Application of the Bischler Reaction to the Preparations of Some Pyrrolopyridines and the Novel Dipyrrolopyridine System

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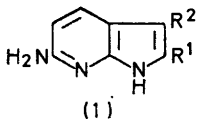
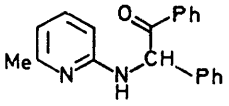
The Bischler reaction, using α-hydroxy-ketones and 2,6-diaminopyridine, has yielded 6-amino-1*H*-pyrrolo-[2,3-*b*]pyridines and the novel system 1,7-dihydrodipyrrolo[2,3-*b*:3',2'-*e*]pyridine with a variety of alkyl and aryl substituents. The reaction failed to give the corresponding unsubstituted heterocycles. 2,6-Diphenyl-1,7-dihydrodipyrrolo[2,3-*b*:3',2'-*e*]pyridine is shown to undergo ready reaction with electrophilic reagents to give 3,5-substituted derivatives.

THE Bischler reaction has been widely used in the synthesis of indoles,[1,2] and a few applications to the synthesis of pyrrolopyridines have been reported. A patent [3] claimed the preparation of 5,6,7,8-tetrahydro-α-carboline but this was shown to be incorrect.[4,5]

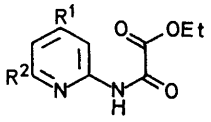


(1)

a; $R^1 = R^2 = Ph$
b; $R^1 = R^2 = C_6H_4OMe\text{-}p$
c; $R^1 = Me, R^2 = H$
d; $R^1 = R^2 = Me$
e; $R^1 = R^2 = H$
f; $R^1 = H, R^2 = Ph$
g; $R^1 = R^2 = Et$
h; $R^1 = R^2 = C_6H_4Cl\text{-}p$
i; $R^1 R^2 = [CH_2]_4$
j; $R^1 = Ph, R^2 = H$



(2)



(3)

a; $R^1 = R^2 = Me$
b; $R^1 = H, R^2 = MeCONH_2$

Bernstein *et al.*[6] prepared 6-amino-2,3-diphenyl-1*H*-pyrrolo[2,3-*b*]pyridine (1a) by the treatment of 2,6-diaminopyridine with benzoin. Similarly Herbert and Wibberley [7] prepared 6-amino-2,3-bis-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1b) from anisoin. Attempts to extend the scope of this reaction using 4-hydroxyhexan-3-one and ω-hydroxyacetophenone were unsuccessful. 2-(α-Benzoylbenzylamino)-6-methylpyridine (2) and the 2-ethoxalylaminopyridines (3a and b) were prepared but could not be cyclised.

Despite these reported failures there seemed no obvious reason why the Bischler reaction should not proceed with activated pyridines and we therefore decided to re-investigate this ring closure. We now report the successful preparation of novel pyrrolo- and dipyrrolopyridines from 4-hydroxyhexan-3-one and other α-hydroxy-ketones. We also report a preliminary study of the reactivity of the dipyrrolopyridines towards electrophilic reagents.

Preparations.—A typical melt reaction to produce a monopyrrolopyridine is that of 2,6-diaminopyridine hydrochloride, 2,6-diaminopyridine, and 3-hydroxybutan-2-one in the molar ratio 1 : 0·2 : 1. This mixture was heated for 30 min at 130—140 °C and then for 30 min at 180—190 °C. This two stage heating was chosen in order to minimise volatilisation of the hydroxyketone. The yields of monopyrrolopyridine by this melt procedure are given in the Table. The methyl group in the monomethylpyrrolopyridine (1c) was assigned to the 2-position, by comparison of its chemical shift (τ 7·7) with those for the methyl groups in the 2,3-dimethylpyrrolopyridine (1d) (τ 7·74 and 7·91). This accords with the mechanism of the Bischler reaction (Scheme 2, below). Attempts to extend this approach to the synthesis of unsubstituted 6-amino-

Preparation of substituted 6-amino-1*H*-pyrrolo[2,3-*b*]-pyridines

Starting materials: 2,6-Diaminopyridine (g) [a]	Conc. hydrochloric acid (cm³) [a]	Carbonyl compound (g) [a]	Product	M.p. (°C)	Yield (%) *b*	Yield (%) *c*
120·0	90	1-Hydroxypropan-2-one (74·0)	(1c)	182—183	9·7	Trace
6·5	4·5	3-Hydroxybutan-2-one (4·4)	(1d)	152—153	12·5	37·5
		4-Hydroxyhexan-3-one	(1g)	104—106		37·5
16·4	9·0	4,4'-Dichlorobenzoin (28·1)	(1h)	278—281	26·6	
		2-Hydroxycyclohexanone	(1i)	169—171		49·5
		ω-Hydroxyacetophenone	(1j)			Nil

[a] Quantities of reagents used in the 'melt' method. [b] Yield in the 'melt' method. [c] Yield in the 'toluene solvent' method. In each case, 2,6-diaminopyridine (10·9 g, 0·1 mol), the appropriate carbonyl compound (0·11 mol), and conc. hydrochloric acid (0·5 cm³) in toluene (100 cm³) was refluxed for 18 h with continuous removal of water.

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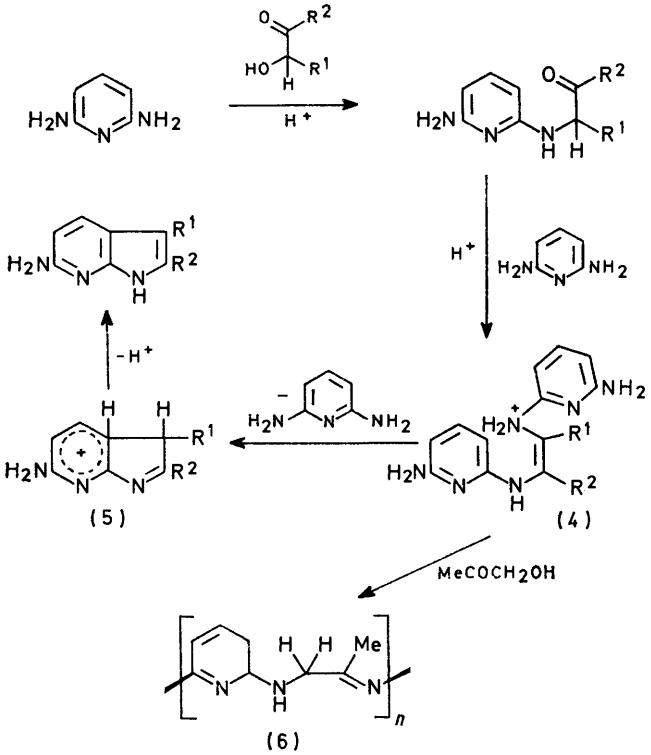
[1] W. A. Remers and R. K. Brown, 'The Chemistry of Heterocyclic Compounds,' eds. E. C. Taylor and A. Weissberger, Interscience, New York, 1972.
[2] R. J. Sundberg, 'The Chemistry of Indoles,' ed. A. T. Blomquist, Academic Press, New York and London, 1970.
[3] G.P. 547,985/1930.
[4] N. Campball and E. B. McCall, *J. Chem. Soc.*, 1951, 2411.
[5] W. L. Mosby, 'Heterocyclic Systems with Bridgehead Nitrogen Atoms,' ed. A. Weissberger, Interscience, New York, Part I, 1961.
[6] J. Bernstein, W. A. Lott, E. Shaw, and B. Stearns, *J. Amer. Chem. Soc.*, 1947, **69**, 1151.
[7] R. Herbert and D. G. Wibberley, *J. Chem. Soc.* (*C*), 1969, 1505.

1*H*-pyrrolo[2,3-*b*]pyridine (1e) by using commercial or freshly prepared samples of hydroxyacetaldehyde were unsuccessful. No product having the expected R_F



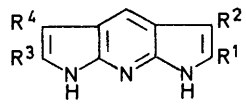
SCHEME 1

value or colour reaction with Ehrlich's reagent [8] was observed. Various solvent systems were tried in order to improve the low yields of the melt reaction; the most successful procedure was to use toluene as solvent in an apparatus fitted with a Dean and Stark water trap. However, 1-hydroxypropan-2-one and ω-hydroxyacetophenone gave only intractable polymers under these conditions, which may reflect the greater energy required to reach a transitions state with considerable carbonium ion character (5) (Scheme 1) from the intermediate (4; $R^1 = H$). Failure to cyclise at this stage could then lead to polymer formation (6). In agreement with this the amorphous material obtained from the reaction of 1-hydroxypropan-2-one and 2,6-diaminopyridine had a u.v. spectrum similar to that of 2,6-diaminopyridine.

Although the normal course of the reaction between the readily available α-halogenoketones and 2-aminopyridines is the formation of imidazo[1,2-*a*]pyridines [5] rather than the pyrrolo[2,3-*b*]pyridine system we investigated the use of 2,6-diaminopyridine with some α-halogenoketones. 2,6-Diaminopyridine was treated with ω-chloroacetophenone under melt conditions and gave the 3-phenylpyrrolopyridine (1f) in 4% yield. We assign the structure to the 3-phenyl derivative on the following evidence. The n.m.r. spectrum shows a 1H signal at τ −1·1, characteristic of the pyrrolic NH, and a 2H signal at 4·3 exchangeable with D_2O. This confirms the product as a pyrrolopyridine rather than an imidazopyridine. The mass spectrum however, does not show the presence of an M — PhCN ion as would be expected for a 2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine [9] and as found in the mass spectrum of the 2,6-diphenyldipyrrolopyridine (7e) (see below). This contrasts with the formation of 2-phenylindole from the corresponding cyclisation of 2-phenacylaniline.[1]

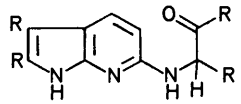
In a second approach to the use of α-halogenocarbonyl compounds for synthesis of pyrrolopyridines, the monosodium salt of 2,6-diaminopyridine was treated with bromoacetaldehyde diethyl acetal in toluene and gave 2-amino-6-(2,2-diethoxyethylamino)pyridine. Treatment of this acetal under ring closure conditions gave intractable products only. Acidic hydrolysis under mild conditions also gave only an intractable solid; the i.r. spectrum did not indicate the presence of a carbonyl group. The n.m.r. spectrum showed broad peaks roughly corresponding to the 3,5- and 4-protons in the starting material, no aldehydic or side chain protons being distinguishable. α-Anilinoaldehydes are also reported to be unstable.[10] Attempts to cause 1-bromopropan-2-one diethyl acetal to react with the monosodium salt of 2,6-diaminopyridine under identical conditions led only to the recovery of starting materials.

Since only α-hydroxy-ketones produce monopyrrolopyridines in reasonable yield, these were now used in the stepwise preparation of 1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyridines. The pyrrolopyridine (1a) (2 mol), benzoin (1 mol), and hydrochloric acid (1 mol) were heated together under melt conditions to give the tetraphenyldipyrrolopyridine (7a) hydrochloride (9·3%)



(7)

a; $R^1 = R^2 = R^3 = R^4 = Ph$
b; $R^1 = R^2 = Me, R^3 = R^4 = Ph$
c; $R^1 = R^2 = R^3 = R^4 = Me$
d; $R^1 = R^2 = R^3 = R^4 = Et$
e; $R^1 = R^3 = Ph, R^2 = R^4 = H$
f; $R^1 = R^3 = Me, R^2 = R^4 = H$
g; $R^1 = R^3 = Ph, R^2 = R^4 = Br$
h; $R^1 = R^3 = Ph, R^2 = R^4 = Me_2NCH_2$
i; $R^1 = R^3 = Ph, R^2 = R^4 = Et_2NCH_2$



(8) a, R = Ph
b; R = Me

and 6-(α-benzoylbenzylamino)-2,3-diphenyl-1*H*-pyrrolo[2,3-*b*]pyridine (8a) (36%). Similar reaction of 3-hydroxybutan-2-one with the pyrrolopyridine (1a) gave

[8] J. G. Kirchner, ' Technique of Organic Chemistry, Vol. XII, Thin-layer Chromatography,' Interscience, New York, 1967.

[9] R. Herbert and D. G. Wibberley, *J. Chem. Soc.* (*B*), 1970, 459.

[10] M. Chastrette, *Ann. Chim.* (*France*), 1962, **7**, 643.

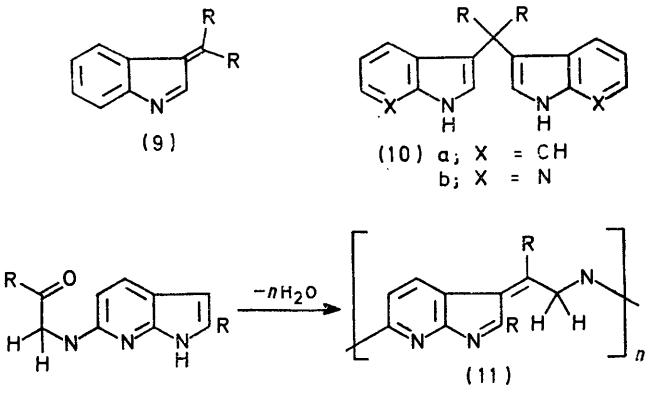
the 2,3-dimethyl-5,6-diphenyldipyrrolopyridine (7b) in 27·6% yield.

In an effort to improve the synthesis of dipyrrolopyridines, the reaction of the dimethylpyrrolopyridine (1c) with 3-hydroxybutan-2-one in toluene was attempted. The expected 2,3,5,6-tetramethyldipyrrolopyridine (7c) was only isolated in low yield (14·9%). Chromatography of the mother liquors gave the pyrrolopyridine (8b) in 57·7% yield.

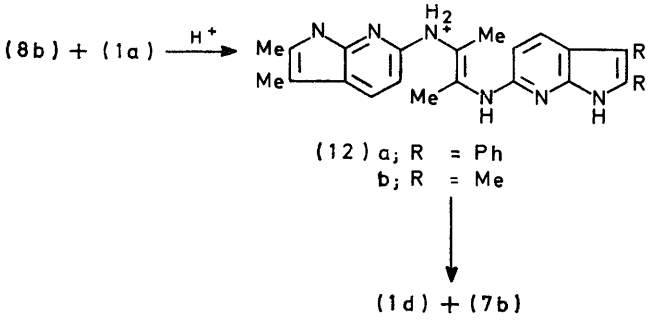
Having established that dipyrrolopyridines could be prepared in a two step Bischler reaction, the possibility of a one-step production of symmetrical 1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyridines was investigated. A mixture of 2,6-diaminopyridine hydrochloride (1 mol) and 3-hydroxybutan-2-one (2 mol) was heated under melt conditions and gave the expected tetramethyldipyrrolopyridine (7c) in 37·6% yield. Similar reactions using 4-hydroxyhexan-3-one or ω-hydroxyacetophenone gave the 2,3,5,6-tetraethyl- (7d) (20%) and the 2,6-diphenyl-dipyrrolopyridine (7e) (9·7%) respectively. The orientation of the phenyl groups in the latter product was confirmed by the mass spectrum which contained a significant M — PhCN ion. This fragmentation has been shown to be important in the fragmentation of 2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridines [9] and 2-phenylindoles.[11] Furthermore this compound gave a positive test with Ehrlich's reagent so confirming the absence of substituents in the 3- and 5-positions.[2] The preparation of other dipyrrolopyridines unsubstituted in the 3,5-positions by one step reaction of hydroxyacetaldehyde or 1-hydroxypropan-2-one with 2,6-diaminopyridine hydrochloride gave only amorphous intractable solids. Similar results were obtained when 1-hydroxypropan-2-one was treated under melt conditions with the 2-methylpyrrolopyridine (1c) in an attempt to prepare the 2,6-dimethyldipyrrolopyridine (7f).

These results show that the Bischler reaction provides a convenient route to 2,3,5,6-tetrasubstituted-1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyridines (7), but not in general to 3,5-unsubstituted dipyrrolopyridines. This failure may be due to the instability of the more reactive 3,5-unsubstituted dipyrrolopyridines under the reaction conditions: it is notable that the only 3,5-unsubstituted dipyrrolopyridine synthesised, in poor yield, by this method is the 2,6-diphenyl derivative (7e) in which the molecule is stabilised by phenyl conjugation. Indoles undergo acid catalysed condensation with aldehydes or ketones at the 3-position to give 3-methyleneindoles (9) or di-indol-3-ylmethanes (10a). 1*H*-Pyrrolo[2,3-*b*]pyridines condense with aldehydes at the 3-position to give di-3-(1*H*-pyrrolo[2,3-*b*]pyridyl)methanes (10b).[7] The 3,5-unsubstituted-dipyrrolopyridines (7; $R^2 = R^4 = H$) may be formed in these reactions and then undergo similar condensations with the carbonyl function of the hydroxy-ketone to give polymeric products. Alternatively the intermediate aminoketone may polymerise when the 3-position is free (11).

It was of interest to observe the results of a crossed Bischler reaction, and a mixture of the aminoketone (8b), the 2,3-diphenylpyrrolopyridine (1a), and hydrochloric acid was treated at 180—190 °C for 0·75 h. A sample of the crude reaction mixture was separated by preparative



t.l.c. and gave the 2,3-dimethyl-5,6-diphenyl- (7b) and the 2,3,5,6-tetramethyl-dipyrrolopyridine (7c), in a ratio of 4 : 1 respectively. The formation of (7b) is consistent with the formation of the intermediate enediamine (12a) (Scheme 2).



SCHEME 2

The most characteristic feature of the i.r. spectra of the dipyrrolopyridines is the presence of a strong sharp peak at 3445 ± 25 cm^{-1}, assigned to the non-hydrogen-bonded NH stretching vibration. A broad variable band in the region 3250—2700 cm^{-1} usually having a maximum near 3170 cm^{-1} is assigned to the hydrogen-bonded NH stretching vibration. The NH stretching vibration in 1*H*-pyrrolo[2,3-*b*]pyridine absorbs at 3472 cm^{-1} in chloroform and 3200 in KBr or Nujol.[12]

In the n.m.r. spectra of these dipyrrolopyridines the 4-proton appears as a singlet usually in the region τ 2·25—2·50, and no fine splitting is revealed for this signal upon scale expansion. The 3,5-protons in the 2,6-diphenyldipyrrolopyridine (7e) appeared as a singlet at τ 3·13, and no splitting due to 1,3- or 3,4-coupling was observed. Similarly no 1,3-coupling is observed in 1*H*-pyrrolo[2,3-*b*]pyridine,[12] although indole shows 1,3-coupling (2·1 Hz).[13]

Reactions.—Pyrrolopyridines undergo electrophilic substitution in the 3-position like indole, but with greater difficulty. This reflects the electron-withdraw-

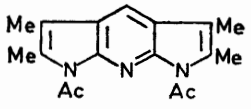
[11] J. C. Powers, *J. Org. Chem.*, 1968, **33**, 2044.
[12] R. E. Willette, *Adv. Heterocyclic Chem.*, 1968, **9**, 27.
[13] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 1964, 981.

ing effect of the pyridine nitrogen atom, which is enhanced by protonation in the acidic media normally used for electrophilic substitution reactions.

Fusion of a second electron-rich pyrrole ring to the pyridine ring will tend to neutralise the electron-withdrawing effect of the pyridine nitrogen atom, and the dipyrrolopyridine system was therefore expected to be more reactive towards electrophilic substitution than the pyrrolopyridines and possibly comparable with indole in reactivity. The pyrrolopyridines fail to give a positive test with Ehrlich's reagent, while indoles unsubstituted in the 3-position give a positive test. The 2,6-diphenyldipyrrolopyridine (7e) gave a mauve-pink colouration on standing at room temperature or on gentle warming with Ehrlich's reagent in acetic acid. This confirms that, in this case at least, the 1,7-dihydrodipyrrolo[2,3-*b*:3′,2′-*e*]pyridine system is more reactive than the pyrrolopyridines, as predicted above.

Treatment of (7e) with pyridinium perbromide hydrobromide in pyridine readily gave the 3,5-dibromo-derivative (7g). That the bromine had entered at the 3,5-positions was confirmed by the failure of the product to give a positive test with Ehrlich's reagent, and the absence in the n.m.r. spectrum of the high field signal at τ 3·13 assigned to the 3,5-protons. Treatment with either dimethylamine or diethylamine, and formaldehyde in acetic acid–dioxan as for 2-phenylindole [14] gave the 3,5-dialkylaminomethyl-derivatives (7h) and (7i) in 85 and 44% yields respectively. 3,5-Substitution was assigned to these products from a negative Ehrlich's test and the n.m.r. spectrum which showed that both dialkylaminomethyl groups occupied magnetically equivalent environments, and lacked the high field aromatic protons. Treatment under reflux with acetic anhydride for up to 20 h led to recovery of starting material instead of the expected 1,7-diacetyl-, 3,5-diacetyl-, or 1,3,5,7-tetra-acetyl derivatives. Treatment of an acetic acid solution with 2 equiv. of nitric acid led only to precipitation of the nitrate salt of the starting material.

Since the 3,5-unsubstituted derivatives were not readily available, the possibility of carrying out substitution reactions on the tetra-alkyl derivatives was considered. Plant and Tomlinson [15] studied the bromination of 2,3-disubstituted indoles: treatment of 2,3-dimethylindole with bromine gave 3-hydroxymethyl-2-methylindole, and in a similar manner 1-acetyl-2,3-dimethylindole gave 1-acetyl-2-hydroxymethyl-3-methylindole. Treatment of the tetramethyldipyrrolopyridine (7c) under reflux with acetic anhydride for 2 h readily gave the 1,7-diacetyl derivative (13) in



(13)

59·6% yield. This contrasts with the non-acetylation of the 2,6-diphenyldipyrrolopyridine (7e) under more vigorous conditions. Treatment of this diacetyl derivative in acetic acid with 1 or 2 moles of bromine gave no isolable bromo-derivatives (see Experimental section).

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer SP 337 grating spectrophotometer, u.v. spectra for solutions in ethanol in a Pye–Unicam SP 800 spectrometer, and n.m.r. spectra with a JEOL C-60 HL machine. Mass spectra and 100 MHz n.m.r. spectra were measured by the P.C.M.U. at Harwell.

Monopyrrolopyridines.— 6-*Amino*-2-*methyl*-1H-*pyrrolo*-[2,3-*b*]*pyridine* (1c). This is typical of the ' melt ' method. A mixture of 2,6-diaminopyridine (120 g, 1·1 mol) and concentrated hydrochloric acid (90 cm³, 1 mol) was heated to dryness. 1-Hydroxypropan-2-one (74 g, 1 mol) was added at 180—190 °C to the stirred residue, and stirring at 180—190 °C was continued for 0·5 h. The melt was cooled, dissolved in water (400 cm³), basified by addition of sodium carbonate (65 g), and the aqueous phase was decanted from the heavy tar which separated. The aqueous phase was extracted with chloroform (150 cm³), and the extract was refluxed with the tarry material for 10 min, and decanted from the tar. This procedure was repeated with three fresh portions (150 cm³) of chloroform. The chloroform extracts were combined, dried, and evaporated to yield a brown oil (73 g) which crystallised on standing. The solid was heated under reflux with water (400 cm³) for 0·25 h and the hot solution decanted from the tarry residue through a pad of cotton wool. The solution was treated with charcoal (10 g) and upon cooling buff needles separated. The tarry residue was again re-extracted with water (400 cm³) as above, to give buff needles, and further extraction of the tar gave no more crystalline material. The crystalline product was the 2-*methylpyrrolopyridine* (1c) (14 g, 9·7%), m.p. 178—180 °C, m.p. 183 °C (from water) (Found: C, 64·9; H, 6·3; N, 28·9. $C_8H_9N_3$ requires C, 65·3; H, 6·2; N, 28·6%), $\nu_{max.}$ (KCl) 3460, 3330, 3190br, 2970, 2930, and 2860 cm^{-1}, τ ($CDCl_3$) 2·55 (1H, d, $J_{4,5}$ 8 Hz, 4-H), 3·8 (1H, d, 5-H), 4·11 (1H, q, $J_{3\text{-H,Me}}$ 1 Hz, 3-H), and 7·7 (3H, d, 2-Me), *m/e* 147 (97%), 146 (100), 129 (5·5), and 119 (9).

6-*Amino*-2,3-*dimethyl*-1H-*pyrrolo*[2,3-*b*]*pyridine* (1d). Recrystallisation from water gave m.p. 147—149 °C; further recrystallisation from benzene gave needles, m.p. 152—153 °C (Found: C, 67·5; H, 6·9; N, 26·2. $C_9H_{11}N_3$ requires C, 67·1; H, 6·9; N, 26·1%), $\nu_{max.}$ (KCl) 3430, 3320, and 3240—3100 cm^{-1}, τ ($CDCl_3$) −1·15 (1H, s, NH), 2·55 (1H, d, $J_{4,5}$ 8 Hz, 4-H), 3·76 (1H, d, 5-H), 5·98 (2H, s, NH_2), 7·74 (3H, s, 2-Me), and 7·91 (3H, s, 3-Me), *m/e* 161 (100%), 160 (92), 146 (25), 143 (6), and 133 (4), $\lambda_{max.}$ (MeOH) 324 (ε 10,500), 242 (24,100), and 210 nm (15,100 dm² mol^{-1}).

6-*Amino*-2,3-*diethyl*-1H-*pyrrolo*[2,3-b]*pyridine* (1g). Recrystallisation from cyclohexane and sublimation gave needles, m.p. 104—106 °C (Found: C, 69·8; H, 8·2; N, 22·35. $C_{11}H_{15}N_3$ requires C, 69·8; H, 7·9; N, 22·2%), $\nu_{max.}$ (KCl) 3470, 3380, and 3050—3250 cm^{-1}, τ (CCl_4) −0·23 (1H, s, NH), 2·6 (1H, d, $J_{4,5}$ 8 Hz, 4-H), 3·9 (1H, d, 5-H), 5·68 (2H, s, NH_2), 7·15—7·75 (4H, m, CH_2), and 8·86 (6H, t, J 9 Hz, Me), *m/e* 189 (64%), 174 (100), and 159 (21).

6-*Amino*-2,3-*bis*-(4-*chlorophenyl*)-1H-*pyrrolo*[2,3-b]*pyridine* (1h). Crystallisation from chloroform gave fine

[14] H. M. Kissman and B. Witkop, *J. Amer. Chem. Soc.*, 1953, 1971.
[15] S. G. P. Plant and M. L. Tomlinson, *J. Chem. Soc.*, 1933, 955.

golden needles, m.p. 278—281 °C (Found: C, 64·4; H, 3·8; N, 12·0. $C_{19}H_{13}Cl_2N_3$ requires C, 64·4; H, 3·7; N, 11·9%), ν (KBr) 3485, 3395, 3200—2700, 1635, and 835 cm^{-1}, τ [$(CD_3)_2SO$] −1·4 (1H, s, NH), 2·4—2·9 (9H, m, 4-H and Ph), 3·68 (1H, d, $J_{4,5}$ 9 Hz, 5-H), and 4·23 (2H, s, NH).

2-*Amino*-5,6,7,8-*tetrahydro*-α-*carboline* (1i). Crystallisation from aqueous alcohol gave m.p. 169—171 °C (Found: C, 70·4; H, 7·1; N, 22·1. $C_{11}H_{13}N_3$ requires C, 70·6; H, 7·0; N, 22·4%), $\nu_{max.}$ (C_4Cl_6) 3425, 3330, 3250—2700, and 1630 cm^{-1}, τ ($CDCl_3$) 0·70 (1H, s, NH), 2·51 (1H, d, $J_{4,5}$ 8 Hz, 4-H), 3·72 (1H, d, 5-H), 6·1 (2H, s, NH_2), 7·40 (4H, m, CH_2), and 8·19 (4H, m, CH_2).

6-*Amino*-3-*phenyl*-1H-*pyrrolo*[2,3-b]*pyridine* (1f). A mixture of 2,6-diaminopyridine (4·4 g, 0·04 mol) and ω-bromoacetophenone (4 g, 0·02 mol) was stirred at 180—190 °C for 0·5 h. The melt was cooled, extracted with cold M-hydrochloric acid (50 cm^3) and the residue neutralised by suspension in dilute ammonia solution. The solid was collected and examined by t.l.c. which showed it to be a complex mixture, containing a component with similar R_F value and colour reaction with 4-*NN*-dimethylaminobenzaldehyde as 6-amino-2,3-diphenyl-1*H*-pyrrolo[2,3-*b*]-pyridine (1a). The solid was extracted by refluxing with ether (3 × 50 cm^3). The ether extracts were combined and evaporated, and the residue (0·5 g) crystallised from aqueous alcohol to give the 3-*phenylpyrrolopyridine* (1f) (0·08 g, 4%) as buff plates, m.p. 199—202 °C (Found: C, 74·3; H, 5·4; N, 19·6. $C_{13}H_{11}N_3$ requires C, 74·6; H, 5·3; N, 20·1%), $\nu_{max.}$ (KCl) 3470, 3415, 3350—2900, 1605, 755, and 705 cm^{-1}, τ [$(CD_3)_2SO$] −1·1 (1H, s, NH), 2·0 (1H, d, $J_{4,5}$ 9 Hz, 4-H), 2·18—2·8 (6H, m, 2-H and Ph), 3·57 (1H, d, 5-H), and 4·3 (2H, s, NH_2), *m/e* 209 (100%), 208 (11), 191 (5), 181 (8), 154 (3), and 133 (3).

2,3,5,6-*Tetramethyl*-1,7-*dihydrodipyrrolo*[2,3-*b*:3′,2′-e]*pyridine* (7c).—A mixture of 2,6-diaminopyridine (10·9 g, 0·1 mol) and concentrated hydrochloric acid (9 cm^3, 0·1 mol) was heated to dryness. 3-Hydroxybutan-2-one (17·6 g, 0·2 mol) was added at 130—140 °C to the stirred residue, and the melt was stirred at 130—140 °C for 0·5 h, and then at 180—190 °C for a further 0·5 h. The melt was cooled, pulverised, and stirred with M-hydrochloric acid (100 cm^3) for 1 h. The insoluble residue was collected and suspended in 4M-ammonia solution (100 cm^3) for 1 h. The free base (7c) was then collected, dried, and crystallised from acetic acid as buff needles (8 g, 38%), m.p. 265—267 °C (Found: C, 73·6; H, 7·20; N, 19·6. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1; N, 19·7%), $\nu_{max.}$ 3470, 3160, 2860, 2910, and 2960 cm^{-1}, τ [$(CD_3)_2SO$] −0·43 (2H, s, NH), 2·39 (1H, s, 4-H), 7·72 (6H, s, 2-Me), and 7·83 (6H, s, 3-Me), *m/e* 213 (100%), 212 (80), and 198 (26·5).

2,3,5,6-*Tetraethyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7d).—The ' melt ' method described in the previous preparation was used. The free base was obtained as a tarry solid, which could not be crystallised. The product was dissolved in hot acetone (10 cm^3), concentrated hydrochloric acid (2·5 cm^3) was added, and on cooling fine needles separated; these were collected and washed with acetone to give the *hydrochloride* of (7d) (1·5 g, 21%), m.p. >330 °C (Found: C, 67·4; H, 8·0; N, 13·8. $C_{17}H_{24}ClN_3$ requires C, 66·8; H, 7·9; N, 13·7%), τ [$(CD_3)_2SO$] −1·85 (2H, s, NH), 1·6 (1H, s, 4-H), 7·25 (8H, m, CH_2), and 8·79 (12H, m, Me).

Attempted Preparation of 2,6-*Dimethyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7f).—2,6-Diaminopyridine (5·5 g, 0·05 mol) was treated with 1-hydroxypropan-2-one (7·4 g, 0·1 mol) as above to yield an amorphous solid which t.l.c. indicated to be mainly polymeric. The solid was extracted by refluxing with two portions (25 cm^3) of chloroform. The chloroform extracts were combined and evaporated to yield an oily solid (0·25 g). Preparative t.l.c. (silica gel; toluene–acetone 3 : 2) gave one major band, which was found to be the 2-methylpyrrolopyridine (1c) (0·15 g, 2%) by comparison of m.p. and i.r. data.

Attempted Preparation of 1,7-*Dihydrodipyrrolo*[2,3-*b*:3′,2′-e]*pyridine*.—2,6-Diaminopyridine (1·1 g, 0·01 mol) was treated with hydroxyacetaldehyde (1·2 g, 0·02 mol) as above to yield a black amorphous solid, m.p. >330 °C, insoluble in acetic acid, alcohol, and hydrochloric acid. The material could not be obtained crystalline. T.l.c. examination indicated the material to be polymeric, and no material having the expected R_F value or colour reaction with Ehrlich's reagent was observed.

2,6-*Diphenyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7e).—The free base was prepared by the method as described above. Crystallisation from acetic acid gave the 2,6-*diphenyldipyrrolopyridine* (7e) (3 g, 9·7%) as yellow needles, m.p. 329—331 °C (Found: C, 81·2; H, 5·0; N, 13·4. $C_{21}H_{15}N_3$ requires C, 81·5; H, 4·9; N, 13·6%), $\nu_{max.}$ (KBr) 3450, 3300—3100, 695, and 750 cm^{-1}, τ [$(CD_3)_2SO$] −1·2 (2H, s, NH), 1·9—2·8 (11H, m, 4-H and Ph), and 3·14 (2H, s, 3- and 5-H), *m/e* 309 (100%), 282 (3), and 206 (6).

Attempted Preparation of 6-*Methyl*-2,3-*diphenyl*-1H-*pyrrolo*[2,3-b]*pyridine*.—A mixture of 2-amino-6-methylpyridine (1·08 g, 0·01 mol) and concentrated hydrochloric acid (0·9 cm^3, 0·01 mol) was heated to dryness, and benzoin (2·12 g, 0·01 mol) was added to the residue. The mixture was stirred and heated at 195 °C for 1 h. The melt was cooled, pulverised, suspended in dilute ammonia solution, and extracted into ether (25 cm^3). The ether extract was stirred with 2·5M-hydrochloric acid (25 cm^3) for 2 h at 0 °C. The white solid (2 g) which separated was collected, washed with ether, and crystallised from aqueous alcohol to give 2-(α-benzoylbenzylamino)-6-methylpyridine hydrochloride (1·1 g), m.p. >330 °C. A sample of the hydrochloride was neutralised to give the free base, m.p. 112—113 °C (lit.,[7] 114—116 °C), $\nu_{max.}$ (KBr) 1675 cm^{-1}.

2-*Amino*-6-(2,2-*diethoxyethylamino*)*pyridine*.—A solution of sodamide was prepared by addition of sodium (2·3 g, 0·1 mol) to liquid ammonia (50 cm^3) containing hydrated iron(III) nitrate (0·1 g). To this solution dry toluene (30 cm^3) and 2,6-diaminopyridine (10·9 g, 0·1 mol) were added. The ammonia was allowed to evaporate and the residue was heated under reflux for 3 h beneath a dry nitrogen atmosphere. Bromoacetaldehyde diethyl acetal (19·9 g, 0·1 mol) was then added and the mixture heated under reflux for 20 h. Water (250 cm^3) was added, the toluene phase separated, and the aqueous phase extracted with ether (2 × 50 cm^3). The toluene and ether extracts were combined, dried, and evaporated to give a brown oil (19 g). The oil was distilled under vacuum to give 2-*amino*-6-(2,2-*diethoxyethylamino*)*pyridine* (11 g, 48%) as a viscous oil, b.p. 150—160 °C at 0·1 mmHg (Found: C, 58·5; H, 8·5; N, 18·5. $C_{11}H_{19}N_3O_2$ requires C, 58·6; H, 8·5; N, 18·7%), $\nu_{max.}$ (thin film) 3500—3180, 2985, 2890, 1600, and 780 cm^{-1}, τ (CCl_4) 3·07 (1H, t, $J_{4,5}$ 8 Hz, 4-H), 4·46 (2H, t, 3- and 5-H), 5·07 (1H, t, *J* 6 Hz, NH), 5·55 (1H, t, $J_{\alpha,\beta}$ 5·5 Hz, β-CH), 5·76 (2H, s, NH), 6·35—6·9 (6H, m, α-CH_2 and $-OCH_2$), and 8·85 (6H, t, *J* 7 Hz, Me). On addition of D_2O the multiplet at τ 6·35—6·9 was resolved into an over-

lapping d and q, owing to decoupling of the α-CH_2 protons with the NH proton.

Attempted Cyclisation of 2-*Amino*-6-(2,2-*diethoxyethylamino*)*pyridine*.—A mixture of the foregoing compound (2·27 g, 0·01 mol) and 2M-hydrochloric acid (5 cm³) was heated under reflux for 10 min. 2,6-Diaminopyridine (0·1 g) was added, the solution distilled to dryness, and the residue stirred at 180—190 °C for 20 min. The melt was cooled, pulverised, dissolved in hot water (20 cm³), and neutralised with ammonia solution. The solid which separated was collected. The product was insoluble in organic solvents. Reprecipitation from acid solution after charcoal treatment gave 1·2 g of amorphous material, which t.l.c. indicated to be polymeric; no material having the expected R_F value or colour reaction of 6-amino-1*H*-pyrrolo[2,3-*b*]pyridine (1e) was detected.

Hydrolysis of 2-*Amino*-6-(2,2-*diethoxyethylamino*)*pyridine*.—A solution of the pyridine in 2M-hydrochloric acid (5 cm³) was heated under reflux for 10 min. The clear solution was cooled and neutralised by addition of ammonia, and the white precipitate was collected (0·7 g). Attempted crystallisation from a variety of solvents was unsuccessful, $\nu_{max.}$ (KCl) 3500—2800, 1600, 775, and 720 cm⁻¹ (all br), τ [$(CD_3)_2SO$] 2·0—2·3 and 3·5—3·7.

Dipyrrolopyridines.—*Reaction of benzoin with the* 2,3-*diphenylpyrrolopyridine* (1a). A mixture of the pyrrolopyridine (1a) (17·2 g, 0·06 mol) and concentrated hydrochloric acid (2·7 cm³, 0·03 mol) was heated to dryness. Benzoin (6·4 g, 0·03 mol) was added to the residue, and the mixture was stirred and heated at 180—190 °C for 50 min. The melt was cooled, pulverised, stirred with 4M-ammonia solution (100 cm³), and collected. Extraction with boiling acetic acid yielded 2,3,5,6-*tetraphenyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7a) *hydrochloride* (1·6 g, 9·3%) as an insoluble yellow solid, m.p. >330 °C (Found: C, 79·0; H, 4·8; N, 8·2. $C_{33}H_{24}ClN_3$ requires C, 79·6; H, 4·9; N, 8·5%), $\nu_{max.}$ (KCl) 3420, 3300—2600, 762, and 695 cm⁻¹, τ [$(CD_3)_2SO$] −1·62 (2H, s, NH), 2·22 (1H, s, 4-H), and 2·35 (20H, m, Ph). The acetic acid extract was poured into water and the precipitated solid (21 g) collected. A sample (2·5 g) of this acetic acid-soluble material was introduced onto an alumina column (2·2 × 30 cm). Elution with benzene containing increasing proportions of ether (maximum 30% ether) gave 6-(α-*benzoylbenzylamino*)-2,3-*diphenyl*-1H-*pyrrolo*[2,3-b]*pyridine* (0·62 g, 36%) as a yellow solid, m.p. 189·5—190 °C (from aqueous alcohol) (Found: C, 82·65; H, 5·3; N, 8·8. $C_{33}H_{25}N_3O$ requires C, 82·7; H, 5·3; N, 8·8%), $\nu_{max.}$ (KCl) 3420, 3295, 3065, 1695, and 1605 cm⁻¹, τ [$(CD_3)_2SO$] 2·0—3·1 (m), *m/e* 496 (100%).

2,3-*Dimethyl*-5,6-*diphenyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7b). A mixture of the pyrrolopyridine (1a) (2·85 g, 0·01 mol), 3-hydroxybutan-2-one (0·88 g, 0·01 mol), and concentrated hydrochloric acid (0·9 cm³, 0·01 mol) was stirred and heated at 130—140 °C for 0·5 h, then at 180—190 °C for 0·5 h. The melt was cooled, pulverised, dissolved in hot alcohol (20 cm³), and basified by addition of potassium hydroxide (1 g). The solution was poured into water and the precipitated solid gave the *dipyrrolopyridine* (7b) (0·9 g, 27%), m.p. 318—320 °C (from benzene) (Found: C, 82·1; H, 5·8; N, 12·45. $C_{23}H_{19}N_3$ requires C, 81·9; H, 5·7; N, 12·5%), $\nu_{max.}$ (KBr) 3465 and 3160 cm⁻¹, τ [$(CD_3)_2SO$–C_6F_6] −1·4 (1H, s, NH), −0·58 (1H, s, NH), 2·3—2·9 (11H, m, 4-H and Ph), 7·62 (3H, s, 2-Me), and 7·83 (3H, s, 3-Me), *m/e* 337 (100%), 336 (25), and 322 (6).

Reaction of 3-*hydroxybutan*-2-*one with the* 2,3-*dimethylpyrrolopyridine* (1d). A solution of (1d) (4 g, 0·025 mol), 3-hydroxybutan-2-one (2·4 g, 0·028 mol), and concentrated hydrochloric acid (0·15 g) in toluene (30 cm³) was heated under reflux for 12 h with continuous removal of water. The toluene was then evaporated off. The residue was crystallised from acetic acid to give the tetramethyldipyrrolopyridine (7c) (0·7 g, 13·9%), m.p. and mixed m.p. 264—266 °C. The acetic acid mother liquors were poured onto water and extracted with chloroform. The chloroform extract was washed with water and dilute sodium carbonate solution, dried (Na_2SO_4), and evaporated to give a brown oil. The oil was introduced onto an alumina (activity II) column. Elution with benzene gave 2,3-*dimethyl*-6-(1-*methyl*-2-*oxopropylamino*)-1H-*pyrrolo*[2,3-b]-*pyridine* (8b) (2·5 g, 58%), as a yellow oil (Found: C, 67·3; H, 7·4; N, 18·0. $C_{13}H_{17}N_3O$ requires C, 67·5; H, 7·4; N, 18·2%), $\nu_{max.}$ (thin film) 3450—3150 and 1720 cm⁻¹, τ ($CDCl_3$) 1·5 (1H, s, NH), 2·58 (1H, d, $J_{4,5}$ 8 Hz, 5-H), 3·82 (1H, d, 4-H), 5·12 (1H, m, NH), 5·5 (1H, m, CH), 7·8 (3H, s, 2-Me), 7·83 (3H, s, 3-Me), 7·92 (3H, s, MeCO), and 8·63 (3H, d, *J* 7 Hz, CH_3CHN). Upon addition of D_2O the signal at τ 5·5 decays to a q, *J* 7 Hz.

Reaction of 2,3-*Dimethyl*-6-(1-*methyl*-2-*oxopropylamino*)-1H-*pyrrolo*[2,3-b]*pyridine* (8b) *with* 6-*Amino*-2,3-*diphenyl*-1H-*pyrrolo*[2,3-b]*pyridine* (1a).—A mixture of the pyrrolopyridines (1a) (1·43 g, 5 mmol) and (8b) (1·15 g, 5 mmol) and concentrated hydrochloric acid (0·5 g) was stirred at 180—190 °C for 0·75 h. The melt was cooled, pulverised, and stirred with M-hydrochloric acid (10 cm³), and the insoluble residue was collected, dissolved in alcohol (10 cm³), and basified by addition of sodium hydroxide (2 g). The solution was poured into water and the precipitated solid was purified by preparative t.l.c. (silica gel; acetone–toluene 1 : 2 to give the 2,3-dimethyl-5,6-diphenyl- (7b) (0·133 g) and the 2,3,5,6-tetramethyl-1,7-dihydrodipyrrolo-[2,3-*b*:3′,2′-*e*]pyridine (7c) (0·021 g) identified by comparison of i.r. and n.m.r. spectra.

Acetylation of the Tetramethyldipyrrolopyridine (7c).—A solution of (7c) (2·13 g, 0·01 mol) in acetic anhydride (10 cm³) was heated under reflux for 2 h. The reaction was cooled in ice, and the crystalline solid which separated was collected, and washed with benzene to give 1,7-*diacetyl*-2,3,5,6-*tetramethyl*-1,7-*dihydrodipyrrolo*[2,3-*b*:3′,2′-e]*pyridine* (13) (1·77 g, 60%) as off-white needles, m.p. 254—255·5 °C (Found: C, 68·5; H, 6·5; N, 14·2. $C_{17}H_{19}N_3O_2$ requires C, 68·7; H, 6·4; N, 14·1%), $\nu_{max.}$ (KBr) 2985, 2940, 2880, 1710, and 1480 cm⁻¹, τ [$(CD_3)_2SO$] 2·50 (1H, s, 4-H), 7·10 (6H, s, CH_3CO), 7·43 (6H, s, 2- and 6-Me), and 7·84 (6H, s, 3- and 5-Me).

Attempted Dibromination of the 1,7-*Diacetyl Derivative* (13).—A suspension of the 1,7-diacetyl derivative (13) (1·5 g, 5 mmol) in acetic acid (75 cm³) was treated with bromine (1·6 g, 10 mmol) over 15 min at 45—50 °C. As the bromine was added, the suspended starting material dissolved to give a clear solution, and on continued addition of bromine yellow needles separated. After addition was complete the reaction was left to stand for 15 min and the crystalline solid collected. On standing and drying the product decomposed to give a black solid (1·3 g), m.p. >330 °C. This material could not be crystallised and was too insoluble for n.m.r. analysis, $\nu_{max.}$ (KBr) 3300—2500 and 1710 cm⁻¹.

Attempted Monobromination of (13).—A suspension of the 1,7-diacetyl-compound (13) (0·75 g, 2·5 mmol) in acetic acid (30 cm³) was treated with bromine (0·44 g, 2·8 mmol) over 15 min at 40 °C. The starting material dissolved, and

no precipitate formed. The solution was poured into water and extracted with chloroform, and the extract was dried and evaporated to give an amorphous solid which could not be crystallised. Preparative t.l.c. (silica gel; toluene–acetone 19 : 1) gave starting material (0·08 g, 11%) as the only significant band.

Mannich Reaction of the Diphenyldipyrrolopyridine (7e).—(a) *With diethylamine.* The dipyrrolopyridine (7e) (0·31 g, 1 mmol) was added over 1 h to a stirred mixture of diethylamine (0·292 g, 4 mmol), formaldehyde (0·3 g; 40% w/v; 4 mmol), dioxan (2 cm^3), and acetic acid (2 cm^3). The mixture was stirred for a further 0·5 h, neutralised with 2M-ammonia solution, and extracted with ether. The ether extract was dried and evaporated to yield a yellow oil which crystallised on standing. Recrystallisation from carbon tetrachloride–light petroleum gave 3,5-*bis*(*diethylaminomethyl*)-2,6-*diphenyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7i) (0·21 g, 44%), m.p. 173—175 °C (Found: C, 77·3; H, 6·6; N, 14·2. $C_{31}H_{37}N_5$ requires C, 77·6; H, 6·9; N, 14·6%), $\nu_{max.}$ (KBr) 3435, 3415, 2985, 2800, 1615, 765, and 700 cm^{-1}, τ ($CDCl_3$) −1·21 (2H, s, NH), 1·39 (1H, s, 4-H), 2·1—2·8 (10H, m, Ph), 6·13 (4H, s, CH_2), 7·40 (8H, q, J 7 Hz, CH_2), and 8·95 (12H, t, J 7 Hz, Me).

(b) *With dimethylamine.* The dipyrrolopyridine (7e) (0·21 g, 1 mmol) was treated with dimethylamine (0·68 g; 25% w/v; 4 mmol) and formaldehyde (0·3 g; 40% w/v) as above. Recrystallisation from carbon tetrachloride–light petroleum gave 3,5-*bis*(*dimethylaminomethyl*)-2,6-*diphenyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7h) (0·35 g, 85%), m.p. 203—205 °C (Found: C, 75·3; H, 6·9; N, 15·9. $C_{31}H_{37}N_5$ requires C, 76·6; H, 6·9; N, 16·5%), $\nu_{max.}$ (KBr) 3440, 2950, 2875, 1615, 770, and 705 cm^{-1}, τ (CDCl) −1·28 (2H, s, NH), 1·64 (1H, s, 4-H), 2·1—2·8 (10H, m, Ph), 6·30 (4H, s, CH_2), and 7·67 (12H, s, Me_2N).

Bromination of the Diphenyldipyrrolopyridine (7e).—Pyridinium perbromide hydrobromide (0·7 g, 2·2 mmol) was added over 10 min to a stirred suspension of the dipyrrolopyridine (7e) (0·31 g, 1 mmol) in pyridine (4 cm^3) maintained below 5 °C. The solution was stirred for a further 10 min, then poured into water and basified by addition of ammonia solution. The solid which separated gave 3,5-*dibromo*-2,6-*diphenyl*-1,7-*dihydrodipyrrolo*[2,3-b:3′,2′-e]*pyridine* (7g) (0·25 g, 55·6%) as yellow needles, m.p. 281—284 °C (decomp.) (from acetic acid) (Found: C, 54·4; H, 3·0; N, 8·9. $C_{21}H_{13}Br_2N_3$ requires C, 54·0; H, 2·8; N, 9·0%), $\nu_{max.}$ (KBr) 3415, 1635, 1450, 765, and 700 cm^{-1}, τ [$(CD_3)_2SO$] −2·12 (2H, s, NH) and 1·9—2·8 (11H, m, 4-H and Ph).

Attempted Acetylation of the Diphenyldipyrrolopyridine (7e).—The dipyrrolopyridine (7e) (0·31 g, 1 mmol) and acetic anhydride (25 cm^3) were heated under reflux for 2 h. Yellow needles separated on cooling (0·3 g) and were shown to be starting material by i.r. analysis. Similar results were obtained when the reflux period was extended to 20 h.

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