225. *β-Cycloylpropionitriles. Part II. Conversion into Bis-2-(5-cyclylpyrrole)azamethin Salts.*

By Edward B. Knott.

The blue dyes obtained by heating β-cycloylpropionitriles with hydroxylamine salts are *salts* of bis-2-(5-cyclylpyrrole)azamethin (II; R = cyclyl, R′ = H). One of the dyes (II; R = Ph, R′ = H) was also prepared from α-cyano-β-benzoylpropionic acid and hydroxylamine hydrochloride. Bis-2-(3 : 5-diphenylpyrrole)azamethin (II; R = R′ = Ph) (Rogers, *J.*, 1943, 590) was prepared similarly from β-benzoyl-α-phenylpropionitrile. The new dyes exhibit remarkable colour reactions with concentrated sulphuric acid.

The remarkable stability of the 2-bis-(3 : 5-diarylpyrrole)azamethins (II; R = R′ = aryl), discovered by Rogers (*loc. cit.*; B.P. 544,101) and less accurately named 2 : 2′ : 4 : 4′-tetra-aryldipyrroazamethins by him, prompted the search for similarly constituted products, simpler in nature and of higher general solubility.

(I.)

(II.)

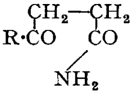
One of the methods employed by Rogers for the preparation of the above dyes consisted in heating β-aroyl-α-arylpropionitriles (I; R, R′ = aryl) with ammonium formate in the presence of air, whilst Davies and Rogers (*J.*, 1944, 126) heated the same nitriles with formamide to obtain formylated 2-amino-3 : 5-diarylpyrroles, which can be used as intermediates for the above dyes. Although Rogers had not treated the simple β-aroylpropionitriles (I; R = aryl, R′ = H) with either reagent in the expectation of obtaining dyes (II; R = aryl, R′ = H), he had found that γ-nitrobutyrophenone gave no dye of this type under conditions which, when applied to γ-nitro-β-arylbutyrophenones, gave good yields of dye (II; R, R′ = aryl).

Since a variety of β-cycloylpropionitriles were readily available by the method described in Part I (preceding paper), an investigation of their possible use as intermediates was undertaken.

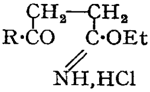
On heating β-benzoylpropionitrile with ammonium formate in the presence of air at various temperatures, no trace of dye formation could be observed, nor could any formylated 2-amino-5-phenylpyrrole be isolated from a formamide melt. These negative results thus fell into line with the behaviour of γ-nitrobutyrophenone (Rogers, *loc. cit.*). It appeared, therefore, that dye formation required, not only a β-aroyl group in the starting nitrile (where R = Me, R′ = aryl, no dye was formed; Rogers, *loc. cit.*, p. 595), but also an α-substituent (aryl?).

It is known, however (Biedermann, *Ber.*, 1891, **24**, 4071; Tiemann, *ibid.*, p. 4077), that β-benzoylpropionamide (III; R = Ph) shows a tendency on fusion or dissolution to give a blue coloration, and this was also observed (see Part I) on melting or recrystallising β-*p*-hydroxybenzoylpropionamide. It was also noticed that, in attempting to form the amidine from ethyl β-benzoylpropimino-ether hydrochloride (IV; R = Ph) by solution in alcoholic ammonia and also on boiling (IV) with aqueous ammonia, a blue colour developed. There seemed, therefore, the possibility that this colour could be attributed to the formation of dyes of type (II; R′ = H).

(III.)



$$R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NH_2$$



$$R{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}C(OEt){:}NH,HCl$$

(IV.)

It is also known (Klobb, *Ann. Chim. Phys.*, 1897, **10**, 184; Bougault, *ibid.*, 1908, **15**, 504) that α-cyano-β-benzoylpropionic acid (I; R = Ph, R′ = CO_2H) gives a blue dye on evaporation of solutions of its salts or on acidification of an alkaline solution of the acid which has been in contact with air. Klobb also reported that the dye could be sublimed with some decomposition, the vapours being red. This stability to heat is possessed to a greater degree by Rogers's dyes. It seemed therefore possible that this dye also might belong to type (II), in which R′ is a carboxyl group.

Attempts to prepare and purify the dyes from (III) or (IV) in sufficient quantities for analysis were unsuccessful, but the dye from (I; R = Ph, R′ = CO_2H) was obtained in a small amount. It was insoluble in strong alkalis, but dissolved in concentrated sulphuric acid to give a pale yellow-green solution which gave blue flocks on pouring into water. In aqueous pyridine it was decolorised by sodium dithionite. It was almost insoluble in most solvents but dissolved in nitrobenzene or pyridine giving a magenta solution. Analysis suggested the formula $C_{20}H_{14}O_2N_2$ which rules out the possibility of its belonging to the dipyrroazamethin class of dye. It is also readily prepared in low yield from β-benzoylpropionamide by a different method, and the proposed structure and mechanism of formation are discussed later. The non-identity of these dyes with dipyrroazamethins was disappointing, and work on the preparation of (II; R′ = H) was about to be abandoned when, by chance, an unusual reaction was observed. Whilst engaged on the preparation of various derivatives of the β-aroylpropionitriles (I; R′ = H) for their characterisation, difficulty was encountered in the formation of their oximes. Thus, β-benzoylpropionitrile (I; R = Ph, R′ = H) failed to give an oxime with either hydroxylamine acetate or the base itself on refluxing in ethyl alcohol, most of the original nitrile being recovered unchanged. On refluxing an alcoholic solution of the nitrile with hydroxylamine hydrochloride, however, the mixture darkened and a brilliant blue coloration developed. When a large excess of the hydroxylamine salt was employed the dye crystallised during the refluxing, giving an almost solid mass of needles. The dye was slightly soluble in boiling water, the solution giving an immediate precipitation of silver chloride on addition of silver nitrate. It was soluble in alcohols, acetone, and pyridine. Analysis suggested the formula $C_{20}H_{15}N_3,2HCl$. Its alcoholic solution when poured into water gave magenta flocks soluble in alcohol to a blue solution and which on purification gave a second blue dye of the formula $C_{20}H_{15}N_3,HCl$. Attempts to isolate the base were fruitless since, although it had some stability in solution, it readily decomposed on attempted isolation. The *dye salts* were very stable to boiling concentrated hydrochloric acid, dissolved in concentrated sulphuric acid to give a blue solution, and were reduced to a colourless leuco-compound by sodium dithionite. The leuco-compound was reoxidised by aerial oxygen to a blue dye. The salts did not sublime on heating under reduced pressure. Apart from the last property (which might be expected of the salts) the behaviour of these dyes is similar to that of Rogers's dye (II; R = R′ = Ph), and the analysis agrees well with their being the *dihydrochloride* and *monohydrochloride* of bis-2-(5-phenylpyrrole)azamethin (II; R = Ph, R′ = H). Degradation experiments with hydriodic acid, and with an acetic anhydride–sodium acetate mixture which discharged the colour, did not lead to any definite products. Rogers (*loc. cit.*) proved the constitution of his dyes by an alternative synthesis which consisted in the condensation of 3 : 5-diphenylpyrrole with 2-nitroso-3 : 5-diphenylpyrrole. Nitrosation of 2-phenylpyrrole, however, either with nitrous acid or with alkaline amyl nitrite, failed to give a pure nitroso-derivative. The dark green solid obtained when employing nitrous acid gave a magenta dye on heating with 2-phenylpyrrole in acetic anhydride–acetic acid mixtures but not in sufficient quantities for isolation. Since 2-phenylpyrrole is readily converted into a magenta dye in the presence of mineral acids and acetic anhydride, it is possible that the green solid causes dye formation by virtue of its being a hydrochloride. Alternatively, if nitrosation occurs in the β-position, as is usual with pyrroles (cf. Fischer and Orth, " Die Chemie des Pyrrols," Vol. I, p. 104), the interaction of 4-nitroso-2-phenylpyrrole hydrochloride with 2-phenylpyrrole might well lead to a magenta dye. The structure of the dye was proved beyond reasonable doubt, however, by obtaining analogously bis-2-(3 : 5-diphenylpyrrole)azamethin (II; R, R′=Ph) from β-benzoyl-α-phenylpropionitrile and hydroxylamine hydrochloride. The reaction proceeded best in boiling butanol to give the unstable dye salt, or in ethylene glycol at 120° to give the dye base. It was also found to proceed rapidly to give a low yield of dye on using formamide as solvent. The salt rapidly lost hydrogen chloride on contact with the atmosphere. The base had all the properties of the dye prepared according to Rogers (*loc. cit.*) and analysis confirmed the identity.

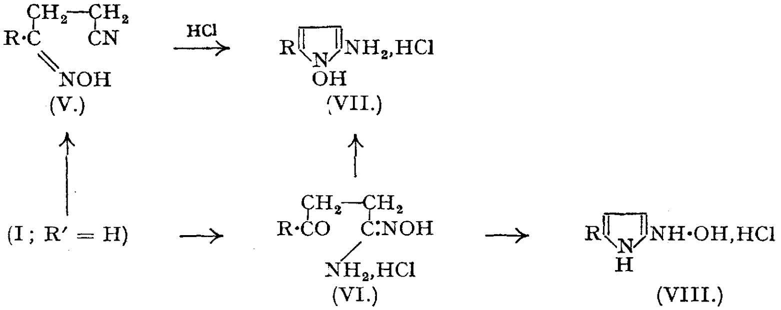
The instability of the new dye base may explain the non-formation of dye on heating γ-nitrobutyrophenone and ammonium formate (Rogers, *loc. cit.*), although further attempts at dye formation by this reaction in the presence of salts such as ammonium chloride or hydroxylamine hydrochloride also failed.

β-Benzoylpropionitrile and hydroxylamine sulphate gave *bis-2-(5-phenylpyrrole)azamethin sulphate.*

The reaction was then applied to a variety of β-cycloylpropionitriles in order to determine its scope. In every case β-aroylpropionitriles gave the required dye. β-2-Thienoylpropionitrile (I; R = 2-C_4H_3S, R′ = H) gave the corresponding dye in low yield, but β-2-furoylpropionitrile and 2-benzfuryl 2-cyanoethyl ketone gave only brown solutions on similar treatment.

On heating α-cyano-β-benzoylpropionic acid (I; R = Ph, R′ = CO_2H) with alcoholic hydroxylamine hydrochloride a blue, alkali-insoluble dye resulted. Its analysis, and physical and chemical properties, showed that it was identical with the dye obtained from β-benzoylpropionitrile. The loss of carbon dioxide took place before dye formation occurred, a copious evolution being observed on heating the reactants at 95° in butenol. It is possible that the substituted pyrrole-β-carboxylic acid which may be an intermediate in the dye formation, like other such acids, is readily decarboxylated (cf. Ciamician, *Ber.*, 1880, **13**, 2235; 1881, **14**, 1054).

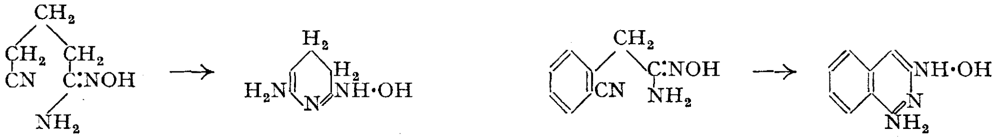
The mechanism of the reaction is obscure, since no intermediates could be isolated. The first stage reaction could take place in two ways, either by oxime formation (V), or by hydroxylamine addition to the nitrile group to give an amidoxime (VI). At this stage, cyclisation in two ways might occur to give either 2-amino-1-hydroxy-5-R-pyrrole (VII) or 2-hydroxylamino-5-R-pyrrole (VIII) hydrochlorides.



(V.) (VII.) (I; R′ = H) (VI.) (VIII.)

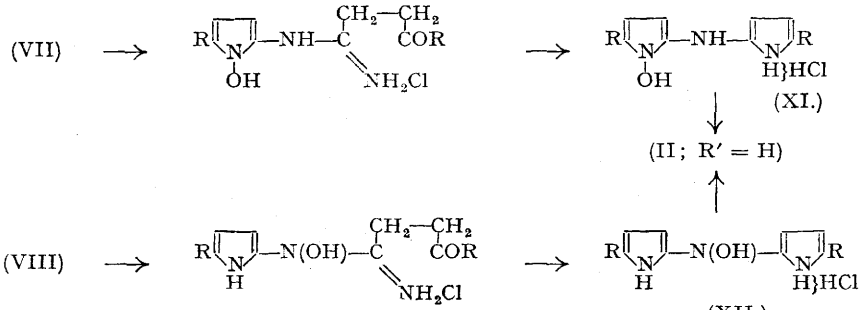
Oxime formation would appear to be the natural step, but it is significant that under no conditions could an oxime be isolated. It is well known (Nordmann, *Ber.*, 1884, **17**, 2747; Tiemann, *Ber.*, 1884, **17**, 126, 1685; 1886, **19**, 1475; 1889, **22**, 2391, 2942, etc.) that aliphatic nitriles, particularly those which are also readily hydrolysable, react with hydroxylamine or its salts to yield amidoximes. Thus the formation of (VI) is quite feasible, although under conditions used by Tiemann no product could be isolated.

There are no indications of the second-stage reaction, although it is known that γ-diketones will react with hydroxylamine to give substances analogous to (VII) (Knorr, *Annalen*, 1886, **236**, 296). It is also known that hydroxylamine will react with 1 : 3-dicyanopropane (Tiemann, *Ber.*, 1889, **22**, 2945; Biedermann, *ibid.*, p. 2967) or *o*-cyanobenzyl cyanide (Eichelbaum, *ibid.*, p. 2973) to give substances which are not the expected amidoximes, as they are insoluble in alkali. It is possible that cyclisation occurred, not as proposed by the above authors, but so as to give a dihydropyridine (IX) and an *iso*quinoline (X).



(IX.) (X.)

Such ring closures would then be analogous to the formation of (VIII). The third-stage reaction could proceed from either (VII) or (VIII) by addition of a further nitrile molecule followed by cyclisation and elimination of water to give the dye.



(XI.) (II; R′ = H) (XII.)

The precipitation of the dihydrochloride, which is more soluble in alcohol than the monohydrochloride, is difficult to explain, since it is unlikely that the dye is a stronger base than hydroxylamine.

Rogers (*loc. cit.*) found that 2-amino-3 : 5-diphenylpyrrole is readily oxidised to the azamethin, but such a mechanism for dye formation cannot be applied here, since no oxygen is present. He found also that 2-nitroso-3 : 5-diphenylpyrrole gives the azamethin on heating, and it is possible that (VIII) may also undergo self-condensation with the elimination of water and hydroxylamine.

All the dye salts gave similar blue solutions in organic solvents but differed in colour in the crystalline state. Striking differences, however, were shown in their behaviour towards concentrated sulphuric acid. The different colours given in hot and cold sulphuric acid and on precipitating the dye from the latter with water allow the identification of nearly all the dyes so far prepared (see Table I).

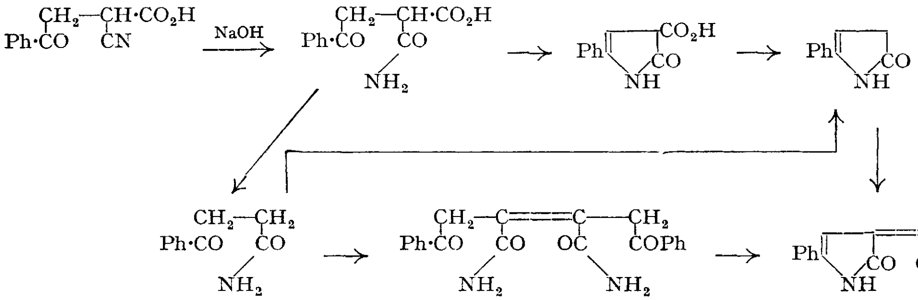
TABLE I.

II.	Cold H_2SO_4.	Addition to water.	Hot H_2SO_4.
R′ = H, R =			
Phenyl	Blue *	Magenta	Green → yellow
p-Tolyl	Green	Blue	Yellow → brown
p-Chlorophenyl	Blue	Blue	Green → yellow → brown
p-Bromophenyl............	Blue	Blue	Yellow → red-yellow
p-Hydroxyphenyl.........	Orange	Magenta	Red
p-Methoxyphenyl	Orange	Blue-green	Red
m-Hydroxyphenyl	Purple	Magenta	Blue → yellow
m-Methoxyphenyl	Purple → blue	Magenta	Blue → yellow
3 : 4-Dimethoxyphenyl	Orange	Blue	Brown → red → brown
1-Naphthyl	Yellow → purple → blue	Blue	Blue → green → yellow
2-Naphthyl	,, ,, ,,	Blue	,, ,, ,,
2-Thienyl	Green	Blue	Red → yellow
R = R′ = Phenyl	Blue	Blue	Green → yellow

* Sulphate gave green solution.

As stated above, the dye obtained by Klobb from α-cyano-β-benzoylpropionic acid does not belong to the azamethin class. Apart from the analysis figures, the pale colour it gives in concentrated sulphuric acid is quite different from the deep colours given by (II). An alternative synthesis was found whilst experimenting with β-benzoylpropionamide with a view to the preparation of the dye observed on fusing the latter. Whereas alcoholic hydroxylamine salts did not give any dye on refluxing them with the amide, yet on replacing the alcohol by formamide and heating to 120° the latter reacted suddenly with the hydroxylamine hydrochloride (shown by separate experiment) with the evolution of ammonia, probably due to the formation of a hydroxamic acid (cf. Hoffmann, *Ber.*, 1889, **22**, 2854), and a secondary reaction caused the separation of a crystalline dye. The same dye was formed in very small amounts when the hydroxylamine hydrochloride was omitted. The dye had all the properties of Klobb's dye and analysis confirmed the identity.

Insufficient data have been collected on the dye to prove its structure, but it is suggested that it belongs to the *iso*indigotin class (cf. Wahl and Bagnard, *Bull. Soc. chim.*, 1909, **5**, 1039; 1914, **15**, 329). Analysis agrees with its being *bis*-3-(2-*keto*-5-*phenyl*-2 : 3-*dihydropyrrolylidene*) (XIII). Its formation from (I; R = Ph, R′ = CO_2H) can be explained by hydrolysis by



(XIII.)

alkali to the amide, followed by cyclisation, decarboxylation, and oxidation, or by decarboxylation, oxidation, and cyclisation as shown. The hydroxylamine salt–formamide process involves oxidation at one stage and it is not clear how this takes place.

The same dye is also readily formed from β-benzoylpropionamide, acetamide, and hydroxylamine hydrochloride, and the β-benzoylpropionamide may be replaced by the acid or ester. Lævulic acid did not give any dye under similar conditions.

EXPERIMENTAL.

(Microanalyses are by Drs. Weiler and Strauss, Oxford; m. p.s are uncorrected.)

Bis-2-(5-phenylpyrrole)azamethin Dihydrochloride.—(*a*) β-Benzoylpropionitrile (15·9 g., 0·1 mol.), hydroxylamine hydrochloride (28 g., 0·4 mol.), and industrial methylated spirit (150 c.c.) were refluxed for 2 hours. After the semi-solid reaction mixture had cooled, the dye was collected and washed well with acetone. The yield of crude solid (16·2 g.) was 87·7%. The filtrate gave hydroxylamine hydrochloride (10·1 g.) on concentration. If boiling butanol is used as the solvent a magenta dye is also formed. It is readily removed, however, by washing with acetone. The *dye*, recrystallised from pyridine, formed purple needles of no definite m. p. (Found: C, 64·4; H, 5·05; N, 11·2; Cl, 20·2. $C_{20}H_{17}N_3Cl_2$ requires C, 64·85; H, 4·6; N, 11·35; Cl, 19·15%). The *monohydrochloride* was obtained as short needles from butanol or pyridine by pouring an alcoholic solution of the dihydrochloride into water (Found: C, 71·73; H, 4·8; N, 12·5; Cl, 10·5. $C_{20}H_{16}N_3Cl$ requires C, 71·95; H, 4·8; N, 12·6; Cl, 10·65%). The *sulphate*, obtained in low yield (37%) from the nitrile and hydroxylamine sulphate, was very insoluble in most organic solvents. It was obtained as small bronze needles (Found: N, 10·5. $C_{20}H_{17}O_4N_3S$ requires N, 10·65%).

(*b*) α-Cyano-β-benzoylpropionic acid hydrate (2·2 g., 0·01 mol.), hydroxylamine hydrochloride (1·4 g., 0·02 mol.), and industrial methylated spirit (10 c.c.) were refluxed for 90 minutes. The dye (1·0 g., 54%) was collected after cooling and recrystallised from pyridine. It formed alkali-insoluble purple needles (Found: C, 64·25; H, 5·0; N, 11·5%).

Bis-2-(3 : 5-diphenylpyrrole)azamethin.—(*a*) β-Benzoyl-α-phenylpropionitrile (4·7 g., 0·02 mol.), hydroxylamine hydrochloride (1·4 g., 0·02 mol.), and ethylene glycol (20 c.c.) were heated at 120° in an oil-bath for 2 hours. The dye separated as coppery crystals. These were collected when cold, and recrystallised from nitrobenzene forming short needles (0·3 g., 6·7%), m. p. 286° (Found: C, 84·9; H, 5·05; N, 9·5. Calc. for $C_{32}H_{23}N_3$: C, 85·5; H, 5·1; N, 9·4%). (*b*) With the same procedure as in (*a*) but using *n*-butyl alcohol (20 c.c.) as solvent and refluxing for 2 hours, the deep blue solution deposited the dye salt on chilling. The purple solid rapidly acquired a coppery sheen on standing in the atmosphere, owing to hydrolysis to the base (m. p. 286°) (1·2 g.; 26·7%). (*c*) The nitrile (4·7 g.), hydroxylamine hydrochloride (1·4 g.), and formamide (20 c.c.) were placed in an oil-bath at 120°. The temperature of the mixture rose to 90°, then with evolution of gas the temperature rose to 150° and the dye separated. It (0·8 g., 17·8%) was collected after dilution with alcohol, ground with alcohol, and washed with alcohol and water. It had m. p. 286° and was identical with the sample prepared according to (*a*).

TABLE II.

II; R′ = H, R =	Yield, %.	Solvent.	Crystal form.	Formula.	Analysis, %. Found.	Analysis, %. Requires.
p-Tolyl	49·8	Acetic acid	Short bronze needles	$C_{22}H_{21}N_3Cl_2$	N, 10·4	10·55
p-Bromophenyl	41·5	Acetic acid	Short gold-green needles	$C_{20}H_{15}N_3Cl_2Br_2$	N, 7·5	7·95
p-Chlorophenyl	55	Acetic acid	Fine purple needles	$C_{20}H_{15}N_3Cl_4$	N, 9·5	9·6
p-Hydroxyphenyl *	—	Pyridine	Short green needles	$C_{20}H_{17}O_2N_3Cl_2$	C, 60·05 H, 4·2 N, 10·9 Cl, 17·1	59·7 4·25 10·45 17·65
p-Methoxyphenyl	57	Pyridine	Short coppery needles	$C_{22}H_{21}O_2N_3Cl_2$	C, 60·65 H, 5·3 N, 9·55 Cl, 16·15	61·4 4·9 9·75 16·5
m-Hydroxyphenyl †	40	Pyridine	Short green needles	$C_{20}H_{17}O_2N_3Cl_2$	N, 10·55	10·45
m-Methoxyphenyl	46·5	Acetic acid	Short coppery needles	$C_{22}H_{21}O_2N_3Cl_2$	N, 9·45	9·75
3 : 4-Dimethoxyphenyl	52	Pyridine	Coppery needles	$C_{24}H_{25}O_4N_3Cl_2$	N, 8·5	8·55
1-Naphthyl	44·5	Pyridine	Purple threads	$C_{28}H_{21}N_3Cl_2$	C, 71·55 H, 4·65 N, 9·15	71·5 4·45 8·95
2-Naphthyl	37	Pyridine	Purple needles	$C_{28}H_{21}N_3Cl_2$	N, 9·2	8·95
2-Thienyl	23	Acetic acid	Short green needles	$C_{16}H_{13}N_3S_2Cl_2$	N, 10·45 S, 16·35	11·0 16·8

* Soluble in alkali to green solution. † Soluble in alkali to blue solution.

Hydroxylamine Hydrochloride and β-Benzoylpropionamide.—The amide (7·08 g., 0·04 mol.), hydroxylamine hydrochloride (2·8 g., 0·04 mol.), and formamide (20 c.c.) were placed in an oil-bath at 120°. After a while the evolution of gas commenced and the *dye* separated rapidly. After 5 minutes the melt was diluted with alcohol, and the dye collected, and washed with alcohol until the washings were colourless. It (0·5 g.) formed brassy, irregular plates from pyridine, in which it gives a magenta solution. It sublimed with some decomposition, giving red vapours. It was readily decolorised in pyridine solution with aqueous sodium dithionite (Found: C, 75·7; H, 4·6; N, 9·0. $C_{20}H_{14}O_2N_2$ requires C, 76·45; H, 4·45; N, 8·9%).

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