*Steric Hindrance in Analytical Chemistry. Part III.** 1-2′-*Pyridyl*iso*quinoline and the Ferroin Reaction.*

By H. Irving and A. Hampton.

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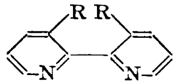
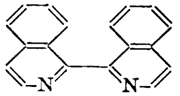
1-2′-Pyridyl*iso*quinoline has been synthesised. It gives a colour with traces of ferrous iron ($\lambda_{max.}$ 585 mμ; $\varepsilon_{max.}$ 11,500) confirming that the failure of this reaction with 1 : 1′-di*iso*quinolyl is due to steric hindrance. 3 : 4-Dihydro-1-2′-pyridyl*iso*quinoline gives a stronger coloured complex ($\lambda_{max.}$ 586 mμ; $\varepsilon_{max.}$ 15,600).

The formation of an intensely red, water-soluble complex between ferrous iron and 1 : 10-phenanthroline forms the basis of the well-known " ferroin " reaction which is also given by 2 : 2′-dipyridyl (I; R = H) and many compounds related to it by substitution or annelation. The reaction even functions with certain aza-derivatives such as 7-ethoxycarbonyl-8-hydroxy-1-methyl-3 : 4 : 5-triazaphenanthrene and 4-*p*-methoxyphenyl-3-2′-pyridylcinnoline (Irving and Williams, *Analyst*, 1952, **77**, 813). From a review of published data and a study of new compounds (Irving and Mellor, to be published) it is clear that the essential condition for the ferroin reaction is the specific grouping $-N{=}\overset{|}{C}-\overset{|}{C}{=}N-$ forming part of an aromatic system, and capable of forming a five-membered chelate ring. However substituents (or rings) adjacent to the nitrogen atoms can cause steric hindrance to co-ordination and partly, or completely inhibit the reaction with ferrous ions (cf. Irving, Cabell, and Mellor, *J.*, 1953, 3417).

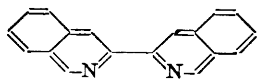
Case (*J. Org. Chem.*, 1952, **17**, 471) reports that the di*iso*quinolyl (III) gives an orange colour with ferrous iron while the ferroin reaction fails completely with (II), although this compound has no substituents adjacent to the nitrogen atoms This latter observation is not surprising for, in addition to the frontal or " packing " effect, the intensity of the ferroin reaction is reduced to a greater or less extent by substituents remote from the co-ordinating nitrogen atoms if, through steric hindrance, they tend to prevent the coplanarity of the heterocyclic rings with the five-membered ring formed by co-ordination to metal. Fig. 1 represents the plane of a chelated molecule of the dipyridyl (I) based on conventional van der Waals radii and interatomic distances. The " interference envelopes " shown by broken lines demonstrate the degree of steric hindrance between a 3-methyl and a 3′-hydrogen atom, and the considerably greater interference between a 3-methyl and a 3′-methyl group. In accordance with the predictable loss of resonance energy it is found (Cagle and Smith, *J. Amer. Chem. Soc.*, 1947, **69**, 1860) that 3 : 3′-dimethyl-2 : 2′-dipyridyl gives a weaker coloured ferrous complex ($\varepsilon_{max.}$ = 1770) than the parent dipyridyl ($\varepsilon_{max.}$ = 8650) although the wave-length of maximum absorption remains almost unchanged. Many other examples of this " coplanarity effect " are known among reagents which undergo the " cuproin " reaction (Irving and Mellor, to be published).



(I)



(II)



(III)

The failure of the di*iso*quinolyl (II) to exhibit the ferroin reaction is doubtless due to the strong interference between the 8 and the 8′ position where, as may be inferred from Fig. 2, the hydrogen atoms would completely overlap if the molecule were coplanar. To test this point we have synthesised 1-2′-pyridyl*iso*quinoline (V) where, as shown in Fig. 2, steric hindrance is limited to interference between the more remote 8 and 3′ position and should be less than that operating in 3 : 3′-dimethyl-2 : 2′-dipyridyl (cf. Fig. 1).

2-Phenyl-*N*-picolinoylethylamine (conveniently prepared from methyl picolinate and 2-phenylethylamine) was cyclised to 3 : 4-dihydro-1-2′-pyridyl*iso*quinoline (IV) by Dekker

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* Part II. *J.*, 1953, 3417.

and Kropp's modification (*Ber.*, 1909, **42**, 2075) of the Bischler–Napieralski reaction. This dihydro-base was not oxidised by hot acid permanganate under the conditions used by Pictet and Kay (*ibid.*, 1909, **42**, 1973) to dehydrogenate 3 : 4-dihydro-1-phenyl*iso*quinoline, but catalytic dehydrogenation to the desired 1-2′-pyridyl*iso*quinoline (V) was effected with palladium black in a modification of the procedure used by Hey and Williams (*J.*, 1951, 1527) to prepare 1-3′-pyridyl*iso*quinoline.

After this paper had been submitted we learnt that the base (V) had been synthesised independently by the direct action of pyridyl-lithium upon *iso*quinoline (Knott and Breckenridge, *Canad. J. Chem.*, 1954, **32**, 512). This synthesis is not unequivocal, but the possibility of substitution's having occurred in the 4-position of the *iso*quinoline system appeared unlikely from the close similarity between the spectrum of the pyridyl*iso*quinoline and that of compounds prepared from 4-methyl-quinolines by treatment with pyridyl-lithium. Identity with our preparation of 1-2′-pyridyl*iso*quinoline (V), whose structure is unambiguously determined by synthesis, was first established by the comparison of absorption spectra of the base and its ferrous complex, and confirmed by mixed melting-point determinations on a specimen of the base (and its picrate) kindly made available by Professor Breckenridge.

FIG. 1.

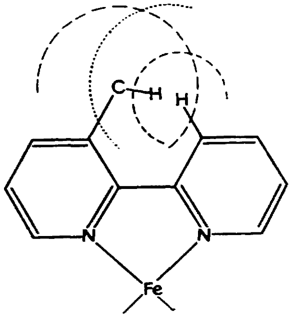
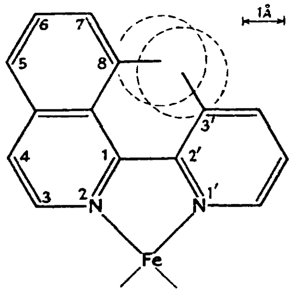
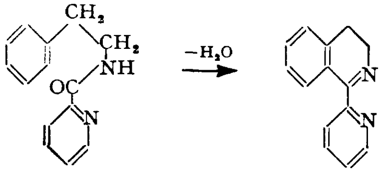
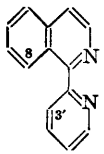


FIG. 2.





(IV)



(V)

With traces of ferrous iron in a buffer of pH 5—6 containing hydroxylamine, 1-2′-pyridyl*iso*quinoline gave a clear reddish-blue colour which was stable for some days. The absorption spectrum showed a single broad band in the visible region with $\lambda_{max.} = 585$ mμ; $\varepsilon_{max.} = 11{,}500$; $\lambda_{min.} = 430$ mμ; $\varepsilon_{min.} = 1{,}100$. The ferroin reaction with this reagent is thus considerably more delicate than with 2 : 2′-dipyridyl ($\varepsilon_{max.} = 8650$) and comparable with that of 1 : 10-phenanthroline ($\varepsilon_{max.} = 11{,}100$). 1-2′-Pyridyl*iso*quinoline also gave a brown cuprous complex extractable into *iso*amyl alcohol. Its spectrum consisted of two broad overlapping bands causing general absorption from 475 to 575 mμ ($\varepsilon \sim 3{,}300$) and was very similar to that of the cuprous complex of the analogous 1-2′-quinolyl*iso*quinoline (λ 450—550 mμ; $\varepsilon \sim 2{,}550$) reported by Hoste (*Analyt. Chim. Acta*, 1950, **4**, 23).

3 : 4-Dihydro-1-2′-pyridyl*iso*quinoline (IV) also formed a ferrous complex which did not fade during several days. The spectrum closely resembled that of the base (V) since $\lambda_{max.} = 586$ mμ but the intensity of absorption was much greater ($\varepsilon_{max.} = 15{,}600$). Ferric ions gave a very pale yellow colour, and cuprous ions gave a brownish yellow precipitate at pH 6 which dissolved in amyl alcohol to give a brown solution which faded rapidly.

That the ferroin reaction should be more sensitive with the dihydro-base (IV) than with 1-2′-pyridyl*iso*quinoline (V) was unexpected : presumably the increase in conjugation and aromaticity on dehydrogenation is more than offset by the increased steric hindrance due to the less flexible *iso*quinoline ring.

EXPERIMENTAL

*2-Phenyl-*N*-picolinoylethylamine.*—Methyl picolinate (6·75 g.; Engler, *Ber.*, 1894, **27**, 1784) and 2-phenylethylamine (9 ml.) were boiled for 30 min., methanol (1 ml.) being collected through a 50-cm. Vigreux column. The mixture was refluxed for a further 12 hr. and then heated at 80—100°/4 mm. to remove excess of phenylethylamine. Distillation of the residue gave an oil (10·3 g., 92%), b. p. 156—158°/4 mm., which on cooling formed crystals of *2-phenyl-*N*-picolinoylethylamine.* The compound crystallised from light petroleum (b. p. 40—50°; 25 parts) as white needles, m. p. 36° (Found: C, 74·5; H, 6·2. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%).

3 : *4-Dihydro-*1*-2'-pyridyl*iso*quinoline.*—Phosphorus pentachloride (9 g.) was added to a solution of the above amide (7·8 g.) in thiophen-free benzene (80 ml.) and the mixture refluxed for 1 hr. Anhydrous aluminium chloride (9 g.) was then added and refluxing continued for 3 hr.; the benzene was then distilled off and the dark residue decomposed with water. The mixture was shaken with chloroform (50 ml.) and the chloroform layer extracted with N-hydrochloric acid (3 × 20 ml.). The combined acid extracts were extracted with ether (2 × 30 ml.), the ethereal extracts being discarded, and concentrated to approximately 100 ml. After the addition of concentrated hydrochloric acid (50 ml.) the solution was refluxed for 17 hr. to hydrolyse any starting material. The hot solution was treated with animal charcoal, the filtrate made strongly alkaline with sodium hydroxide, and the liberated oil extracted with ether. The ethereal solution was dried (K_2CO_3), the solvent removed, and the residue distilled, giving 3 : *4-dihydro-*1*-2'-pyridyl*iso*quinoline* as a pale yellow oil (2·91 g., 39%), b. p. 142—143°/4 mm. (Found: C, 80·4; H, 6·0. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8%). This base yielded a *monopicrate* which formed yellow needles, m. p. 149°, from ethanol (50 parts) (Found: C, 54·6; H, 3·5; N, 16·2. $C_{14}H_{12}N_2,C_6H_3O_7N_3$ requires C, 54·9; H, 3·5; N, 16·0%). The *perchlorate* formed white needles, m. p. 212° (decomp.), from acetic acid (10 parts) (Found: C, 54·4; H, 3·6; N, 9·1. $C_{14}H_{12}N_2,HClO_4$ requires C, 54·5; H, 4·2; N, 9·1%).

1*-2'-Pyridyl*iso*quinoline.*—3 : 4-Dihydro-1-2'-pyridyl*iso*quinoline (29·0 mg.) and palladium black (30·0 mg.; prepared according to Willstätter, *Ber.*, 1921, **54**, 113) were heated for 2 hr. at 240—245° in a 1-ml. bulb attached to a length of glass tubing. After liquid condensate had been washed back into the bulb with acetone and the solvent distilled off, heating was continued at 265—270° for 1½ hr. The mixture was distilled at 130—135°/0·2 mm. (air-bath) giving an oil which on cooling formed crystals (19·7 mg.). Crystallisation from ether–light petroleum (b. p. 60—75°) yielded white needles of 1*-2'-pyridyl*iso*quinoline*, m. p. 72° (Found: 81·6; H, 4·8; N, 13·5. $C_{14}H_{10}N_2$ requires C, 81·5; H, 4·9; N, 13·6%), which did not depress the m. p. of a specimen supplied by Prof. Breckenridge. The *picrate* formed yellow needles, m. p. 166—167°, from ethanol (Found: N, 15·9. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires N, 16·1%) and did not depress the m. p. of the picrate of Breckenridge's base.

Absorption Spectra.—(a) 3 : *4-Dihydro-*1*-2'-pyridyl*iso*quinoline.* A solution of the perchlorate in a mixture of ethanol (95 ml.) and 0·1N-sodium hydroxide (5 ml.) gave the absorption spectrum of the free base. This was a single band with $\lambda_{max.}$ = 265 mμ, $\varepsilon_{max.}$ = 11,100; $\lambda_{min.}$ = 240 mμ, $\varepsilon_{min.}$ = 7,800. In 0·05N-hydrochloric acid there was a bathochromic shift to $\lambda_{max.}$ = 290 mμ, $\varepsilon_{max.}$ = 14,100; $\lambda_{min.}$ = 245 mμ, $\varepsilon_{min.}$ = 4,460. Solutions of the ferrous complex (8 × 10^{-5}M in an acetate buffer of pH 4·9 containing hydroxylamine) showed $\lambda_{max.}$ = 586 mμ, and $\varepsilon_{max.}$ = 15,600. Beer's law was obeyed up to at least 25 p.p.m. of iron.

(b) 1*-2'-Pyridyl*iso*quinoline.* The free base in 95% ethanol gave a simple band spectrum with $\lambda_{max.}$ = 221 mμ, $\varepsilon_{max.}$ 41,800, and $\lambda_{max.}$ = 320 mμ, $\varepsilon_{max.}$ = 6,600. In acid solution there was a bathochromic shift to $\lambda_{max.}$ = 231 mμ, $\varepsilon_{max.}$ = 33,700 in 0·1N-hydrochloric acid, and $\lambda_{max.}$ = 239 mμ, $\varepsilon_{max.}$ = 31,000 in 2·5M-hydrochloric acid. An isosbestic point at 235 mμ suggests that a second proton is being co-ordinated in the more acid solutions. The absorption spectra of the ferrous and cuprous complexes are reported above.

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THE INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

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