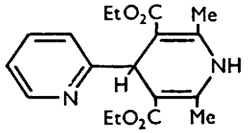
313. *The Synthesis of 2 : 4′-Dipyridyl and Some Derivatives.*

By R. F. HOMER.

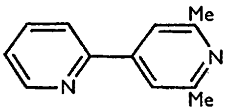
Several synthetic routes to 2 : 4′-dipyridyl derivatives have been examined. The parent base has been unambiguously synthesised by oxidation of 1 : 8-phenanthroline and decarboxylation of the resulting 2 : 4′-dipyridyl-3 : 3′-dicarboxylic acid. The Hantzsch reaction proceeds well with pyridine-2- and -4-aldehydes and acetoacetic ester, and provides a route to 2 : 6-dimethyl-2′ : 4- and -4 : 4′-dipyridyl. 1-4′-Pyridyl*iso*quinoline has also been prepared.

A DIPYRIDYL, m. p. 61°, was isolated by Smith[1] from among the products of the treatment of pyridine with sodium. Smith assigned the 3 : 4′-structure to this base because on oxidation it was alleged to give a mixture of *iso*nicotinic and nicotinic acid. Morgan and Burstall[2] isolated the same dipyridyl from the treatment of pyridine with ferric chloride and also described it as the 3 : 4′-isomer. More recently Krumholtz[3] has shown that it is found among the products of pyrolysis of pyridine, and oxidised it to a mixture of *iso*nicotinic and picolinic acid. On these grounds, and with supporting evidence from ultraviolet absorption data, Krumholtz concluded that the dipyridyl, m. p. 61·5° (picrate, m. p. 215°), is the 2 : 4′-isomer. In order conveniently to obtain a quantity of authentic 2 : 4′-dipyridyl a number of synthetic routes have been examined, and the base and a number of its derivatives have now been unambiguously synthesised. The properties of the synthetic material confirm Krumholtz's conclusions.

The Hantzsch reaction with pyridine aldehydes does not appear to have been reported. However, pyridine-2-aldehyde readily condensed with ethyl acetoacetate and ammonia to give 3 : 5-diethoxycarbonyl-1 : 4-dihydro-2 : 6-dimethyl-2′ : 4-dipyridyl (I) which on oxidation with nitric acid, followed by hydrolysis and decarboxylation, gave 2 : 6-dimethyl-2′ : 4-dipyridyl (II). Incidentally it was found that an analogous series of reactions carried out with pyridine-4-aldehyde gave 2 : 6-dimethyl-4 : 4′-dipyridyl.

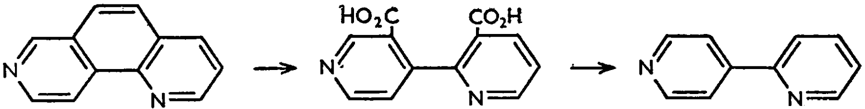


(I)



(II)

Attempts to convert the base (II) into 2 : 4′-dipyridyl by oxidation to the acid followed by decarboxylation were not encouraging and this route was not further pursued when it became clear that a synthesis by way of 1 : 8-phenanthroline (III) was more profitable.



(III) (IV) (V)

Although the synthesis of this phenanthroline by a Skraup reaction with 5-amino*iso*quinoline has been reported by Misani and Bogert,[4] their yield was only 5%; but modifications in the method have now improved it to 35%, making this route a feasible preparative one. 1 : 8-Phenanthroline with permanganate gave 2 : 4′-dipyridyl-3 : 3′-dicarboxylic acid (IV) which could not be decarboxylated satisfactorily by distillation with lime but on

---

[1] Smith, *J. Amer. Chem. Soc.*, 1924, **46**, 419.

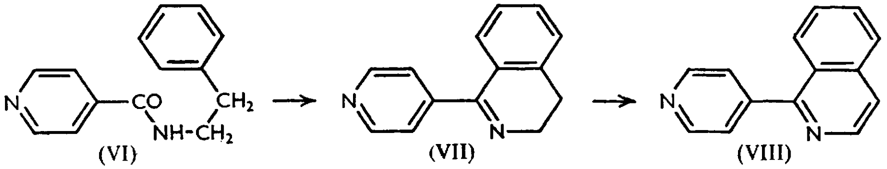
[2] Morgan and Burstall, *J.*, 1932, 20.

[3] Krumholtz, *J. Amer. Chem. Soc.*, 1951, **73**, 3487, 4449.

[4] Misani and Bogert, *J. Org. Chem.*, 1945, **10**, 358.

treatment with copper bronze in nitrobenzene was smoothly converted into 2 : 4′-dipyridyl (V).

1-2′-Pyridyl*iso*quinoline has recently been reported by Irving and Hampton,[5] who cyclised *N*-phenethylpicolinamide. By a similar cyclisation of *N*-phenethyl*iso*nicotinamide (VI) there is obtained 1-4′-pyridyl*iso*quinoline (VIII) by way of the dihydro-compound (VII). Oxidation of the base (VIII) with permanganate gave a mixture of acidic products which on distillation with lime gave a mixture of volatile products among which only pyridine could be identified.



(VI) (VII) (VIII)

The bases described have been quaternised with methyl iodide.

EXPERIMENTAL

3 : 5-*Diethoxycarbonyl*-1 : 4-*dihydro*-2 : 6-*dimethyl*-2′ : 4-*dipyridyl.*—Pyridine-2-aldehyde (43 g.), ethyl acetoacetate (104 g.), ethanol (50 c.c.), and ammonia (20·5 c.c.; *d* 0·880) were mixed and heated slowly to 80° for 4 hr.; more ammonia (5 c.c.) was then added, and heating was continued for a further 4 hr. The pale fawn prisms which separated were filtered off and washed with a little ethanol followed by ether. The *ester* (62·5 g.) had m. p. 196—198° unchanged on crystallisation from ethanol (Found: C, 65·9; H, 6·8; N, 8·7. $C_{18}H_{22}O_4N_2$ requires C, 65·4; H, 6·7; N, 8·5%).

3 : 5-*Diethoxycarbonyl*-2 : 6-*dimethyl*-2′ : 4-*dipyridyl.*—The above dihydro-compound (55 g.) was warmed in water (57 c.c.) and sulphuric acid (9 c.c.; *d* 1·84) to 40°, and nitric acid (11 c.c.; *d* 1·4) added all at once. When the vigorous reaction had subsided the mixture was cooled with added ice and basified with ammonia solution. The solid was filtered off, washed with water, and crystallised from aqueous ethanol to yield the *ester* (22 g.), m. p. 99—100° (Found: C, 65·9; H, 6·4. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1%).

2 : 6-*Dimethyl*-2′ : 4-*dipyridyl.*—3 : 5-Diethoxycarbonyl-2 : 6-dimethyl-2′ : 4-dipyridyl (20 g.) was heated to the b. p. with ethanol (45 c.c.). Potassium hydroxide (10 g.) in ethanol (45 c.c.) was added in three portions during ¼ hr. The mixture was heated under reflux for ¾ hr. more and evaporated to dryness in an evaporating dish. The residue was ground with calcium oxide (40 g.) and distilled at 400—500°. The crude distillate (10 g.) gave on redistillation 2 : 6-*dimethyl*-2′ : 4-*dipyridyl* (6·0 g.), b. p. 180—183°/27 mm. (Found: C, 78·3; H, 6·9; N, 15·2. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5; N, 15·2%). The *picrate* melted at 202° (Found: N, 17·2. $C_{18}H_{15}O_7N_5$ requires N, 17·0%).

2 : 6-*Dimethyl*-4 : 4′-*dipyridyl.*—This was prepared by a similar reaction sequence from pyridine-4-aldehyde. The *base* had b. p. 178°/17 mm. and solidified (Found: N, 15·2%). The intermediate 3 : 5-*diethoxycarbonyl*-1 : 4-*dihydro*-2 : 6-*dimethyl*-4 : 4′-*dipyridyl*, crystallised from aqueous ethanol, had m. p. 195° (Found: C, 65·1; H, 6·7; N, 7·9%). 3 : 5-*Diethoxycarbonyl*-2 : 6-*dimethyl*-4 : 4′-*dipyridyl* had m. p. 112° (from aqueous ethanol) (Found: C, 66·1; H, 6·5; N, 8·8%).

2 : 6-*Dimethyl*-2′ : 4-*dipyridyl Monomethiodide.*—2 : 6-Dimethyl-2′ : 4-dipyridyl (1·4 g.), ethanol (15 c.c.), water (2 c.c.), and methyl iodide (3 c.c.) were stirred under reflux for 16 hr. When the cooled mixture was poured into dry ether (50 c.c.) the *monomethiodide* separated; it had m. p. 232—234° after crystallisation from ethanol (Found: N, 8·5; I, 38·9. $C_{13}H_{15}N_2I$ requires N, 8·4; I, 38·0%).

2 : 6-*Dimethyl*-2′ : 4-*dipyridyl Dimethiodide.*—The above monomethiodide (0·7 g.) was heated with 95% ethanol (20 c.c.) and methyl iodide (5 c.c.) in a sealed tube at 100—110° for 6 hr. The mixture was evaporated to dryness and the residue triturated with acetone to give the *dimethiodide* (0·65 g.), m. p. 222° (Found: N, 5·9; I, 55·0. $C_{14}H_{18}N_2I_2$ requires N, 6·0; I, 54·3%).

---

[5] Irving and Hampton, *J.*, 1955, 430.

2 : 6-*Dimethyl*-4 : 4′-*dipyridyl Dimethiodide*.—The base (2·5 g.), 95% ethanol (75 c.c.), and methyl iodide (10 c.c.) were stirred under reflux for 8 hr. The solid was filtered off and washed with acetone, giving the *dimethiodide*, m. p. 310° (decomp.) (Found: N, 6·0%).

1 : 8-*Phenanthroline*.—5-Amino*iso*quinoline (54 g.) was added to a mixture of sulphuric acid (720 c.c.; *d* 1·84), water (230 c.c.), glycerol (171 c.c.), and arsenic acid solution (150 c.c.; *d* 1·95). The mixture was stirred at 140° for 2½ hr., cooled, poured on ice, and made alkaline with aqueous ammonia (*d* 0·880). The mixture was stirred with chloroform (500 c.c.) for 1 hr., then filtered, and the lower layer separated and evaporated to give a residue of crude 1 : 8-phenanthroline (29 g.) which on distillation yielded 24·5 g. of product, b. p. 138—140°/0·3 mm., m. p. 105—108°.

2 : 4′-*Dipyridyl*-3 : 3′-*dicarboxylic Acid*.—1 : 8-Phenanthroline (20 g.) was suspended in water containing sodium hydroxide (8·5 g., 2 mol.) at 80—85°, and potassium permanganate (*ca.* 70 g.) added at such a rate as to keep the temperature at 80—95°, the end-point of the reaction being marked by a persistent pink colour on spotting on filter-paper. The mixture was filtered, and the filtrate evaporated to 100 c.c. and adjusted to pH 3·2 with hydrochloric acid. The *acid* (16·5 g.) separated. Crystallisation from water gave material of m. p. 275° (rapid heating) (Found: C, 59·5; H, 3·5; N, 11·4. $C_{12}H_8O_4N_2$ requires C, 59·0; H, 3·3; N, 11·4%).

2 : 4′-*Dipyridyl*.—2 : 4′-Dipyridyl-3 : 3′-dicarboxylic acid (16·5 g.) was added during 1 hr. to a stirred mixture of nitrobenzene (100 c.c.) and copper bronze (0·5 g.) at 205—210°. Carbon dioxide was evolved. The mixture was heated at 205—210° for 1 hr. after the end of the addition, cooled to 100°, treated with carbon, and filtered. The filtrate was extracted with 2N-hydrochloric acid (3 × 50 c.c.), and the combined acid extracts were washed with ether and basified with sodium hydroxide solution. The base was extracted with chloroform and distilled, to give 2 : 4′-dipyridyl, b. p. 148—150°/11 mm., m. p. 59—60°, raised by crystallisation from light petroleum (b. p. 60—80°) to 61·5°. The picrate had m. p. 214°.

2 : 4′-*Dipyridyl Mono- and Di-methiodide*.—2 : 4′-Dipyridyl (2 g.), 95% ethanol (20 c.c.), and methyl iodide (4 c.c.) were heated at 100—110° for 7½ hr. The solid was filtered off and fractionally crystallised from 95% ethanol, to give the *monomethiodide*, m. p. 188—190° (1·0 g.) (Found: N, 8·7. $C_{11}H_{11}N_2I,H_2O$ requires N, 8·8%), and, as the less soluble fraction, the dimethiodide, m. p. 225° (0·8 g.) (Found: N, 6·5. Calc. for $C_{12}H_{14}N_2I_2$: N, 6·4%).

N-*Phenethyl*iso*nicotinamide*.—Ethyl *iso*nicotinate (75 g.) and phenethylamine (90 g.; 1·5 mol.) were heated at 170—180°, and the ethanol (22 c.c.) distilled off. Heating was continued for 6 hr. After cooling, the residue crystallised from benzene to give the *compound* (117 g.), m. p. 120° (Found: C, 73·7; H, 6·3; N, 12·6. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

3 : 4-*Dihydro*-1-4′-*pyridyl*iso*quinoline*.—*N*-Phenethyl*iso*nicotinamide (39 g.) was dissolved in benzene (400 c.c.). Phosphorus pentachloride (45 g.) was added, and the mixture stirred under reflux for 1 hr. The mixture was cooled, and powdered aluminium chloride (45 g.) added, a vigorous reaction ensuing. The mixture was stirred under reflux for 3 hr. more, the benzene distilled off, and the residue decomposed by adding water (200 c.c.). The aqueous solution was strongly basified with sodium hydroxide solution and extracted with chloroform. This extract was extracted with 2N-hydrochloric acid (3 × 100 c.c.), and the combined acid extracts were heated under reflux for 7 hr. to hydrolyse an unreacted amide. On basification with sodium hydroxide solution an oil separated which was extracted with chloroform and distilled. The *base* (13 g.) distilled at 145—148°/0·3 mm. and solidified. Crystallisation from light petroleum (b. p. 60—80°) gave material of m. p. 56° (Found: C, 81·3; H, 6·0; N, 12·8. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8; N, 13·4%).

1-4′-*Pyridyl*iso*quinoline*.—The dihydro-base (4 g.) was heated at 260—280° for 7 hr. with 5% palladium–carbon (4·5 g.). Extraction of the mixture with ethanol gave a solid *base* which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 91° (2·5 g.) (Found: C, 82·1; H, 5·3. $C_{14}H_{10}N_2$ requires C, 81·6; H, 4·9%).

3 : 4-*Dihydro*-1-4′-*pyridyl*iso*quinoline Dimethiodide*.—The base (3·5 g.) was heated in a sealed tube at 100—110° for 7 hr. with 95% ethanol (50 c.c.) and methyl iodide (10 g.). The solid which separated was filtered off and crystallised from aqueous ethanol to give the *dimethiodide* (8·0 g.), m. p. 245° (Found: C, 37·6; H, 4·1; N, 5·7; I, 51·7. $C_{16}H_{18}N_2I_2,H_2O$ requires C, 37·6; H, 3·9; N, 5·5; I, 49·8%). In a similar manner was obtained 1-4′-*pyridyl*iso*quinoline dimethiodide*, m. p. 248° from aqueous ethanol (Found: C, 37·7; H, 3·5; N, 5·6; I, 50·9. $C_{16}H_{16}N_2I_2,H_2O$ requires C, 37·8; H, 3·5; N, 5·5; I, 50·0%).

Oxidation of 1-4′-*Pyridyl*iso*quinoline by Permanganate*.—The base (1·0 g.), potassium permanganate (2·2 g., 3 mol.), potassium hydroxide (0·5 g.), and water (100 c.c.) were heated at

80—90° until the permanganate colour was discharged (10 min.). The mixture was filtered and evaporated to 15 c.c., and the pH adjusted to 3·2 with hydrochloric acid. The solid acidic product (0·52 g.) was filtered off, dried, mixed with calcium oxide (2 g.), and distilled at dull red heat. The distillate was dissolved in ethanol and treated with picric acid. Repeated recrystallisation of the crude picrate gave a small yield of pyridine picrate, m. p. 163—166° undepressed on admixture with an authentic sample of m. p. 167°.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, JEALOTT'S HILL RESEARCH STATION,
BRACKNELL, BERKS.

[*Received, November 4th*, 1957.]