*; it was very soluble in alcohol and crystallised from water in green needles, m. p. 154° (Found : N, 8·5. $C_{31}H_{31}O_2N_3$ requires N, 8·8%). Light absorption (alcohol) : Max. 6530, 6080 A.; I > II.

Bis-2-(1-*phenyl*-3-*methylquinoxaline*)*trimethincyanine* (X, R = Ph).—*o*-Aminodiphenylamine (2 g.) was condensed with diacetyl (1 c.c.). Sodium formate (1 g.) and acetic anhydride (10 c.c.) were added, and the whole stirred at room temperature with cooling. No dye was formed until acetyl chloride (1 c.c.) was added; a bronze deposit then rapidly separated. After stirring overnight, water was added and the green crystalline *acetate* of the dye (2 g.) was collected and crystallised from water; m. p. 161° (Found : N, 10·1. $C_{35}H_{28}O_2N_4$ requires N, 10·4%). The colour is pure blue in water or alcohol, but the crude preparations are contaminated with a small amount of a green dye which is soluble not in water but in alcohol. When the acetic anhydride was diluted with aqueous sodium chloride, the *chloride* of the dye was salted out; it separated from water as a crystalline material with a bright brass-like lustre, decomposing above 300° (Found : N, 11·0. $C_{33}H_{27}N_4Cl$ requires N, 10·9%). Light absorption (alcohol) : Max. 6990, 6410 A.; I > II.

2-(1-*Phenylquinoxaline*)-2-(1 : 3 : 3-*trimethylindoline*)*trimethincyanine* (XVI).—*o*-Aminodiphenylamine (1 g.) and methylglyoxal (0·7 g.) were condensed in acetic anhydride (5 c.c.). 1 : 3 : 3-Trimethyl-2-methyleneindoline-ω-aldehyde (1·1 g.) was added, followed by a 10% solution of boron trifluoride in acetic acid (1 c.c.) and then, with cooling, by pyridine (5 c.c.). After 10 minutes the solution was diluted with concentrated aqueous potassium iodide, and the oily deposit rubbed repeatedly with more aqueous potassium iodide and finally with ether. The *iodide* of the dye was finally crystallised repeatedly from alcohol to give a microcrystalline powder, m. p. 177° after softening at 150° (Found : N, 8·1; I, 23·1. $C_{28}H_{26}N_3I$ requires N, 7·9; I, 23·4%). Solutions of the dye in water are deep blue but in alcohol are violet. Light absorption (alcohol) : Max., 6350, 5950, 5600 A.; I > II > III.

2-(1-*Phenylquinoxaline*)-1-(4-*dimethylaminobenzene*)*dimethincyanine* (XVII).—*o*-Aminodiphenylamine (1 g.) was treated with methylglyoxal (0·7 g.) in acetic anhydride (5 c.c.). The solution became slightly warm. When it was cold, *p*-dimethylaminobenzaldehyde (0·85 g.), followed by phosphorus oxychloride or acetyl chloride (2 c.c.), was added. With the first catalyst strong cooling is necessary to avoid violent reaction and acetyl chloride is therefore preferable. After 1 hour (using the former) or several hours (using acetyl chloride) the intensely green solution was diluted with aqueous potassium iodide. The resinous deposit was stirred several times with warm aqueous potassium iodide, and resin removed from the dried product by boiling with ether. The residue was crystallised repeatedly from alcohol to give the *iodide* of the dye as a microcrystalline solid with a green lustre, decomposing above 300°. The dye was practically insoluble even in warm water, but dissolved in alcohol or acetone to give dull green solutions (Found : N, 8·5. $C_{24}H_{22}N_3I$ requires N, 8·7%).

The authors thank Professor I. M. Heilbron, D.S.O., F.R.S., for his constant encouragement; they also thank I.C.I. (Dyestuffs), Limited, for grants, gifts of chemicals, and permission to publish the results.

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[*Received, June 6th*, 1942.]