959. *Steric Hindrance in Analytical Chemistry. Part VI.** 1-*Methyl- and* 1,6-*Dimethyl*-3,4,5-*triazaphenanthrene as Reagents for Iron and Copper.*

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The nitration of 4-methylcinnoline has been re-examined. 1-Methyl-3,4,5-triazaphenanthrene has been synthesised from 8-amino-4-methylcinnoline. It is a weak base (pK ~1) which forms a blue complex with copper(II) ($\lambda_{\text{max.}}$ 660 mμ; $\varepsilon \approx 100$) and a strongly coloured tris-complex with ferrous ions ($\lambda_{\text{max.}}$ 535; ε 14,700). 1,6-Dimethyl-3,4,5-triazaphenanthrene, prepared similarly, forms a bis-complex with copper(I) ($\lambda_{\text{max.}}$ 470 mμ; ε 7890) but does not react with ferrous iron.

The bright red tris-complexes of ferrous ions with 2,2′-bipyridyl and 1,10-phenanthroline have been used extensively for the absorptiometric determination of iron,[1] as redox indicators,[2] and as precipitants for certain anions.[3] Many substituted bipyridyls and 1,10-phenanthrolines have been synthesised in attempts to improve the sensitivity or selectivity of the parent reagents, but bithiazolyl and 2-2′-pyridylbenzimidazole are among the few representatives of other heterocyclic systems known to give the " ferroin reaction," *i.e.*, similar coloured complexes with ferrous ions.

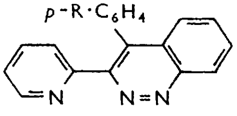
* Part V, *J.*, 1959, 288.

[1] Sandell, " Colorimetric Determination of Traces of Metals," Third Edition, Interscience, New York, 1959, and refs. therein.

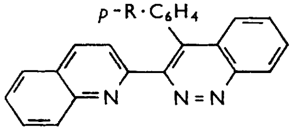
[2] Smith and Richter, *Ind. Eng. Chem.*, *Analyt.*, 1944, **16**, 580.

[3] Brandt and Smith, *Analyt. Chem.*, 1949, **21**, 1313; cf. Feigl, " The Chemistry of Specific, Selective, and Sensitive Reactions," Academic Press, New York, 1949.

In a study of the structural factors which determine a reagent's ability to give the ferroin reaction, Mellor [4] examined the compounds (I; R = H and OMe), (II), and (III). The pyridylcinnolines (I) gave pink tris-complexes with ferrous iron (Ia, ε 18,200 at $\lambda_{max.}$ 530 mμ; Ib, ε 18,300 at $\lambda_{max.}$ 535 mμ) and showed a considerable gain in sensitivity over the substituted phenanthrolines prepared up to that time.[5] The bulky 4-substituent in compounds (I) and (II) certainly prevents the coplanarity of the chelate ring system in the ferrous complex and so reduces the transition probability in the optical absorption spectra.[6] Should it prove possible to prepare the parent 3-2′-pyridylcinnoline a still larger molecular extinction coefficient can be predicted. The quinolylcinnolines (II) did not form ferrous complexes in consequence of steric hindrance to co-ordination.[5] Since the blue tris-complex between ferrous ions and the triazaphenanthrene (III) had a higher molecular extinction coefficient (ε 14,600 at $\lambda_{max.}$ 605 mμ) than that of 1,10-phenanthroline (ε 11,000 at $\lambda_{max.}$ 508 mμ) and exhibited such a large bathochromic effect, we were encouraged to attempt the synthesis of other less highly substituted cinnoline derivatives, namely, (V; R = H or Me).



(Ia: R=H)
(Ib: R=OMe)



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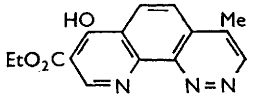
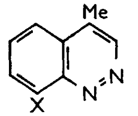
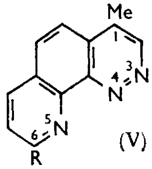


(III)



(IV)



(V)

4-Methyl-8-nitrocinnoline (IV; X = NO_2), our starting material, had been prepared [7,8] by nitration of 4-methylcinnoline (IV; X = H), and was described as having m. p. 137—138° (decomp.). We found that the crystallisation of the crude nitration product of 4-methylcinnoline is extremely difficult and, in most experiments in which more than a few milligrams were employed, only a black gum separates. Chromatography, however, afforded two isomeric nitro-compounds, with m. p.s 148—150° (decomp.) and 134°, severally. The former gave an amine which was converted into 1-methyl-3,4,5-triazaphenanthrene (V; R = H) by a Skraup reaction, and by crotonaldehyde diacetate into 1,6-dimethyl-3,4,5-triazaphenanthrene (V; R = Me). The nitro-compound of m. p. 148—150° is therefore 4-methyl-8-nitrocinnoline (IV; X = NO_2). By analogy with the nitration of quinoline and 1-nitronaphthalene, the second nitro-compound, of m. p. 134°, which can be reduced to a different amine, is 4-methyl-5-nitrocinnoline. The presence of an infrared band at 762 cm.$^{-1}$ (indicative of three adjacent hydrogen atoms on a benzene ring) supports this. The authentic 8-nitro-compound shows a similar band at 772 cm.$^{-1}$.

EXPERIMENTAL

4-Methylcinnoline,[9,10] repeatedly recrystallised from hexane, formed lemon-yellow needles, m. p. 76°. The m. p. falls when the compound is exposed to air for a time.

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[4] Mellor, D.Phil. Thesis, Oxford, 1954.
[5] Irving and Williams, *Analyst*, 1952, **77**, 813.
[6] Braude, *Nature*, 1954, **173**, 117.
[7] Schofield and Swain, *J.*, 1949, 1367.
[8] McKenzie and Hamilton, *J. Org. Chem.*, 1951, **66**, 1414.
[9] Jacobs, Winstein, Henderson, and Spaeth, *J. Amer. Chem. Soc.*, **1946**, **68**, 1310.
[10] Atkinson and Simpson, *J.*, 1947, 808.

Nitration of 4-Methylcinnoline.—Powdered pure 4-methylcinnoline (10 g.) was slowly added to stirred concentrated sulphuric acid, cooled in acetone–solid carbon dioxide, and nitrating mixture (sulphuric acid, 16·3 ml., and fuming nitric acid, 3·7 ml.) was added while the temperature was kept at −15°. Stirring was continued while the bath was allowed to attain room-temperature and then for a further 2—3 hr. The acid mixture was slowly stirred into ice surrounded by acetone–solid carbon dioxide and then exactly neutralised at as low a temperature as possible by the slow addition of 8N-ammonia. The brown precipitate was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide, giving a light-brown solid, m. p. 122—124° (8—10 g.). This was extracted with boiling benzene (5 × 100 ml.) and after the extract had been shaken with alumina (10 ml.; H-type deactivated by treatment with 0·5 ml. of 10% acetic acid) it was chromatographed on deactivated alumina (600 ml. in a column of diameter 4 cm.). Bands formed were successively brown (top), mustard-yellow, pale yellow, red, and pink (bottom). On elution with benzene the red band gave 4-*methyl*-?5-*nitrocinnoline* (1·65 g.), which crystallised from dilute ethanol as pale yellow plates m. p. 132—133°, raised to 134° by further recrystallisation (Found: C, 57·5; H, 3·8; N, 21·8. $C_9H_7N_3O_2$ requires C, 57·1; H, 3·7; N, 22·2%). The pale yellow band yielded 4-methyl-8-nitrocinnoline (IV; X = NO_2) (3·67 g.) which crystallised from aqueous ethanol as yellow plates, m. p. 148—150° (decomp.) (Found: C, 57·3; H, 3·5; N, 21·8%). The other bands did not yield crystalline material.

8-Amino-4-methylcinnoline (IV; X = NH_2), prepared by Schofield and Swain's method,[7] was obtained from aqueous ethanol as brown needles, m. p. 128—133° (Schofield and Swain give m. p. 126—127°). With boiling acetic anhydride and sodium acetate (1·5 hr.) it gave 8-*acetamido*-4-*methylcinnoline*, m. p. 158°, needles from ethanol (Found: C, 65·7; H, 5·4; N, 20·9. $C_{11}H_{11}N_3O$ requires C, 65·7; H, 5·5; N, 20·9%); benzoylation (Schotten–Baumann) afforded 8-*benzamido*-4-*methylcinnoline*, m. p. 170°, prisms from ethanol (Found: N, 16·7. $C_{16}H_{13}N_3O$ requires N, 16·3%).

(?)5-*Amino*-4-*methylcinnoline.*—The nitro-compound of m. p. 134° (0·5 g.) in hydrochloric acid (10 ml.) was treated with stannous chloride (2·5 g.) in hydrochloric acid (2·5 ml.) at 50° for 10 min. The cooled mixture was decomposed at <30° with aqueous potassium hydroxide and extracted with chloroform. Removal of the solvent left 5-*amino*-4-*methylcinnoline* which separated from aqueous ethanol as orange needles, m. p. 174—176° (0·23 g.). Drying at 100° gave a yellow solid, m. p. 165—166°, which became orange again on exposure to air (Found, on the solid dried *in vacuo* at 100°: C, 68·1; H, 5·8; N, 26·1. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%).

1-*Methyl*-3,4,5-*triazaphenanthrene* (V; R = H).—A mixture of 8-amino-4-methylcinnoline (1·47 g.), 69% sulphuric acid (7·5 ml.), glycerol (1·15 g.), 80% aqueous arsenic acid (7·5 ml.), and water (0·3 ml.) was heated under reflux for 3·5 hr. at 155°. The resulting solution was diluted with water, made basic with ammonia, and extracted with benzene. The solid obtained after drying (Na_2SO_4) and evaporation of the solvent recrystallised from benzene from which 1-*methyl*-3,4,5-*triazaphenanthrene* separated as brown needles, m. p. 196° (0·83 g.). The colour was removed by sublimation *in vacuo* (Found: C, 73·9; H, 4·6. $C_{12}H_9N_3$ requires C, 74·0; H, 4·6%).

1,6-*Dimethyl*-3,4,5-*triazaphenanthrene* (V; R = Me).—Crotonaldehyde diacetate (2·45 g.) was added to a stirred mixture of 8-amino-4-methylcinnoline (2 g.), hydrochloric acid (5 ml.), and arsenic pentoxide (0·25 g.) at 120°, and heating was continued for 2 hr. The excess of aldehyde was removed in steam, the remaining solution was made basic with sodium hydroxide, then extracted with boiling benzene, and the extracts were dried and evaporated. The resulting solid was washed with ethanol and then with tetrahydrofuran and recrystallised from benzene from which 1,6-*dimethyl*-3,4,5-*triazaphenanthrene* separated as brown needles, m. p. 222° (0·15 g.) (Found: C, 74·3; H, 5·3; N, 20·0. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%). The colour was removed by sublimation *in vacuo.*

Investigation of Complex Formation.—Absorption spectra were measured with a Unicam S.P. 500 instrument at room temperature with matched silica cells. Salts were of "AnalaR" grade. Hydroxylamine hydrochloride was freed from traces of iron by passage through a column of cation-exchange resin (H form).

Dissociation Constants of the Conjugate Acids.—Aliquot portions (2 ml.) of aqueous $5{\cdot}338 \times 10^{-4}$M-solutions of the 1-methyl compound were added to buffer solutions (20 ml.) of constant ionic strength (0·1M), and the absorbancies (A) were measured in 2 cm. silica cells at

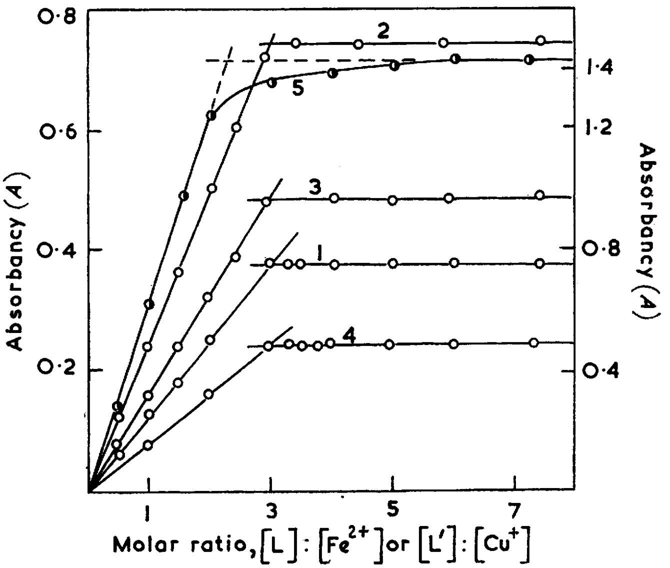
328, 330, and 337 mμ. The pH of the solutions was measured subsequently with a Cambridge pH-meter. Plots of A against pH led to the value $pK = 1{\cdot}0 \pm 0{\cdot}1$.

Similar measurements were made with the 1,6-dimethyl compound.

Optimum pH *of Formation and Composition of the Complex between Iron*(II) *and* 1-*Methyl*-3,4,5-*triazaphenanthrene.*—The absorbancies (A) in a 1 cm. cell of $1{\cdot}9749 \times 10^{-3}$M-solutions (5 ml.) of the amine, $2{\cdot}806 \times 10^{-4}$M-solutions of iron(II), and various buffers (5 ml.) containing hydroxylamine hydrochloride were measured with the following results:

pH	3·45	4·30	5·50	7·60	9·30	10·8
A at 535 mμ	0·95	1·00	0·98	0·975	0·97	0·37

The formula for the complex was established by measuring the absorbancy at 535 mμ of solutions of the same total volume, each containing a fixed concentration of ferrous iron, a buffer containing hydroxylamine hydrochloride, and various known amounts of ligand. The results are shown plotted in the Figure.



(a) Open circles and left-hand ordinates: Harvey–Manning curves for the system iron(II)–1-methyl-3,4,5-triazaphenanthrene. In curves 1—4 $10^4[Fe^{2+}] = 1{\cdot}003$, 0·5015, 0·3343, and 0·1672M, respectively. For curve 4 the absorbancies were divided by 4 before being plotted. (b) Shaded circle and right-hand ordinates: Harvey–Manning curve (5) for the system copper(I)–1,6-dimethyl-3,4,5-triazaphenanthrene. $[Cu^+] = 4{\cdot}55 \times 10^{-5}$M. Measurements at 475 mμ in a 4 cm. cell.

$10^4[Fe^{2+}]$	1·003	0·5015	0·3343	0·1672
pH of buffer	4·00	3·45	3·45	4·00
Total vol. (ml.)	6	8	6	12
Curve no.	1	2	3	4

Complex of 1,6-*Dimethyl*-3,4,5-*triazaphenanthrene and Copper*(I).—The colour of this complex was formed only slowly at pH 4, but developed rapidly at pH 7·0 and 9·3. The brown complex was readily extracted by higher alcohols; the spectrum of the extract in pentyl alcohol showed a single band with $\lambda_{max.}$ 480 mμ. The colours of the complex in aqueous or organic solutions faded rather rapidly, especially after exposure to light.

The absorbancies of a series of solutions containing a fixed concentration of copper (2 ml.; $2{\cdot}5 \times 10^{-4}$M), buffer of pH 7·0 (5 ml., containing an excess of hydroxylamine hydrochloride), and various amounts of the amine in a total volume of 11 ml. were measured at 475 mμ in a 4 cm. cell. The results, shown in the Figure, establish the formula as that of a 2 : 1 complex.

RESULTS AND DISCUSSION

The addition of a second nitrogen atom adjacent to one already present in a hetero-aromatic ring is known to have a base-weakening effect (cf. pyridine pK = 5·23 and pyridazine pK = 2·33; quinoline 4·97 and cinnoline 2·76; 4-aminoquinoline 9·17 and 4-aminocinnoline 6·84).[11] 3,4,5-Triazaphenanthrene should therefore be a weaker base than 4,5-diazaphenanthrene (1,10-phenanthroline, pK 4·96). The introduction of the 1-methyl group into 4,5-diazaphenanthrene has a small base-strengthening effect but the conjugate acid of 1-methyl-3,4,5-triazaphenanthrene should be quite a strong acid.

The absorption spectra of solutions of this 1-methyl compound in water or 0·1N-sodium hydroxide (not reproduced) proved almost indistinguishable, with strong absorption in the ultraviolet region ($\lambda_{\text{max.}}$ 234, ε 26,700; $\lambda_{\text{min.}}$ 246, ε 11,500; $\lambda_{\text{min.}}$ 266, ε 28,500; $\lambda_{\text{min.}}$ 290) and also a band of medium intensity at $\lambda_{\text{max.}}$ 308 (ε 5440) which had shoulders at 320 and 336 mμ. The addition of acid caused a bathochromic shift ($\lambda_{\text{min.}}$ 254; $\lambda_{\text{max.}}$ 277, ε 29,000 $\lambda_{\text{min.}}$ 300—305) and two new overlapping bands appeared at ~330 and 342 mμ ($\varepsilon_{\text{av.}}$ 8000). That there was a small increase in the intensity and resolution of these bands (with an increase in the ratio $\varepsilon_{342}/\varepsilon_{330}$ on changing from 2M- to 10M-hydrochloric acid indicated that protonation was incomplete in the former medium. Although measurements in a medium of constant ionic strength could not be made to include the system in which the protonated species is certainly present to the extent of 99% or more of the total ligand concentration, measurements of the absorbancies of buffer solutions covering the range pH −2·0 to 12·0 (all containing the same total concentration of ligand) led to the value for $K = \{H^+\}[L]/[HL^+]$ (where L = the 1-methyl-amine) such that pK = 0·1 ± 0·1. That this base is so much weaker than predicted from the effect of introducing a nitrogen atom at the 2-position of 1,10-phenanthroline is doubtless due to a second effect of this substitution, namely, that it destroys the identity of the two basic centres. For a substantial contribution to the high basicity of 1,10-phenanthroline (phenan) must be the resonance stabilisation through hydrogen bonding in the cation H.phenan$^+$.

A transient blue colour is observed when ferrous ions are added to an aqueous solution of 1-methyl-3,4,5-triazaphenanthrene. This rapidly gives place to the red colour of a complex which shows a single absorption band in the visible region ($\lambda_{\text{max.}}$ 535 mμ) which differs slightly from that reported for the complex of iron(II) and 1,10-phenanthroline in having a slight shoulder at 470 mμ. The new complex was formed quantitatively in the range pH 3·5—9·5 and is stable to light and storage. From the position of the intersection of the branches of the Harvey–Manning curves[12] (cf. Figure, left-hand ordinates), the formula of the complex is $[FeL_3]^{2+}$. The strict linearity of the rising branches right up to the point of intersection at the molar ratio of 3 : 1 proves the complex to be exceptionally stable. The complex of ferrous iron with three molecules of compound (III)[4,5] seems to be somewhat less stable, with $\beta_3 = 10^{15}$. It follows from the Figure that Beer's law is obeyed at least up to $[Fe^{2+}] = 10^{-4}$M. The value for the molecular extinction coefficient, $\varepsilon_{\text{max.}} = (14{\cdot}7 \pm 0{\cdot}2) \times 10^3$ is well in excess of that for 1,10-phenanthroline and almost identical with that for the substituted triazaphenanthrene previously reported.[4,5] As expected, the sparingly soluble perchlorate of the ferrous tris-complex ion was diamagnetic.

Other bivalent transition metal ions only gave weakly coloured complexes with 1-methyl-3,4,5-triazaphenanthrene: thus Cu^{2+} (blue complex; $\lambda_{\text{max.}}$ 600, ε ~75), Ni^{2+} (green changing slowly to yellow), and Co^{2+} (pink changing to yellow before precipitation occurred) did not interfere in the determination of iron when present in up to 100-fold excess.

The reaction between this base and copper(I) produced a brown complex which could be extracted into pentanol. The colour faded, even in the dark, and no reproducible values could be obtained for its absorption spectra.

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[11] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

[12] Harvey and Manning, *J. Amer. Chem. Soc.*, 1950, **72**, 4488.

Although it possesses two equivalent nitrogen atoms 1,10-phenanthroline acts only as a monoacid base. Lee *et al.*[13] rejected the idea of a second stage of protonation, but Näsänen *et al.*[14] speculated on the formation of a species $H_2phenan^{2+}$ on the basis of a shift in absorption spectrum when this substance is dissolved in concentrated hydrochloric acid. Krumholtz [15] found an indication that the related compound 2,2′-bipyridyl acts as a diacid base in strong acids with $K = 1{\cdot}4 \pm 0{\cdot}3$. Westheimer and Benfey [16] find $K = 3{\cdot}3$. Here, of course, the possibility of rotation about the bond joining the two pyridine nuclei permits the 'onium ions to take up a *trans*-position. The introduction of a methyl group into 1,10-phenanthroline destroys the identity of the two basic centres and increases the basicity of the molecule as a whole (pK of 2-methyl-1,10-phenanthroline, 5·42; of 5-methylphenanthroline, 5·28), and there is some indication from partition measurements [17] that the latter, at least, can take up a second proton to give a very strong acid of pK ~0·4. It was then to be expected that 1,6-dimethyl-3,4,5-triazaphenanthrene (L′) would be more basic than the 1-methyl analogue and might show signs of taking up a second proton. In the issue the absorption spectrum of the dimethyl compound resembled that of its analogue in general form, but was far more complicated and very sensitive to changes in pH. The existence of isosbestic points for sets of curves in the pH range 3—5 indicated equilibria between two species, and from plots of absorbancy against pH at 325, 310, and 290 mμ for a series of buffer solutions each containing the same total concentration of base the position of the inflection gave a value of pK = 4·15. Similar measurements at 332·5 and 345 mμ with more acidic buffers identified a second protonation equilibrium with pK ~0·85.

In contrast to the 1-methyl compound, the dimethyl analogue did not form a red complex with ferrous ions: this behaviour is doubtless due to steric hindrance to co-ordination, as previously noted with 2-methylphenanthroline [18] and other systems.[5] On the other hand, the dimethyl compound readily formed a complex with copper(I) which could be extracted into higher alcohols. By the Harvey–Manning method [12] the formula was shown to correspond to a 1 : 2 complex and since $4s4p^3$-tetrahedral orbitals will hold the two ligands in planes mutually at right angles, the 6-methyl substituent can exert no adverse steric effect. The stability constant for the formation of $[CuL'_2]^+$ is obviously not so large as that noted for $[FeL_3]^{2+}$. Despite the high molecular extinction coefficient (ε 7890 at $\lambda_{max.}$ 470 mμ) which is comparable with that given by copper(I) with 2,9-dimethylphenanthroline (7950) or 2,4,7,9-tetramethylphenanthroline (8860) 1,6-dimethyl-3,4,5-triazaphenanthrene is much less sensitive than the copper-specific reagent 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline ($\varepsilon_{max.}$ 14,200): moreover, its tendency to decompose on storage, especially when exposed to light, renders it unsuitable for analytical practice.

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[13] Lee, Kolthoff, and Leussing, *J. Amer. Chem. Soc.*, 1948, **70**, 2349.
[14] Näsänen and Uusitalo, *Suomen Kem.*, 1950, *B*, **29**, 11.
[15] Krumholtz, *J. Phys. Chem.*, 1956, **60**, 87; cf. *J. Amer. Chem. Soc.*, 1951, **73**, 3487.
[16] Westheimer and Benfey, *J. Amer. Chem. Soc.*, 1956, **78**, 5309.
[17] McBryde, Brisbin, and Irving, *J.*, in the press.
[18] Irving, Cabell, and Mellor, *J.*, 1953, 3417.