105. *Quinoxaline Cyanines. Part III.*

By A. H. Cook and R. F. Naylor.

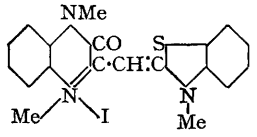
Two quinoxalinemonomethincyanines have been obtained, but attempts to extend the series by modifying procedures which are satisfactory in other heterocyclic systems had no success.

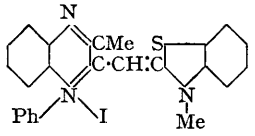
Several quinoxalines carrying reactive methyl groups have been condensed with ethyl oxalate, and the resulting pyruvic esters or acids converted into diquinoxalinylmethanes by reaction with aromatic *o*-diamines. Although it was not possible to quaternise these compounds and so obtain monomethincyanines, the stability of

the diquinoxalinylmethanes is of interest and the striking colours of their acid solutions are probably indicative of the colour of the cyanines, which still remain to be prepared.

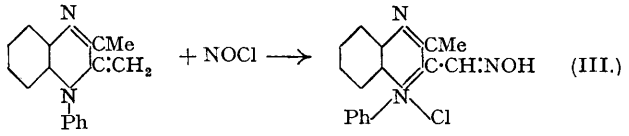
QUINOXALINETRIMETHINCYANINES have already been prepared (Part I, J., 1942, 710) and it was desirable to see whether the bathochromic influence of quinoxaline nuclei extended to monomethincyanines.

The dye (I) was obtained very readily from quaternised 3-keto-2 : 4-dimethyl-3 : 4-dihydroquinoxaline and the methiodide of 2-benzthiazyl methyl sulphide. A similar reaction with 1-phenyl-3-methyl-2-methylene-1 : 2-dihydroquinoxaline gave two products in small yield, one the dye (II), the other unidentified.

(I.) 

 (II.)

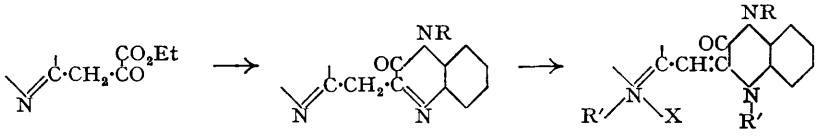
Quinoxaline salts or the corresponding methylene bases were found to react readily with nitrosyl chloride to give oxime salts (cf. B.P. 359,753). We were, however, unsuccessful in condensing (III) with a second quinox-

 (III.)

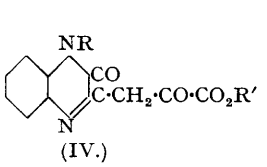
aline or other heterocyclic quaternary salt, nor in spite of the production of deep red colours could any pure cyanine be obtained by a similar single-stage process without isolation of (III). A related procedure using amyl nitrite (D.R.-P. 459,616) was no more satisfactory.

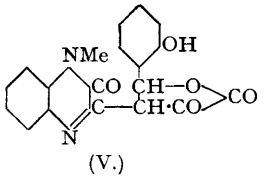
The two quinoxaline cyanines prepared were red, whereas other known monomethincyanines are much paler, so here also the quinoxaline system is strongly bathochromic.

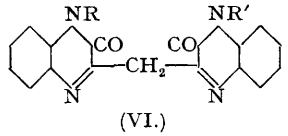
Quinaldine and similar compounds carrying a reactive methyl group condense with ethyl oxalate to give substituted pyruvates (Wislicenus and Kleisinger, *Ber.*, 1897, **30**, 1479; 1909, **42**, 1141; cf. Borsche and co-workers, *Annalen*, 1936, **526**, 22; 1938, **534**, 56; 1939, **537**, 39). We hoped to utilise such pyruvates to obtain substituted methanes and thence by quaternisation to prepare quinoxalinemonomethincyanines :



2 : 3-Dimethylquinoxaline, 3-keto-2-methyl-, 3-keto-2 : 4-dimethyl-, and 3-keto-4-phenyl-2-methyl-dihydroquinoxaline were condensed with ethyl oxalate and potassium ethoxide in presence of pyridine to give the expected pyruvic esters rapidly and in excellent yield. The constitution of these products was placed beyond doubt by the reactions of the typical ester (IV; R = Me, R′ = Et). Thus when its potassio-derivative was boiled with ethanol, and the solution just acidified, the free acid (IV, R′ = H) was obtained. Again, the ester contained both a carbonyl and a reactive methylene group and was characterised as its salicylaldehyde condensation product and its *oxime*; the former was not the stilbene derivative but the *lactone* (V), the pyruvates

 (IV.)

 (V.)

 (VI.)

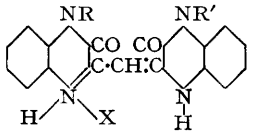
studied by Borsche yielding similar products. No success attended attempts to condense 3-keto-2-methyl-dihydroquinoxaline with ethyl oxalate. Similar non-reactivity of the NH-compound compared with *N*-alkyl homologues in this reaction has been noted by Borsche and his co-workers. Failure must also be recorded of attempts to use α-picoline, 4 : 5-diphenyl-2-methyliminazole, and 1-phenyl-3-methyl-5-pyrazolone in this reaction, though 4 : 5-diphenyl-2-methyloxazole behaved normally and gave a pyruvic ester.

The acid (IV; R = Me, R′ = H) or its ester reacted with *o*-phenylenediamine in absence of solvent at 180° to give the *compound* (VI; R = Me, R′ = H), less satisfactorily obtained by condensation in alcoholic hydrochloric acid. This compound reacted exceedingly slowly with diazomethane, but the symmetrical N-*methyl* compound (VI; R = R′ = Me) was prepared by condensing (IV; R = Me, R′ = Et) with *N*-methyl-*o*-phenylenediamine. Finally, reaction of (IV; R = Me, R′ = H), but not its ester, with *o*-aminodiphenylamine and a trace of ammonium chloride at 150° afforded (VI; R = Me, R′ = Ph). The reaction failed even on much stronger heating when ammonium chloride was omitted; later it was found that this condensation and other similar ones proceeded exceedingly well in fused phenol.

By similar means (IV; R = Ph, R′ = Et) was condensed with *o*-phenylenediamine and *N*-methyl-*o*-phenyl-

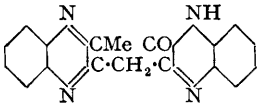
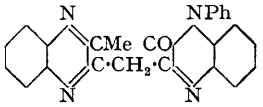
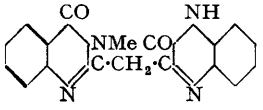
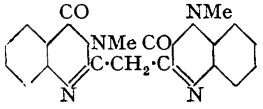
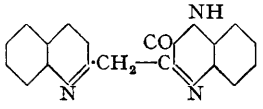
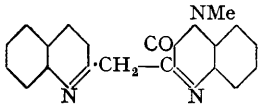
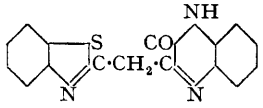
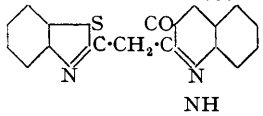
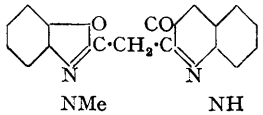
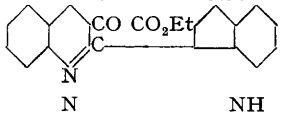
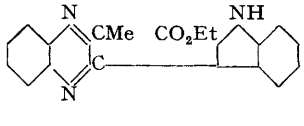
enediamine to give (VI; R = Ph, R′ = H and Me, respectively). The identity of the products from *N*-methyl-*o*-phenylenediamine with (VI; R = Me, R′ = Ph) above provided proof of the constitutions suggested.

Many attempts were made to quaternise compounds of type (VI), even boiling methyl sulphate or *p*-toluenesulphonate alone or in nitrobenzene as diluent being tried. In every case intense colours were observed, but these were destroyed on dilution with water and the original compounds were recovered. The colours appear to be due to salts formed with a small amount of free acid, for they were paralleled by colours in sulphuric acid. All dissolved in concentrated acid to give relatively pale solutions which became intensely coloured on dilution or warming. The colours, shown in the table, disappeared on addition of much water and the original diquinoxalinylmethanes were precipitated if the treatment with acid had not been too drastic. When both heterocyclic nuclei were quinoxaline (oxygenated or non-oxygenated), the disubstituted methanes were extraordinarily stable in concentrated sulphuric acid, retaining in boiling solutions their brilliant blue or permanganate colour without a trace of carbonisation occurring. These colours, it is suggested, are due to salts which may be compared with monomethincyanines. The bases dissolved in alcoholic hydrogen chloride to give similar deep colours and from the solutions dark solids could be precipitated with ether; the composition of these indicated them to be monohydrochlorides.



The table includes further compounds with a variety of heterocyclic systems. In obtaining the derivatives of quinazoline, advantage was taken of the reactivity of the *C*-methyl group in 2 : 3-dimethyl-4-quinazolone to convert this compound into the corresponding pyruvic ester; most of the others were obtained by the methods developed above; the indole derivatives were prepared by the Fischer method from the phenylhydrazones of the appropriate pyruvic esters.

None of the compounds containing one quinoxaline nucleus except the indoles gave such characteristic intense colours in sulphuric acid as the diquinoxalinylmethanes. After being heated with sulphuric acid, the colour of the diquinoxalinylmethanes gave place to a weaker but still bright orange on addition of water or alkali; sulphonation alone seemed to have occurred. When glycerol was added to the sulphuric acid solution in the hot, the red colour gave place to an equally intense blue-green, but these colours were less stable and soon disappeared with carbonisation.

Compound.	Colour of solid.	Colour in hot sulphuric acid.
(VI; R = Me, R′ = H)	Scarlet	Crimson to violet
(VI; R = Me, R′ = Ph)	Orange	Magenta
(VI; R = Ph, R′ = H)	Orange	Magenta
(VI; R = R′ = Me)	Scarlet	Violet
(VI; R = R′ = Ph)	Orange	Magenta
	Orange-red	Blue
	Orange	Blue
	Yellow	Pale yellow
	Pale orange	Pale yellow
	Crimson-red	Light red
	Red	Light red
	Light orange	Orange
	Yellow	Orange
	Dull yellow	Orange
	Dull yellow	Blue-red
	Buff	Deep blue-maroon

Experimental.

[2-(1-*Methylbenzthiazole*)][2-(3-*keto*-1 : 4-*dimethyl*-3 : 4-*dihydroquinoxaline*)]*monomethincyanine Iodide* (I).—2-Keto-1 : 3-dimethyl-1 : 2-dihydroquinoxaline (1 g.) was quaternised by heating with methyl sulphate (2 c.c.) at 180° for 30 mins., 2-methylbenzthiazyl sulphide methiodide (1·85 g.) and pyridine (15 c.c.) added, and the whole boiled for 10 minutes. The *iodide* (1·65 g.) crystallised from acetic acid in orange-red needles, m. p. 242°, which were only slightly soluble in acetone or ethanol (Found: C, 48·6; H, 3·7; N, 9·0; I, 27·3. $C_{19}H_{18}ON_3IS$ requires C, 49·2; H, 3·7; N, 9·1; I, 27·5%).

[2-(1-*Methylbenzthiazole*)][2-(1-*phenyl*-3-*methylquinoxaline*)]*monomethincyanine Iodide* (II).—*o*-Aminodiphenylamine (1·5 g.) and diacetyl (0·75 g.) were condensed in cold ethereal solution. The solvent was removed, the methylene base

diluted with ethanol (10 c.c.), 2-methylbenzthiazyl sulphide methiodide (2·6 g.) added, and the whole boiled for 10 mins. The *iodide*, which separated on cooling and contained a more soluble, unidentified compound, crystallised from ethanol in small red needles, m. p. 188° (Found: C, 56·8; H, 4·2. $C_{24}H_{20}N_3IS$ requires C, 56·5; H, 3·9%).

1-*Phenyl*-3-*methylquinoxaline*-2-*aldoxime Chloride* (III).—*o*-Aminodiphenylamine (4·5 g.) and diacetyl (2·2 g.) were condensed in absence of solvent and the methylene base was dissolved in carbon tetrachloride and added to nitrosyl chloride (1 mol.) in cold carbon tetrachloride. After some hours the *chloride* was collected; it crystallised from ethanol, on addition of ether, in small brown needles, m. p. 283° (Found: N, 14·3. $C_{16}H_{14}ON_3Cl$ requires N, 14·0%).

To the solution prepared from potassium (7·5 g.) in ethanol (36 c.c.) was added 2-keto-1 : 3-dimethyldihydroquinoxaline (17·4 g.) dissolved in pyridine (90 c.c.), followed by ethyl oxalate (13 c.c.). The mixture reddened and set solid almost at once. The liquid was decanted, the potassio-compound washed with ether and shaken with 10% hydrochloric acid (60 c.c.), and the orange ester collected and dried at 80° (yield, 11 g.). *Ethyl* 2-*keto*-1-*methyl*-1 : 2-*dihydroquinoxaline*-3-*pyruvate* (IV; R = Me, R′ = Et) separated from ethanol in yellow needles, m. p. 170° (Found: C, 61·1; H, 5·15; N, 10·0. $C_{14}H_{14}O_4N_2$ requires C, 61·3; H, 5·1; N, 10·2%). The *oxime* (0·9 g.), prepared by refluxing the ester (1·2 g.) with hydroxylamine hydrochloride (0·75 g.) and potassium acetate (1 g.) in ether (25 c.c.) for 4 hours, crystallised from 30% ethanol in needles, m. p. 158·5° (Found: N, 14·5. $C_{14}H_{15}O_4N_3$ requires N, 14·5%). The pyruvate (1·8 g.), salicylaldehyde (0·6 c.c.), and piperidine (4 drops) were mixed in ether (5 c.c.), solvent removed by evaporation, and the residue heated at 150—170° for 1 hour. The product was boiled with ethanol (100 c.c.), and the residue crystallised from decalin–nitrobenzene (2 : 1); the *condensation product* (V) had m. p. 228° (Found: N, 8·2. $C_{19}H_{14}O_5N_2$ requires N, 8·0%). From a hot solution of the pyruvic ester (0·5 g.) and phenylhydrazine (0·25 g.) in 50% acetic acid the *phenylhydrazine* (0·6 g.) separated in orange-red crystals, m. p. 202° after recrystallisation from amyl acetate (Found: N, 15·4. $C_{20}H_{20}O_3N_4$ requires N, 15·4%). The potassio-compound of the pyruvate (2 g.) was refluxed with ethanol (25 c.c.) for 4 hours. The residue was dissolved in water, and the filtered solution acidified with 2N-hydrochloric acid. The precipitated 2-*keto*-1-*methyl*-1 : 2-*dihydroquinoxaline*-3-*pyruvic acid* (IV; R = Me, R′ = H) was purified by solution in alkali bicarbonate and reprecipitation with acid; it then had m. p. 218° and separated from 35% ethanol as an orange microcrystalline powder (Found: N, 11·6. $C_{12}H_{10}O_4N_2$ requires N, 11·4%). The same acid was obtained by acidifying the potassio-compound in the original condensation with 10% hydrochloric acid at 60°.

2-Keto-1-methyldihydroquinoxaline-3-pyruvic ester (2 g.) in hot ethanol (75 c.c.) was added to *o*-phenylenediamine (0·8 g.) in 50% ethanol (8 c.c.) and a small excess of 32% hydrochloric acid. 3-(2-*Keto*-1-*methyldihydroquinoxalinyl*)-3-(2-*ketodihydroquinoxalinyl*)*methane* (VI; R = Me, R′ = H) was precipitated on boiling and was filtered from the cooled solution (yield, 1·7 g.). It separated from aqueous pyridine in dull orange needles, m. p. 355° (Found: N, 17·7. $C_{18}H_{14}O_2N_4$ requires N, 17·7%). The same compound was obtained by heating equimolecular quantities of the pyruvic ester and *o*-phenylenediamine alone for 40 mins. at 150—170°, or with phenol (1 mol.) at 100°; the yields were quantitative. 2-Keto-1-methyldihydroquinoxaline-3-pyruvic acid (9·0 g.), *N*-methyl-*o*-phenylenediamine (4·5 g.), and phenol (3 g.) were heated at 95° for 40 mins. The product, *bis*-3-(2-*keto*-1-*methyl*-1 : 2-*dihydroquinoxalinyl*)*methane*, was ground and thoroughly extracted with hot ethanol and then with ether (yield, 10·5 g.). It separated from nitrobenzene in microcrystalline form, m. p. 331° (Found: C, 68·6; H, 4·85; N, 16·9. $C_{19}H_{16}O_2N_4$ requires C, 68·7; H, 4·8; N, 16·9%). Ketomethyldihydroquinoxalinepyruvic ester (6·3 g.), *o*-aminodiphenylamine (4·7 g.), and ammonium chloride (0·2 g.) were intimately mixed and heated for 50 mins. at 150°. The product was triturated with ethanol, and the residue (6·2 g.) recrystallised from decalin–nitrobenzene; 3-(2-*keto*-1-*methyldihydroquinoxalyl*)-3-(2-*keto*-1-*phenyldihydroquinoxalyl*)-*methane* (VI; R = Me, R′ = Ph) separated in small orange needles, m. p. 300° (Found: N, 14·0. $C_{24}H_{18}O_2N_4$ requires N, 14·2%).

2-Keto-1-phenyl-3-methyldihydroquinoxaline (25 g.) in pyridine (150 c.c.) at 60° was treated with ethyl oxalate (14 c.c.) and then with a mixture of pyridine (20 c.c.) and ethanol (39 c.c.) in which potassium (8 g.) had been dissolved. The yellow solid was collected, decomposed with cold 2N-hydrochloric acid (1500 c.c.), and the orange ester (18 g.) collected. *Ethyl* 2-*keto*-1-*phenyl*-1 : 2-*dihydroquinoxaline*-3-*pyruvate* (IV; R = Ph, R′ = Et) crystallised from ethanol in needles, m. p. 224° (Found: C, 67·5; H, 4·9; N, 8·5. $C_{19}H_{16}O_4N_2$ requires C, 67·9; H, 4·75; N, 8·3%). By acidifying the potassio-compound with warm 2N-hydrochloric acid, 2-*keto*-1-*phenyldihydroquinoxaline*-3-*pyruvic acid* (IV; R = Ph, R′ = H) was obtained; it separated from ethanol as an orange microcrystalline powder, m. p. 226° (decomp.) (Found: N, 9·1. $C_{17}H_{12}O_4N_2$ requires N, 9·1%). The ester (6·7 g.) and *o*-phenylenediamine (2·2 g.) were heated together for 30 mins. at 150° to yield 3-(2-*keto*-1-*phenyldihydroquinoxalyl*)-3-(2-*ketodihydroquinoxalyl*)*methane* (VI; R = Ph, R′ = H); this, washed with ethanol and recrystallised from nitrobenzene, formed orange needles (6 g.), m. p. 372° (Found: N, 14·4. $C_{23}H_{16}O_2N_4$ requires N, 14·7%). The ester (13·4 g.) and *N*-methyl-*o*-phenylenediamine (4·9 g.) were condensed in phenol (3 g.) as in the previous preparation. 3-(2-Keto-1-phenyldihydroquinoxalyl)-3-(2-keto-1-methyldihydroquinoxalyl)methane (VI; R = Ph, R′ = Me) was obtained (yield, 7·5 g.) identical with (VI; R = Me, R′ = Ph) described above.

Potassium (8 g.) was dissolved in ethanol (40 c.c.), the solution mixed with ether (50 c.c.) and ethyl oxalate (24 c.c.) in ether (26 c.c.) added, followed by 2 : 3-dimethyl-4-quinazolone (17·4 g.) dissolved in ethanol (35 c.c.) and ether (15 c.c.); the whole was left overnight in the cold. The yellow potassio-compound was collected and shaken for 1 hour with ice-cold 5% hydrochloric acid (120 c.c.). *Ethyl* 3-*methyl*-4-*quinazolonyl*-2-*pyruvate* (yield, 18 g.) was recrystallised from ethanol; it had m. p. 173° (Found: C, 61·3; H, 5·1; N, 10·2. $C_{14}H_{14}O_4N_2$ requires C, 61·2; H, 5·1; N, 10·2%). The *phenylhydrazone*, pale yellow needles from ethanol, had m. p. 168—169° (Found: C, 66·2; H, 5·5; N, 15·4. $C_{20}H_{20}O_3N_4$ requires C, 65·9; H, 5·5; N, 15·4%). An intimate mixture of the ester (2·8 g.) and *o*-phenylenediamine (1·4 g.) was heated at 120° for 10 mins., and the solid product twice extracted with boiling ethanol. The residual 2-(3-*methyl*-4-*quinazolonyl*)-3-(2-*ketodihydroquinoxalyl*)*methane* (3·2 g.) crystallised from nitrobenzene in long yellow needes, m. p. 354° (Found: C, 68·0; H, 4·4; N, 17·4. $C_{18}H_{14}O_2N_4$ requires C, 68·0; H, 4·4; N, 17·6%). When *N*-methyl-*o*-phenylenediamine was substituted for *o*-phenylenediamine in the preceding preparation, 2-(3-*methyl*-4-*quinazolonyl*)-3-(2-*keto*-1-*methyldihydroquinoxalyl*)*methane* was obtained; it separated from nitrobenzene–decalin (1 : 1) in long yellow needles, m. p. 293° (Found: N, 16·6. $C_{19}H_{16}O_2N_4$ requires N, 16·8%). The corresponding 2-(3-*methyl*-4-*quinazolonyl*)-3-(2-*keto*-1-*phenyldihydroquinoxalyl*)*methane* (from *o*-aminodiphenylamine) separated from nitrobenzene–decalin in yellow needles, m. p. 265° (Found: N, 14·2. $C_{24}H_{18}O_2N_4$ requires N, 14·2%).

Ethyl 3-methylquinoxaline-2-pyruvate phenylhydrazone (2·5 g.) was ground with zinc chloride (5 g.), and the mixture heated at 140° for 5 mins. The dark melt was extracted with dilute sulphuric acid, and the residue crystallised from ethanol. It was further purified by adsorbing impurities on a short column of alumina from ethanol solution, and the recovered material crystallised from light petroleum. 2-*Carbethoxy*-3-(3′-*methyl*-2′-*quinoxalyl*)*indole* had m. p. 153° (Found: N, 12·7. $C_{20}H_{17}O_2N_3$ requires N, 12·7%). 2-*Carbethoxy*-3-(2′-*keto*-1′-*methyldihydro*-3′-*quinoxalyl*)*indole*, prepared similarly from the phenylhydrazone of 2-keto-1-methyldihydroquinoxaline-3-pyruvic ester, formed fine needles, m. p. 246°, from ethyl acetate (Found: N, 11·8. $C_{20}H_{17}O_3N_3$ requires N, 12·1%).

(VI; R = Me, R′ = Ph) (1 g.) was added to a warm solution of excess of hydrogen chloride in ethanol (50 c.c.), and the filtered solution treated with dry ether (400 c.c.). 3-(2-*Keto*-1-*methyldihydroquinoxalyl*)-3-(2-*keto*-1-*phenyldihydroquinoxalyl*)*methane hydrochloride* was precipitated as a dark purple, microcrystalline powder (0·3 g.). After

drying at room temperature, it had m. p. 290° (decomp.) (Found : Cl, 8·2. $C_{24}H_{18}O_2N_4$,HCl requires Cl, 8·17%). 3-(2-*Keto*-1-*methyldihydroquinoxalyl*)-3-(2-*ketodihydroquinoxalyl*)*methane hydrochloride* was prepared by allowing a solution of the parent base (1 g.) to stand for 2 weeks with alcoholic hydrogen chloride. The solid was collected and washed with dry ether. It formed a dark purple powder (1 g.) decomposing above 300° (Found : N, 15·5; Cl, 9·2. $C_{18}H_{14}O_2N_4$,HCl requires N, 15·8; Cl, 10·0%).

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