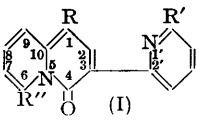
The Lupin Alkaloids. Part XV. Some Derivatives of the 4-Oxo-3-2′-pyridylpyridocoline System.*

By G. R. Clemo, B. W. Fox, and R. Raper.

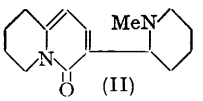
[Reprint Order No. 5269.]

During an examination of possible routes leading to the synthesis of C_{15} lupin alkaloids a number of 4-oxo-3-2′-pyridylpyridocolines and their reduction products were prepared.

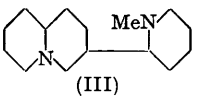
In the investigation of possible synthetic routes to some of the C_{15} lupin alkaloids, we regarded the 4-oxo-3-2′-pyridiylpyridocoline system (I; R = R′ = R″ = H) as a convenient precursor (Clemo, Morgan, and Raper, *J.*, 1936, 1025). Its 1-carboxylic ester (I; R = CO_2Et, R′ = R″ = H) has already been employed by various workers (see Manske and Holmes, "The Alkaloids," Academic Press Inc., New York, Vol. III, pp. 160 *et seq.*). The ethoxycarbonyl group is lost when this base is heated with 2N-hydrochloric acid, giving 4-oxo-3-2′-pyridylpyridocoline (I; R = R′ = R″ = H) (cf. Galinovsky and Kainz, *Monatsh.*, 1947, **77**, 137). Catalytic reduction of the methiodide of this, with Raney nickel and diethylamine (cf. Barltrop and Taylor, *J.*, 1951, 108), gave a colourless solid, five molecules of hydrogen being taken up. Since this product has lost the yellow colour and fluorescence characteristic of the pyridocoline system (cf. Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681), and has an ultra-violet absorption spectrum closely resembling that of 6-methyl-2-pyridone (Fig. 1), it is presumably the piperidyl-tetrahydro-compound (II). Octahydro-4-oxopyridocoline,



(I)



(II)



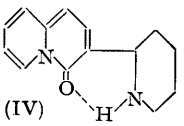
(III)

reduced to norlupinane by lithium aluminium hydride, was obtained as a by-product. Prolonged hydrogenation of the base (II) in acetic acid over platinic oxide gave a viscous oil which gave analytical figures agreeing with those for octahydro-3-2′-*N*-methylpiperidyl-4-oxopyridocoline and was reduced by lithium aluminium hydride to a sparteine-like base, octahydro-3-2′-*N*-methylpiperidylpyridocoline (III). This structure was proposed by Marion and Fenton (*J. Org. Chem.*, 1948, **13**, 780) for the alkaloid pusilline, and our product may contain the externally compensated form of this, together with diastereoisomers. Work is being continued on this substance.

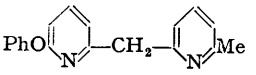
4-Oxo-3-2′-pyridylpyridocoline (I; R = R′ = R″ = H) was hydrogenated in ethanol over platinic oxide at atmospheric temperature and pressure to a light yellow, fluorescent solid, $C_{14}H_{16}ON_2$. Since this has the characteristics of the pyridocoline system and a similar ultra-violet absorption spectrum (Boekelheide and Lodge, *loc. cit.*) (Fig. 2) it is probably 4-oxo-3-2′-piperidylpyridocoline (IV), the hypsochromic shift being due to the shortening of the conjugated system by hydrogen bonding. In order to synthesise a 6- or 6′-substituted ethyl 4-oxo-3-2′-pyridylpyridocoline-1-carboxylate, it was necessary to examine the preparation of suitably 6-substituted ethyl 2-pyridylacetates. We were unable to induce 2-hydroxy-6-methylpyridine to react with phenyl-lithium. 2-Chloro- and 2-bromo-6-methylpyridine (Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 232) were converted into the hitherto unknown 2-methoxy-6-methylpyridine; this did not condense with benzaldehyde, and, when it was treated successively with phenyl-lithium and solid carbon dioxide, unchanged material, 2-hydroxy-6-methylpyridine, and a white solid were obtained. The last has an ultra-violet absorption spectrum greatly resembling those of 2-pyridone and its *N*-methyl derivative and gives a strong van der Moer reaction, and appears therefore to be a hydroxylated 1 : 6-dimethyl-2-pyridone. The possibility of its being the isomer 2-methoxy-6-methylpyridine *N*-oxide was eliminated by preparing it by Murakami and Matsumura's method (Jap. P., 177,949/1949; *Chem. Abs.*, 1951, **45**,

* Part XIV, *J.*, 1949, 663.

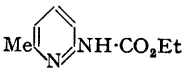
7603). The substances differ markedly. Our product is also different from 4-hydroxy-1 : 6-dimethyl-2-pyridone (Arndt, Eistert, Scholtz, and Aron, *Ber.*, 1936, **69**, 2373) which is the only dimethyl-2-pyridone hitherto described.



(IV)



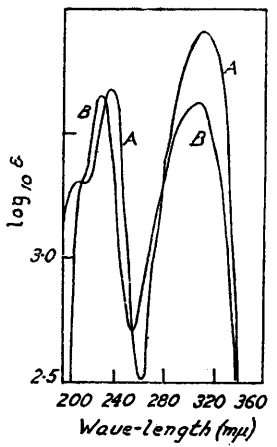
(V)



(VI)

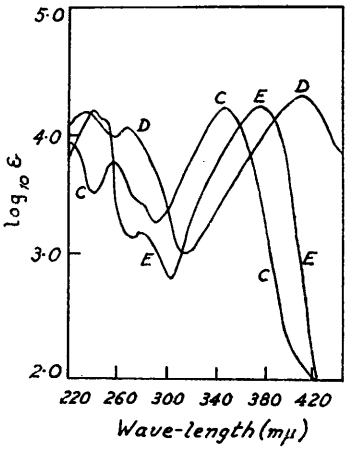
With phenol, 2-bromo-6-methylpyridine gives the 2-phenoxy-derivative but application of the Woodward and Kornfeld process for its conversion into the acetate (*Org. Synth.*, **29**, 44) gave unchanged material, phenol, 2-hydroxy-6-methylpyridine, and an oil which gives a monopicrate and has an ultra-violet absorption spectrum almost identical with that of 2-methyl-6-phenoxypyridine (Fig. 3). Analyses of the base and picrate suggest the molecular formula $C_{18}H_{16-18}ON_2$, and it is probably the bis-derivative (V).

FIG. 1.



A, The compound (II).
B, 6-Methyl-2-pyridone.

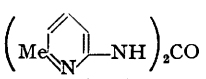
FIG. 2.



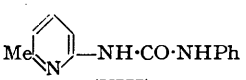
C, 3-2′-Piperidylpyridocoline (IV).
D, The base (I, R = R′ = R″ = H).
E, Octahydro-4-oxopyridocoline.

This structure accounts for the similarity of absorption spectra since the methylene bridge between the two rings prevents conjugation of their double bonds; it accounts also for the formation of only a monopicrate [Renshaw and Conn (*J. Amer. Chem. Soc.*, 1937, **59**, 297) showed that 2-phenoxypyridine was a weak base which did not form salts] and the formation of phenol as a by-product.

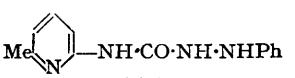
When the product of the action of phenyl-lithium on 2-amino-6-methylpyridine was treated with solid carbon dioxide or ethyl carbonate *N*-(6-methyl-2-pyridyl)urethane (VI) was produced. This forms an azeotrope with the 6-amino-2-picoline, and in an attempt to distil the mixture at a higher pressure a vigorous reaction took place, giving the urea



(VII)



(VIII)

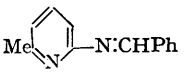


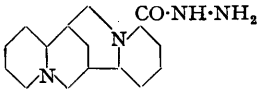
(IX)

(VII). With aniline this urethane gave the corresponding known urea (VIII) (Feist, Awe, and Kublinski, *Arch. Pharm.*, 1936, **274**, 419), and this with phenylhydrazine gave the phenylsemicarbazide (IX), a reaction similar to that discovered by Camps (*ibid.*, 1902, **240**, 350) for 2-pyridylurethane.

Adams and Schrecker (*J. Amer. Chem. Soc.*, 1949, **71**, 1188) claim that 2-acetamido-6-methylpyridine condenses with benzaldehyde to give a stilbazole, but we were unable to repeat their work, and obtained results resembling those of Feist and his co-workers (*loc.*

cit.) who state that the products are amorphous and consist largely of the Schiff's base (X) formed by elimination of the acetyl group, With phenyl-lithium the acetyl group is removed as acetophenone, 6-amino-2-picoline being simultaneously produced.

(X) 

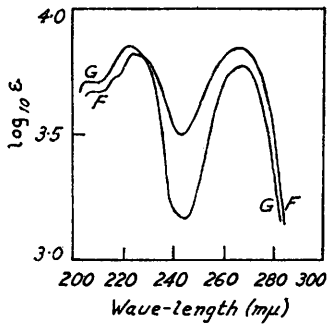


(XI)

Oxidising 2-amino-6-methylpyridine with Caro's acid gave the nitro-compound which did not condense satisfactorily with benzaldehyde, almost the whole being recovered unchanged; by Woodward and Kornfeld's process, apart from unchanged material, only a small amount of 6-chloro-2-picoline was obtained, probably formed by displacement of the nitro-group by the action of the alcoholic hydrogen chloride used in the " esterification " stage.

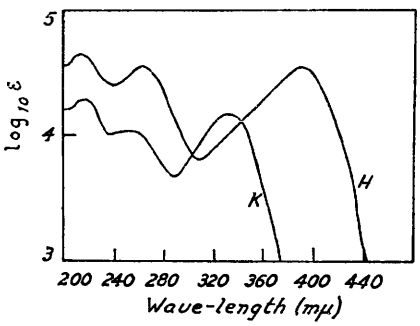
When the Woodward–Kornfeld process was applied to 2 : 6-lutidine, however, ethyl 6-methyl-2-pyridylacetate was obtained. This condensed with ethyl orthoformate to give ethyl 6 : 6′-dimethyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (I; R = CO_2Et, R′ = R″ = Me) only one of the methyl groups of which condensed with benzaldehyde, and since

FIG. 3.



F, 6-*Methyl*-6′-*phenoxydi*-2-*pyridylmethane* (V).
G, 2-*Methyl*-6-*phenoxypyridine*.

FIG. 4.

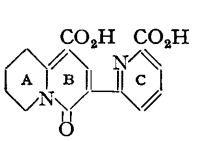


H, *The ester-acid* (I; R = CO_2Et, R′ = CO_2H, R″ = H).
K, *The diacid* (XII).

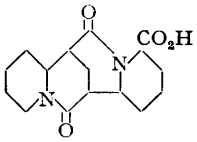
that in the 6′-position is, in effect, that of a 6-substituted 2-methylpyridine, it would be expected to react rather than the 6-methyl group. For our purposes, however, it would have been better to have the 6′-monomethyl product. We therefore condensed ethyl β-hydroxy-α-2-pyridylacrylate (Clemo, Morgan, and Raper, *J.*, 1937, 965) with ethyl 6-methyl-2-pyridylacetate, which could lead to either (I; R = CO_2Et, R′ = Me, R″ = H) or (I; R = CO_2Et, R′ = H, R″ = Me). The alternative product was produced when ethyl β-hydroxy-α-(6-methyl-2-pyridyl)acrylate was condensed with ethyl 2-pyridylacetate. One of these substances melted at 139—140°, the other at 142—143°, but the crystalline forms are different, and only the substance prepared from ethyl β-hydroxy-α-2-pyridylacrylate condenses with benzaldehyde. This substance is therefore the desired product (I; R = CO_2Et, R′ = Me, R″ = H).

Decarboxylation of this isomer gave the compound (I; R = R″ = H, R′ = Me), and its benzylidene derivative similarly gave (I; R = R″ = H, R′ = ·CH:CHPh). When attempts were made to oxidise the 6′-methyl ester or its benzylidene derivative with permanganate under a variety of conditions, the only recognisable oxidation product was benzoic acid. With selenium dioxide at 155°, however, the ester gave a mixture of ethyl 6′-carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (I; R = CO_2Et, R′ = CO_2H, R″ = H) and the corresponding 6′-aldehyde. The 6′-amide was obtained by successive treatment of the acid with thionyl chloride and ammonia, but failed to undergo either the Hofmann or the Curtius reaction. Since the latter reaction proceeds smoothly with lupininhydrazide (Clemo, Ramage, and Raper, *J.*, 1931, 3190) we considered that we might apply it satisfactorily to the hydrazide (XI) of sparteine-15-carboxylic acid, which could

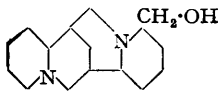
be obtained from (I; R = CO_2Et, R′ = CO_2H, R″ = H) by reductive cyclisation and subsequent reduction of the two carbonyl groups. Before the carboxy-ester could be successfully reduced catalytically residual traces of selenium had to be removed by shaking it with Raney nickel, but it then absorbed 3 mols. of hydrogen at ordinary temperature and pressure over Adams catalyst, giving the diacid (XII). During this process the yellow colour and fluorescence characteristic of the pyridocoline system were lost (see Fig. 4), indicating that the hydrogen had been taken up by ring A since a similar effect was observed by Boekelheide and Lodge (*loc. cit.*) in the reduction of methyl 4-oxopyridocoline-carboxylate to the 6 : 7 : 8 : 9-tetrahydro-compound. A similar shift of absorption bands in the ultra-violet absorption spectra of the two compounds takes place during the reduction and hydrogenolysis. Further catalytic reduction of the diacid (XII) resulted in an uptake of 7 mols. of hydrogen, giving a colourless resin, corresponding in analysis to 10 : 17-dioxosparteine-15-carboxylic acid and soluble in sodium carbonate solution, but it



(XII)



(XIII)



(XIV)

could not be reduced with lithium aluminium hydride on account of its insolubility in suitable solvents. We therefore esterified the second carboxyl group, to give (I; R = R′ = CO_2Et, R″ = H) and, after removal of selenium, hydrogenation over Adams catalyst then gave an oil whose analytical figures suggested it was ethyl dioxosparteine-15-carboxylate (XIII). This product gave no solid derivatives, and lithium aluminium hydride reduction gave no product from which a crystalline picrate could be obtained.

The 6′-aldehyde mentioned above might be expected to give 15-hydroxymethyl-10 : 17-dioxosparteine on hydrogenation, and subsequent lithium aluminium hydride reduction would yield the alcohol (XIV). On hydrogenation over platinum oxide, the aldehyde absorbed 1 mol. of hydrogen and yielded the alcohol (I; R = CO_2Et, R′ = CH_2·OH, R″ = H). A further 8 mols. of hydrogen were taken up during the next 30 hours, giving a pale yellow, viscous oil in low yields (10—15%), not imporved by use of Raney nickel at high temperatures and pressures or copper chromite.

Work is being pursued on these and other lines with the object of synthesing alkaloids of this series whose constitutions need this confirmation.

Experimental

Ethyl 4-Oxo-3-2′-pyridylpyridocoline-1-carboxylate (I; R = CO_2Et, R′ = R″ = H).—Ethyl 2-pyridylacetate (32 g.), ethyl orthoformate (30 g.), and acetic anhydride (36 ml.) were heated on a water-bath for 14 hr., and the product was poured into potassium carbonate (40 g.) in warm water (50 ml.). The oily base was extracted with chloroform, dried ($MgSO_4$), and distilled (yield, 23 g.; b. p. 250—260°/1 mm., m. p. 126°). Light absorption in EtOH: max. at 2650 (ε 22,400) and 4000 Å (ε 21,125).

Attempts were made to reduce the substance by placing it in a Soxhlet thimble through which an ethereal solution of 6 equivs. of lithium aluminium hydride refluxed. The complex mixture of products was separated by chromatography on alumina, ten bands being obtained, from one of which a *substance* forming yellow prisms, m. p. 140° (decomp.), was obtained (Found: C, 70·0, 70·0; H, 5·5, 6·1. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·25%).

4-Oxo-3-2′-pyridylpyridocoline (I; R = R′ = R″ = H).—The above ester (10 g.) was refluxed for 5 hr. with 2N-hydrochloric acid (30 ml.), and the cooled solution basified with 30% aqueous potassium hydroxide; *4-oxo-3-2′-pyridylpyridocoline* separated (7·5 g.). It crystallised from water in shining yellow plates, m. p. 111—112° after loss of water at 100° (Found: C, 70·3; H, 5·0; N, 11·7. $C_{14}H_{10}ON_2,H_2O$ requires C, 70·0; H, 5·0; N, 11·65%. Found, in the anhydrous base: C, 75·8; H, 4·9. $C_{14}H_{10}ON_2$ requires C, 75·5; H, 4·5%). The substance gives a deep crimson colour with a dilute solution of chromic oxide in concentrated sulphuric acid. Light absorption: Max. at 2350 (ε 14,850), 2675 (ε 10,810), and 4125 Å (ε 19,360).

The *methiodide* was obtained by heating the hydrated base (13·5 g.), methyl iodide (10·8 ml.),

and acetone (10 ml.) in a sealed tube in the water-bath for 1 hr. The product was triturated with acetone (20 ml.), collected, and crystallised from acetone in yellow plates with a violet reflex, m. p. 253—254° (Found: C, 49·1; H, 3·8; N, 7·8. $C_{14}H_{10}ON_2,CH_3I$ requires C, 49·5; H, 3·6; N, 7·7%).

6 : 7 : 8 : 9-*Tetrahydro*-3-(1-*methyl*-2-*piperidyl*)-4-*oxopyridocoline*.—The above methiodide (15·2 g.), diethylamine (10 ml.), and Raney nickel (W2) in methanol (150 ml.) were hydrogenated at 170°/160 atm. for 4½ hr. The catalyst and solvents were removed, the residue was basified with potassium carbonate and extracted with chloroform, and the extract dried and distilled. 4-*Oxonorlupinane* (0·6 g.), b. p. 100—103°/2 mm. (Found: C, 70·6; H, 9·9; N, 9·4. $C_9H_{15}ON$ requires C, 70·6; H, 9·8; N, 9·15%), passed over first, followed by a liquid *base* (6·5 g.), b. p. 178—182°/1 mm., which readily solidified and crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 67—68° (Found: C, 73·1; H, 8·65. $C_{15}H_{22}ON_2$ requires C, 73·2; H, 8·95%). The *methiodide* forms colourless needles (from acetone), m. p. 211—212° (Found: C, 49·6; H, 6·7; N, 7·2. $C_{15}H_{22}ON_2,CH_3I$ requires C, 49·5; H, 6·4; N, 7·2%). The styphnate, yellow prisms (from methanol), has m. p. 136—138°. The oxonorlupinane, reduced with lithium aluminium hydride, furnished a base, b. p. 80—85°/18 mm., which gave a picrate, m. p. 211° (norlupinane picrate, 212°).

Octahydro-3-(1-*methyl*-2-*piperidyl*)-4-*oxopyridocoline* (II).—The above tetrahydro-base (1 g.) in acetic acid (40 ml.) was hydrogenated at 100 lb./sq. in. and room temp. over platinum oxide for 30 hr. Solvent and catalyst were removed, the residue was basified with potassium carbonate and extracted with ether, and the dried extract was distilled, giving a pale yellow *octahydro*-base (0·4 g.), b. p. 172—174°/0·1 mm. (Found: C, 72·2; H, 10·8. $C_{15}H_{26}ON_2$ requires C, 72·0; H, 10·4%).

Octahydro-3-(1-*methyl*-2-*piperidyl*)*pyridocoline* (III).—The octahydro-4-oxo-compound (0·3 g.) in dry ether (5 ml.) was added carefully to lithium aluminium hydride (0·2 g.) in ether (10 ml.) and refluxed for 18 hr. Water and then sulphuric acid (10 ml.; 20%) were added, the aqueous layer was basified with 30% aqueous potassium hydroxide and extracted with chloroform, and the dried extract distilled, giving a pale yellow *product*, b. p. 114—116°/0·2 mm. (Found: C, 76·6; H, 12·0; N, 11·3. $C_{15}H_{28}N_2$ requires C, 76·3; H, 11·8; N, 11·8%). When methyl iodide was added to an ethyl acetate solution of the base, an oil and a solid were obtained. The latter recrystallised from ethyl acetate in colourless prisms, m. p. 258—260°. The perchlorate and picrate were oils.

4-*Oxo*-3-2′-*piperidylpyridocoline*.—4-Oxo-3-2′-pyridylpyridocoline (2·5 g.) in ethanol (50 ml.) and hydrochloric acid (1 drop) was hydrogenated at room temp. and pressure for 36 hr., 720 ml. (3 mols.) being absorbed. Working up as usual gave the *piperidyl* compound as a yellow syrup (b. p. 210—220°/2 mm.) which soon solidified and crystallised from light petroleum (b. p. 40—60°) in cream-coloured needles, m. p. 76—77° (Found: C, 74·2; H, 7·4. $C_{14}H_{16}ON_2$ requires C, 73·7; H, 7·0%). The *picrate* softens at 164° and melts at 174—175° (Found: C, 53·0; H, 4·2; N, 14·8. $C_{14}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 52·5; H, 4·2; N, 15·3%); the N-*methyl* derivative *hydriodide* forms colourless needles, m. p. 235°, from acetone (Found: C, 48·4; H, 4·9. $C_{15}H_{19}ON_2I$ requires C, 48·6; H, 5·1%).

4-*Oxo*-3-(1-*methyl*-2-*piperidyl*)*pyridocoline*.—4-Oxo-3-2′-piperidylpyridocoline methiodide (0·5 g.) was warmed for ½ hr. on the water-bath with sodium hydroxide (30%; 5 ml.), and the product was extracted with chloroform and distilled. An oily *base* (0·05 g.; b. p. 160—170°/1 mm.) was obtained which solidified and recrystallised from light petroleum (b. p. 60—80°) in yellow needles, m. p. 89—90° (Found: N, 11·7. $C_{15}H_{18}ON_2$ requires N, 11·6%). The *picrate* forms yellow needles, m. p. 195—196°, from methanol (Found: N, 15·1. $C_{15}H_{18}ON_2,C_6H_3O_7N_3$ requires N, 14·9%).

2-*Chloro*-6-*methylpyridine*.—The following method is better than that of Seide (*J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216). 2-Hydroxy-6-methylpyridine (Adams and Schrecker, *J. Amer. Chem. Soc.*, 1949, **71**, 1188) (10 g.) and phosphorus oxychloride (20 g.) were heated at 150° for 18 hr., the product was basified with 20% aqueous potassium hydroxide and extracted with chloroform, the extract dried, and the solvent removed, giving the base as an oil (9·3 g.), b. p. 75—80°/10 mm.

2-Bromo-6-methylpyridine was prepared in the same way as 2-bromopyridine (Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 232). It is a colourless sweet-smelling oil, b. p. 80—90°/10 mm. Willink and Wibaut (*Rec. Trav. chim.*, 1934, **53**, 417) give b. p. 205—207°/772 mm. It gave a picrate (yellow needles from methanol), m. p. 163°, and a hydrobromide (colourless plates from acetone), m. p. 168—170° with a change of crystal shape between 135° and 140°.

2-*Methoxy*-6-*methylpyridine*.—Sodium (8 g.) was dissolved in methanol (100 ml.) and the

solution evaporated to a syrup which was heated with 2-bromo-6-methylpyridine (50 g.) in an autoclave at 200° for 1 hr. The reaction mixture was poured into water, the liberated base extracted with chloroform, the extract dried, the solvent removed at 70—80°, and the residue fractionated through a 7" Vigreux column, giving the *methoxy*-base (34·3 g.), b. p. 156°/759 mm., n_D^{20} 1·5590 (Found: C, 67·95; H, 7·9. C_7H_9ON requires C, 68·3; H, 7·3%), having a fruity smell and giving a picrate, yellow needles (from ethanol), m. p. 132—133°.

When 2-methoxy-6-methylpyridine was added to phenyl-lithium in ether, the red complex poured on solid carbon dioxide, and the colourless product treated with ethanolic hydrogen chloride as in Woodward and Kornfeld's process, a product was obtained which was fractionated into unchanged material (60%), 2-hydroxy-6-methylpyridine (10%), m. p. and mixed m. p. 159°, and a white *substance* (20%; obtained by sublimation of the fraction, b. p. 125°/1 mm.), m. p. 161°, depressed to 139° by admixture with 2-hydroxy-6-methylpyridine (Found: C, 60·6; H, 6·5; N, 9·8. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%).

2-*Methoxy*-6-*methylpyridine* N-*Oxide*.—2-Methoxy-6-methylpyridine (4·75 g.) was added slowly to ice-cold hydrogen peroxide (4·6 ml.; 100-vol.), After 10 min. finely powdered phthalic anhydride (5·7 g.) was added and the whole stirred at 0° for 30 min., the pale yellow solution becoming more viscous. Hydrochloric acid (30 ml.; 10%) was added, phthalic acid filtered off after 20 min., the filtrate evaporated to dryness, and the residue dissolved in ethanol, filtered, again evaporated, and recrystallised from acetone, giving the *hydrochloride* (5·9 g.), m. p. 134°, of the *N*-oxide (Found: C, 47·9; H, 5·9. $C_7H_9O_2N$,HCl requires C, 47·9; H, 5·7%). This reacted exothermally in methanol with freshly precipitated silver oxide. After filtration and evaporation the residue crystallised from light petroleum (b. p. 60—80°), giving the N-*oxide* as colourless prisms, m. p. 55—56° (Found: N, 10·0. $C_7H_9O_2N$ requires N, 10·1%).

6-*Methyl*-2-*phenoxypyridine*.—The following modification of Renshaw and Conn's method (*loc. cit.*) was used. 6-Chloro-2-picoline (9 g.) and phenol (20 g.) were heated for 14 hr. at 180° in sealed tubes. The product was poured into water (20 ml.), potassium hydroxide solution (20 ml.; 20%) was added, and the whole steam-distilled. The distillate was extracted with ether, and the extracts were dried and fractionated through a 7" Vigreux column, giving 6-*methyl*-2-*phenoxypyridine* (9 g.), b. p. 140°/15 mm., 242—245°/750 mm., n_D^{19} 1·5760 (Found: C, 78·1; H, 6·1. $C_{12}H_{11}ON$ requires C, 77·85; H, 5·95%). Light absorption: max. at 2250 (ε 7219), 2700 Å (ε 5946). When Woodward and Kornfeld's procedure was applied to this base (13·5 g.) the products were phenol (2·1 g.), unchanged material (2·9 g.), and a pale yellow viscous *substance* (5·1 g.), b. p. 190—195°/0·2 mm. (Found: C, 78·3; H, 6·1; N, 10·1%; *M*, determined from the light absorption of picrate, 271. $C_{18}H_{16}ON_2$ requires C, 78·3; H, 5·8; N, 10·1%; *M*, 276). The *picrate* forms yellow needles, m. p. 135—136°, from ethanol (Found: C, 57·2; H, 4·3; N, 14·3. $C_{18}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 57·0; H, 3·8; N, 13·9%).

2-*Amino*-6-*methylpyridine*.—The preparation of this base has been described by Seide (*J. Russ. Phys. Chem. Soc.*, 1918, **50**, 534) but the yield can be improved as follows. Sodium (50 g.) was added to liquid ammonia (750 ml.) containing ferric nitrate (0·3 g.) in a lagged flask, and the excess of ammonia allowed to evaporate. Freshly distilled 2-methylpyridine (200 g.; b. p. 127—128°) in pure xylene (300 ml.) was added carefully and the whole refluxed and stirred at 135—140° for 5 hr., and allowed to cool slowly overnight. Ice was added to decompose sodamide, excess of hydrochloric acid added, the xylene layer removed, and the base liberated by sodium hydroxide, extracted with ether, dried, and distilled through a 7" Vigreux column (138 g.; b. p. 100—105°/15 mm., m. p. 40—41°).

6-*Methyl*-2-*pyridylurethane* (VI).—2-Amino-6-methylpyridine (20 g.) in dry ether (20 ml.) was added slowly to freshly prepared sodamide (7·2 g.) in ether (30 ml.); after 14 hr., ether (200 ml.) was added and the whole refluxed for 10 hr. Ethyl carbonate (11 g.) in ether (20 ml.) was added at such a rate as to maintain gentle reflux, and after boiling for a further ½ hr. the solution was cooled to 0° and acidified to Congo-red. The ethereal layer was removed, the aqueous liquid basified with sodium hydrogen carbonate and extracted with ether, and the extract dried; after removal of solvent, distillation gave the aminopicoline (6·4 g.) and the *urethane* (12·3 g.), b. p. 115—117°, m. p. 55—56° (from dilute ethanol) (Found: C, 59·9; H, 6·9; N, 15·3. $C_9H_{12}O_2N_2$ requires C, 60·0; H, 6·7; N, 15·55%). The *picrate* forms golden-yellow plates, m. p. 131°, from ethanol (Found: C, 43·7; H, 3·9; N, 17·2. $C_9H_{12}O_2N_2,C_6H_3O_7N_3$ requires C, 44·0; H, 3·7; N, 17·1%).

NN'-*Di*-(6-*methyl*-2-*pyridyl*)*urea* (VII).—The above urethane (VI) (3·6 g.) and 2-amino-6-methylpyridine (2·16 g.) were heated to boiling, whereupon reaction occurred exothermally. After cooling, the *urea* was obtained as colourless needles (4·8 g.), m. p. 189—190°, from benzene (Found: C, 64·3; H, 6·05; N, 22·9. $C_{13}H_{14}ON_4$ requires C, 64·4; H, 5·8; N, 23·15%).

N-(6-*Methyl*-2-*pyridyl*)-N′-*phenylurea* (VIII).—The urethane (VI) (1 g.) was boiled with aniline (0·6 g.), and the product crystallised from benzene, giving the urea as colourless needles (1·25 g.), m. p. 186—187° (Found : C, 69·0; H, 6·0. Calc. for $C_{13}H_{13}ON_3$: C, 68·7; H, 5·7%). Feist gives m. p. 186°.

4-(6-*Methyl*-2-*pyridyl*)-1-*phenylsemicarbazide*.—(*a*) The dipyridylurea (VII) and phenylhydrazine (equiv. quantities) were refluxed for 16 hr. in dry pyridine. The solution was added to 3N-sodium carbonate; the precipitated *semicarbazide*, crystallised from dilute ethanol, had m. p. 162—163°, contracting at 100° (25%) (Found : C, 59·8; H, 6·2; N, 21·8. $C_{13}H_{14}ON_4,H_2O$ requires C, 60·0; H, 6·2; N, 21·5%).

(*b*) *N*-(6-Methyl-2-pyridyl)urethane (1 g.) and phenylhydrazine (0·6 g.), refluxed for 30 min., gave the same product (1 g.), m. p. and mixed m. p. 162—163°.

Ethyl 6-*methyl*-2-*pyridylacetate* was prepared from 2 : 6-lutidine by the Woodward–Kornfeld procedure in 40% yield. It is a pale yellow liquid, b. p. 87—89°/0·2 mm. (Found : C, 67·5; H, 7·5; N, 8·2. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3; N, 7·8%). The *picrate* forms yellow plates (from ethanol), m. p. 105—106° (Found : C, 47·5; H, 4·2; N, 14·2. $C_{10}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 47·0; H, 3·9; N, 13·7%).

Ethyl 6 : 6′-*Dimethyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—Ethyl 6-methyl-2-pyridylacetate (8 g.), ethyl orthoformate (7·5 g.), and acetic anhydride (9·3 ml.) were refluxed for 3 hr., the anhydride was removed, and the residue distilled. The fraction of b. p. 220—230°/0·2 mm. (4·63 g.) rapidly solidified and from light petroleum (b. p. 100—120°) yielded the *pyridocoline* as yellow needles, m. p. 119—120° (Found : C, 70·8; H, 5·7; N, 9·0. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%).

This ester (2 g.), benzaldehdye (12 ml.), and acetic anhydride (20 ml.) were refluxed for 66 hr. Benzaldehyde was removed in steam, and on cooling the residual oil solidified and was taken up in hot acetone and boiled with charcoal and filtered. The 6′-*styryl* derivative separated on cooling in orange plates (0·4 g.), m. p. 193—194° (Found : C, 76·1; H, 5·7; N, 7·0. $C_{26}H_{22}O_3N_2$ requires C, 76·1; H, 5·4; N, 6·8%).

Ethyl β-*Hydroxy*-α-2-*pyridylacrylate*.—The following improved method was used. Potassium (10·5 g.) was dissolved in dry ethanol (37·7 ml.) and ether (100 ml.); ether (150 ml.) was added, and a mixture of ethyl 2-pyridylacetate (42 g.) and ethyl formate (21 g.) run into the ice-cooled solution. A solid separated which soon dissolved on shaking. After 40 hr. a pale cream-coloured solid had been deposited. Water (100 ml.) was added, the ether layer removed, and the aqueous solution just acidified to Congo-red and at once basified with potassium carbonate. The solid was extracted with chloroform, the solvent removed, and the residue crystallised from light petroleum (b. p. 60—80°) in almost colourless needles (38 g.), m. p. 99°.

Ethyl 6′-*Methyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—The above hydroxymethylene compound (10 g.), ethyl 6-methyl-2-pyridylacetate (9·4 g.), and acetic anhydride (25 ml.) were refluxed for 1½ hr. Acetic anhydride was removed in a vacuum, and the resulting liquid poured into a solution of potassium carbonate (32 g.) in water (150 ml.) at 100°. The cooled suspension was extracted with chloroform and dried, and the *pyridocoline* left on evaporation crystallised in yellow needles (14·8 g.), m. p. 142—143° (Found : C, 70·3; H, 5·5; N, 8·9. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·3; N, 9·1%. Light absorption, max. at 2670 (ε 19,600) and 4040 Å (ε = 21,110).

6′-*Methyl*-4-*oxo*-3-2′-*pyridylpyridocoline* was produced when this ester (1 g.) was boiled for 16 hr. with 5N-hydrochloric acid (10 ml.), the mixture basified with 20% potassium hydroxide, and the solid filtered off from the cooled solution and crystallised from water. It forms golden yellow plates with blue-green reflex (0·7 g.), m. p. 101—102° (Found : C, 73·6; H, 5·4; N, 11·6. $C_{15}H_{12}ON_2,\frac{1}{2}H_2O$ requires C, 73·5; H, 5·3; N, 11·4%).

Ethyl β-*Hydroxy*-α-(6-*methyl*-2-*pyridyl*)*acrylate*.—This *ester* was prepared in the same way as the methyl-free compound and forms prisms (m. p. 67—68°) and needles (m. p. 59—60°) from light petroleum (b. p. 60—80°). The forms are interconvertible by crystallisation from this solvent (Found : C, 64·1; H, 6·5; N, 7·0. $C_{11}H_{13}O_2N$ requires C, 63·7; H, 6·3; N, 6·8%).

Ethyl 6-*Methyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—Ethyl β-hydroxy-α-(6-methyl-2-pyridyl)acrylate (1 g.), ethyl 2-pyridylacetate (0·9 g.), and acetic anhydride were refluxed for 2 hr. and worked up as for the 6′-methyl compound. The 6-*methyl* compound forms yellow needles (1·4 g.), m. p. 139—140°, from light petroleum (b. p. 100—120°) (Found : C, 70·1; H, 5·5; N, 9·4%).

Ethyl 4-*Oxo*-3-2′-*pyridyl*-6′-*styrylpyridocoline*-1-*carboxylate*.—Ethyl 6′-methyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (3 g.), benzaldehyde (3 ml.), and acetic anhydride (30 ml.)

were refluxed for 80 hr. and worked up as before. The *product* crystallised from acetone in old-gold needles (1·8 g.), m. p. 174—175° (Found: C, 75·5; H, 5·2; N, 7·1. $C_{25}H_{20}O_3N_2$ requires C, 75·8; H, 5·05; N, 7·1%).

4-Oxo-3-2′-pyridyl-6′-styrylpyridocoline was formed when the ester was boiled for 18 hr. with concentrated hydrochloric acid. Crystallised from ethanol–water, it has m. p. 163—164° (Found: C, 81·3; H, 5·4; N, 8·4. $C_{22}H_{16}ON_2$ requires C, 81·5; H, 4·9; N, 8·6%).

Ethyl 6′-Formyl- and 6′-Carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate.—A finely ground mixture of ethyl 6′-methyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (4·2 g.; dried at 100°/15 mm. for 1 hr.) and freshly sublimed selenium dioxide (3·4 g.) were heated to 155—160°; a vigorous reaction took place, steam being evolved. After 15 min. at this temperature, the cooled residue was triturated with N-hydrochloric acid (100 ml.), then heated to boiling and filtered. Sodium acetate solution (20%) was added to the hot filtrate till a yellow solid separated. The suspension was cooled to 80° and immediately filtered, giving the *formyl* derivative, which crystallised from 1 : 1 light petroleum (b. p. 60—80°)–benzene in yellow prisms (2·5 g.), m. p. 179—180° (Found: C, 67·1; H, 4·5; N, 8·5. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·35; N, 8·7%). It gave a deep red colour with benzidine in glacial acetic acid. The *oxime* was formed when the formyl derivative (1 g.) was boiled for 1 hr. with hydroxylamine hydrochloride (0·25 g.) in pyridine (10 ml.). The pyridine was evaporated in a current of air and the solid residue recrystallised from methanol; it had m. p. 275—277° (0·7 g.) (Found: C, 64·55; H, 4·9. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·45%). The original filtrate from the formyl derivative, on cooling to room temperature, deposited the 6′-carboxylic acid (1·4 g.) which crystallised from water as the *dihydrate*, yellow needles, sintering at 120—125°, m. p. 214—216° (Found: C, 57·45; H, 4·7; N, 7·5. $C_{18}H_{14}O_5N_2,2H_2O$ requires C, 57·45; H, 4·8; N, 7·5%). The anhydrous *acid* was obtained (m. p. 215—216°) by careful heating at 130° (Found: N, 8·3. $C_{18}H_{14}O_5N_2$ requires N, 8·3%). Light absorption: max. at 2150 (ε 44,920), 2650 (ε 37,730), and 3930 Å (ε 37,730). The *diacetate* has m. p. 235—236° (decomp.) (Found: C, 57·4; H, 4·3. $C_{18}H_{14}O_5N_2,2C_2H_4O_2$ requires C, 57·6; H, 4·8%).

Ethyl 6′-Carbamoyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate.—The acid (0·45 g.) was refluxed for ½ hr. with thionyl chloride (3 ml.), and the clear yellow-brown solution evaporated on the water-bath; benzene (2 ml.) was added, and the whole again evaporated. Aqueous ammonia (10 ml.; *d* 0·880) was added, and the *amide* collected and recrystallised from dioxan–water (3 : 2) as yellow needles (0·45 g.), m. p. 265—267° (Found: C, 64·4; H, 4·1. $C_{18}H_{15}O_4N_3$ requires C, 64·1; H, 4·45%).

6 : 7 : 8 : 9-Tetrahydro-4-oxo-3-2′-pyridylpyridocoline-1 : 6′-dicarboxylic Acid (XII).—Ethyl 6′-carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate dihydrate (1·1 g.) was suspended in water (50 ml.), and sufficient sodium hydroxide solution (40%) was added dropwise to effect dissolution. The solution was shaken with Raney nickel for 10 min., the nickel filtered off, platinum oxide (0·1 g.) added, and the yellow solution shaken with hydrogen at atmospheric temperature and pressure: 201 ml. were absorbed in 3 hr., the solution becoming bright red and then colourless. The catalyst was removed, and addition of a few drops of 3N-hydrochloric acid precipitated the *tetrahydropyridocoline trihydrate*, which crystallised from water in colourless plates (0·9 g.), m. p. 247—249° (decomp.) (Found: C, 52·3; H, 5·3; N, 7·6. $C_{16}H_{14}O_5N_2,3H_2O$ requires C, 52·2; H, 5·4; N, 7·6%). Light absorption: max. at 2150 (ε 20,100), 2650 (ε 10,000), and 3300 Å (ε 15,010).

10 : 17-Dioxosparteine-15-carboxylic Acid (XIII).—Ethyl 6′-carboxy-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate dihydrate (1·5 g.) was shaken in acetic acid (50 ml.) and water (30 ml.) with Raney nickel and filtered. Platinic oxide (0·1 g.) was added, and the whole shaken with hydrogen at atmospheric temperature and pressure for 70 hr., 705 ml. (7 mols.) being absorbed. After removal of catalyst and solvents a white resin remained (1 g.) which distilled at 200—210°/0·2 mm. (Found: C, 63·2; H, 7·4. $C_{16}H_{22}O_4N_2$ requires C, 62·7; H, 7·2%). This *acid* was soluble in cold 20% sodium hydroxide solution, and in sodium carbonate solution with effervescence. No picrate, picrolonate, or styphnate could be prepared.

Diethyl 4-Oxo-3-2′-pyridylpyridocoline-1 : 6′-dicarboxylate.—The dihydrate of the monoethyl ester (2·7 g.) and thionyl chloride (10 ml.) were refluxed for ½ hr., the excess of thionyl chloride removed by evaporation and treatment with benzene, ethanol (10 ml.) was added (much hydrogen chloride was evolved), and the whole refluxed for ½ hr. Excess of ethanol was removed, and the diester liberated with potassium carbonate and extracted with chloroform. Removing the solvent left the *diester*, which solidified and crystallised from light petroleum (b. p. 100—120°) in golden-yellow needles (2·5 g.), m. p. 146—147° (Found: C, 65·6; H, 5·3; N, 8·0. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9; N, 7·65%).

Ethyl 10 : 17-*Dioxosparteine*-15-*carboxylate*.—The above diethyl ester (1 g.) in glacial acetic acid (25 ml.) was shaken for 10 min. with Raney nickel, and the filtered solution was shaken with platinic oxide (0·2 g.) and hydrogen at 100 lb./sq. in. and room temperature for 18 hr., 7 mols. being absorbed. The solvent was removed, the residue basified as above and extracted with chloroform, and the extract distilled, giving the gummy *ester* (0·4 g.), b. p. 210—220°/0·2 mm. (Found : N, 8·4. $C_{18}H_{26}O_4N_2$ requires N, 8·4%). On reduction of this (0·25 g.) with lithium aluminium hydride, a trace of oil (5 mg.), b. p. 150—160°/0·2 mm., which gave neither solid picrate nor picrolonate, and a glass (0·2 g.) were obtained.

Ethyl 6′-*Hydroxymethyl*-4-*oxo*-3-2′-*pyridylpyridocoline*-1-*carboxylate*.—Ethyl 6′-formyl-4-oxo-3-2′-pyridylpyridocoline-1-carboxylate (0·9 g.) in glacial acetic acid (40 ml.) was shaken with Raney nickel, filtered, and then shaken with platinic oxide (0·2 g.) and hydrogen at room temp. and pressure, 65 ml. (1 mol.) being absorbed in 10 min. The catalyst and solvent were removed, and the residue was basified as above and extracted with chloroform, on removal of which the *hydroxymethyl* compound remained; it crystallised from ethanol in yellow prisms (0·9 g.), m. p. 166—167° (Found : N, 8·8. $C_{18}H_{16}O_4N_2$ requires N, 8·6%).

18-*Hydroxymethyl*-10 : 17-*dioxosparteine* (XIV).—When the preceding hydrogenation was continued for 50 hr., 8 mols. of hydrogen were absorbed and an *alcohol* was obtained as a pale yellow oil (0·1 g.), b. p. 210—220°/0·3 mm. (Found : N, 9·6. $C_{16}H_{24}O_3N_2$ requires N, 9·5%).

One of us (B. W. F.) is indebted to the Society of Chemical Industry for the award of the John Grey Memorial Scholarship, and to the Lancashire Education Authority for a maintenance grant.

KING'S COLLEGE, NEWCASTLE-UPON-TYNE. [*Received, March* 31*st*, 1954.]