An Improved Synthesis of 6*H*-Pyrido[4,3-*b*]carbazole Derivatives

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During the acid-catalysed cyclization of 5-bromo- and 5-amino-2-{1-[3-(1-methoxyethyl)-4-pyridyl]ethylidene}-indolin-3-ones to the corresponding 6*H*-pyrido[4,3-*b*]carbazoles (ellipticines), loss of the substituent on the benzenoid ring severely reduces the product yield. The mechanism of this reaction is discussed, and the problem has been solved by modification of the side chain at position 3 of the pyridyl group. An oxidative mode of ring closure is employed and ellipticine and 9-acetamidoellipticine have thus been prepared. In general, product yields compare favourably with other routes to the 6*H*-pyrido[4,3-*b*]carbazole system. 9-Phenylellipticine has also been prepared and some circumstantial evidence for the mode of action of ellipticines in neoplastic systems is presented.

RECENTLY we described the synthesis of ellipticine (9; R = H) [1] and 9-aminoellipticine (9; R = NH_2) [2] by the route outlined in Scheme 1; these compounds show anticancer activity [3] and we intended to use the method to prepare a number of other derivatives for biological testing.

As a general synthesis of 6*H*-pyrido[4,3-*b*]carbazoles, however, our route suffers from a number of disadvantages. First, the reductive acetylation [4] and subsequent oxidation of 3-(1-methoxyethyl)pyridine (1) involves several steps, not shown in the Scheme, and the overall yield of the intermediate (2) is poor. Secondly, since the conditions required for the ring closure of the indoles (7) to 5,11-dihydroellipticines (8) (60% aqueous hydrobromic acid at 100° for several hours) are severe, only 6*H*-pyrido[4,3-*b*]carbazoles containing relatively stable substituents survive this treatment. In addition, in the formation of 9-aminoellipticine from the indole (7; R = NHAc) a substantial quantity of ellipticine accompanies the desired product.[2]

The production of ellipticine in this reaction is interesting since the direct removal of an amino-substituent from an aromatic nucleus requires a reductive mechanism. In

[1] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.

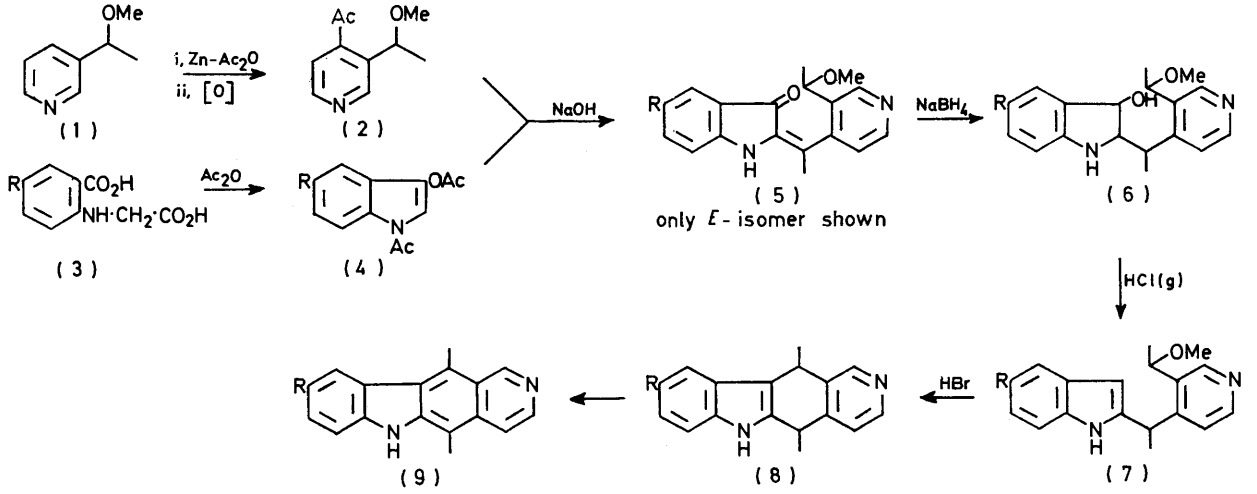
[2] M. Sainsbury and B. Webb, *J.C.S. Perkin I*, 1974, 1580.

[3] M. Hayat, G. Mathe, M. M. Janot, P. Potier, N. Dat-Xuong, A. Cavé, T. Sevenet, C. Kan-Fan, J. Poisson, J. Miet, J. Le Men, F. Le Goffic, A. Gouyette, A. Ahond, L. K. Dalton, and T. A. Connors, *Biomedicine*, 1974, **21**, 101, and references cited therein.

[4] J. P. Wibaut and J. F. Arens, *Rec. Trav. chim.*, 1941, **60**, 119.

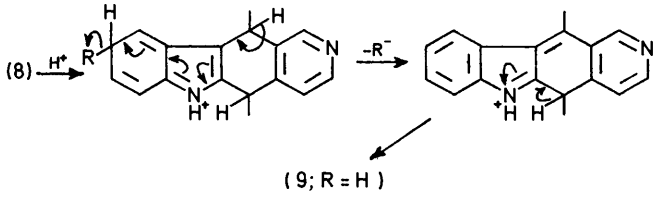
the absence of introduced reducing agents, deamination must be associated with the oxidation of the primary cyclization product (8; R = NH_2), which is not normally isolated, possibly as shown in Scheme 2.

Ellipticine is the main product when the bromoindole (7; R = Br) is treated with hydrobromic acid, but in this



SCHEME 1

case evidence was also obtained (see Experimental section) for the presence of a 9-bromodemethylellipticine

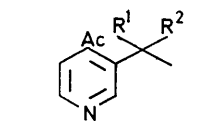


SCHEME 2

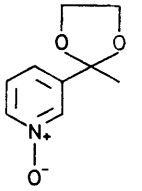
and a demethylellipticine, as well as 9-bromoellipticine (9; R = Br), in the reaction mixture. Clearly demethylation as well as deprotonation can occur during treatment with hydrobromic acid, but no ellipticine or demethyl derivatives were found when 9-phenylellipticine (9; R = Ph) was obtained from (7; R = Ph). This is to be expected, however, since displacement of the phenyl group is much less likely than of either an amino- or a halogeno-substituent.

In view of these limitations to our original approach we decided to replace the ether (2) in Scheme 1 by a more accessible intermediate which when incorporated as a 2-substituent into a suitable indole derivative would require less vigorous cyclization conditions. 3,4-Diacetylpyridine (10) and the acetal (11) seemed to meet the latter requirement and an efficient route to these compounds was sought.

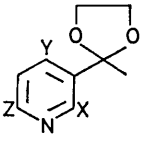
4-Bromo- and 4-iodo-pyridines react with butyllithium and acetonitrile to form 4-acetylpyridines; [5] 4-chloropyridines do not react under these conditions, but chloro-substituents attached to the pyridine nucleus may be exchanged by treatment with potassium iodide.[6] In view of the reported conversion of 3-methylpyridine *N*-oxide into 4-chloro-3-methylpyridine with phosphoric trichloride,[7] our first approach was to heat the *N*-oxide (12) with this reagent, in anticipation of forming (13), which by halogen exchange *etc.* could be converted into (10). The reaction product, however, was a mixture which probably contains the 2- and 6-chloropyridines (14) and (15), the tetracyclic compound (16), and traces of



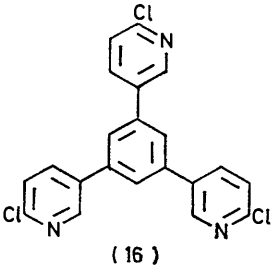
(10) R^1R^2 = O
(11) R^1R^2 = O·CH_2·CH_2·O



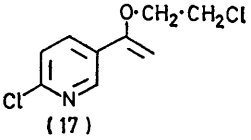
(12)



(13) X = Z = H, Y = Cl
(14) Y = Z = H, X = Cl
(15) X_1 = Y = H, Z = Cl



(16)



(17)

compound (17). No 4-chloropyridine derivatives were detected.

[5] J. P. Wibaut and L. C. Heeringe, *Rec. Trav. chim.*, 1955, **74**, 1003.

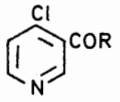
[6] E. Klingsberg, *J. Amer. Chem. Soc.*, 1950, **72**, 1031.

[7] T. N. Riley, D. B. Hale, and M. C. Wilson, *J. Pharm. Sci.*, 1973, **62**, 983.

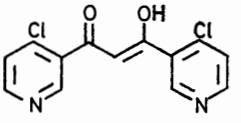
Next the known[8] acid chloride (18) was prepared as the hydrochloride salt and treated with an excess of dimethylcadmium. It was hoped to obtain 3-acetyl-4-chloropyridine (19), but the only product isolated was the stable enol (21) and, although the structure of this compound suggests that some ketone (19) is generated during the reaction, a number of modifications to the conditions failed to provide an efficient route to this compound. On one occasion, when the acid chloride salt was treated with an excess of triethylamine and the product treated directly with dimethyl cadmium, the secondary amide (20) was obtained.

Pyridine-2,5-dicarbonyl chloride affords 2,5-diacetylpyridine when treated with dimethylcadmium;[9] consequently it was anticipated that 3,4-diacetylpyridine might be obtained similarly from pyridine-3,4-dicarbonyl chloride. Such a reaction, however, gave only the lactone (22), identical with the compound obtained by the action of methylmagnesium bromide upon pyridine-3,4-dicarboxylic anhydride.[10]

A further potential route to the required intermediate (10) or (11) was based upon the observation that *N*-alkoxypyridinium salts react with cyanide ion to afford 4-cyanopyridines[11] and such compounds combine with methylmagnesium bromide to give 4-acetyl derivatives. Thus 3-acetyl-1-ethoxypyridinium bromide (23) was prepared and treated with sodium cyanide in aqueous solution, but instead of a single product a complex mixture



(18) R = Cl
(19) R = Me
(20) R = NEt_2



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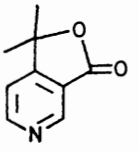
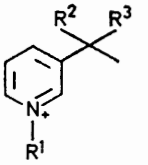


(22)

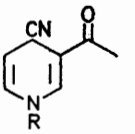
was obtained. Similar results were obtained with the acetal (24).

If 3-acetyl-1-benzylpyridinium bromide is treated with sodium cyanide the 4-cyano-1,4-dihydropyridine (26) is formed.[12] Oxidation and *N*-debenzylaton of this should give 3-acetyl-4-cyanopyridine, but attempts to effect the conversion failed with both this compound and the *para*-nitrobenzyl analogue (27). It is interesting, however, that when the latter was treated with dilute hydrochloric acid, hydrolysis to the amide (28) occurred (*cf.* Anderson and Berkelhammer[12]).

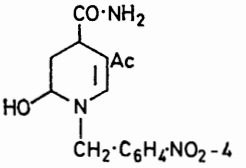
Recently Suzue *et al.*[13] have shown that 4-cyanopyridines may be prepared by the action of potassium cyanide and ammonium chloride upon 1-(*N*-methylacetamido)pyridinium salts, the latter being obtained



(23) R^1=OEt, R^2R^3=O
(24) R^1=OEt, R^2R^3=O·CH_2·CH_2·O
(25) R^1 = Bz, R^2R^3=O



(26) R = $PhCH_2$
(27) R = 4-NO_2·C_6H_4·CH_2



(28)

from the corresponding pyridines by treatment with hydroxylamine-*O*-sulphonic acid followed by acetylation and methylation (Scheme 3).

When 3-acetylpyridine was treated with hydroxylamine-*O*-sulphonic acid the product was a mixture of the oximes (29) and (31), whereas the acetal (30) gave mainly 3-acetylpyridine.

Eventually, however, the intermediate (32) was obtained in good yield by the action of *O*-mesitylsulphonylhydroxylamine[14] and acetic anhydride upon (30). Completion of the sequence (steps c and d of Scheme 3) then gave the cyano-acetal (34) in 77% overall yield from (30). Attempts to convert (34) into the corresponding acetyl compound with methylmagnesium bromide gave unsatisfactory results, but by use of methyl-lithium an almost quantitative conversion into the imine (35) was effected. Treatment of this with dilute acetic acid at 100° for 20 min gave the acetal (36), whereas similar treatment with dilute hydrochloric acid yielded 3,4-diacetylpyridine.

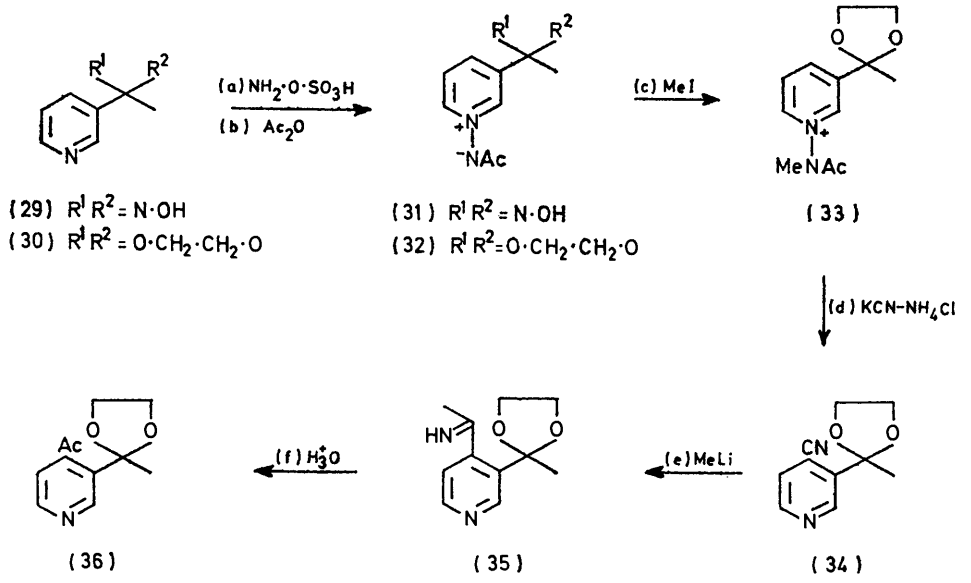
When this last compound was treated with 1 mol. equiv. of ethane-1,2-diol and toluene-*p*-sulphonic acid in benzene the tricyclic compound (37) was obtained, accompanied by (36) and the 3-acetyl isomer (38).

We speculated that an acid-catalysed condensation between indole and 3,4-diacetylpyridine might lead directly to ellipticine. However, no identifiable products were obtained from such a reaction and when 3,4-diacetylpyridine interacted with 1,3-diacetylindoxyl in aqueous sodium hydroxide solution a red gum was

[8] E. C. Taylor and A. J. Crovetti, *J. Org. Chem.*, 1954, **19**, 1633.
[9] T. S. Gardner, E. Weris, and J. Lee, *J. Org. Chem.*, 1961, **26**, 1514.
[10] W. V. Ligon, Ph.D. Thesis, University of Virginia, 1970.
[11] W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.*, 1959, **81**, 4004.
[12] A. G. Anderson, jun., and G. Berkelhammer, *J. Amer. Chem. Soc.*, 1958, **80**, 992; *J. Org. Chem.*, 1958, **23**, 1109.
[13] S. Suzue, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi*, 1973, **93**, 1331.
[14] Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Letters*, 1972, **40**, 4133.

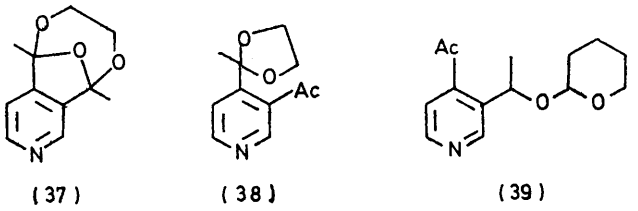
formed. This multicomponent mixture was chromatographed on alumina to give a small amount of a compound allocated structure (40).

Disappointingly, an attempted condensation between (36) and 1,3-diacetylindoxyl failed, and models showed that this failure is probably due to the steric hindrance which the rigid acetal function imparts to the 4-acetyl group. Such a constraint is much less if a single bond is attached to the α-carbon atom of the C-3 side chain and so the reactions of Scheme 3 were modified to give the tetrahydropyran derivative (39). Treatment of this

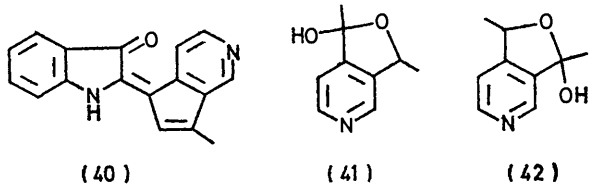


(29) R^1R^2 = N·OH
(30) R^1R^2 = O·CH_2·CH_2·O
(31) R^1R^2 = N·OH
(32) R^1R^2 = O·CH_2·CH_2·O
(33)
(34)
(35)
(36)

SCHEME 3



(37) (38) (39)



(40) (41) (42)

product with dilute hydrochloric acid at 100° gave the hemiacetal (41), and similarly when the acetal (36) was reduced with sodium borohydride, and the product hydrolysed with dilute hydrochloric acid, the isomeric compound (42) was obtained.

The acetylpyridine (39) reacted smoothly with 1,3-diacetylindoxyl in aqueous sodium hydroxide solution to give the indoxylidene (43); when this was reduced with sodium borohydride in ethanol at room temperature and the product treated with hydrogen chloride, the ether (46) was obtained. The formation of (46) results from incomplete reduction of the indoxylidene followed by cleavage of the protecting group to give an intermediate, *e.g.* (45), which then undergoes ring closure, probably as shown. We have demonstrated previously [2] that partial reduction with sodium borohydride of the enone unit of indoxylidenes of type (43) yields products analogous to (45).

However, when the reduction was repeated, this time in ethanol at the b.p., the desired indolinol (47) was obtained, which with hydrogen chloride gave the indole (49). This product, when oxidized with manganese dioxide in dichloromethane, afforded ellipticine (9; R = H), albeit in low yield. Other oxidation attempts with lead tetra-acetate or chromium trioxide in pyridine, or under Oppenauer conditions, failed to form either ellipticine or the ketone (51), whereas treatment with potassium dichromate in acetic acid gave the indoxyl derivative (52), probably *via* initial 3-protonation, nucleophilic attack on the 2-position of the indolinium cation by the hydroxy-group, and finally oxidation at C-3.

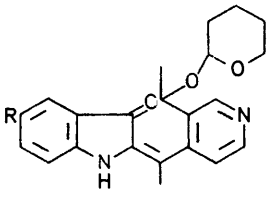
When the indole (49) was treated with phosphoric trichloride in pyridine, 5,11-dihydroellipticine (8; R = H) was formed; this is relatively stable but slowly undergoes aerial oxidation to ellipticine, particularly in the presence of silica.

Finally, when the indole (49) was treated with dimethyl sulphoxide and acetic anhydride, ellipticine was obtained in good yield.

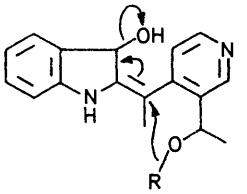
When the entire sequence was repeated using (44) and its *Z*-isomer, 9-acetamidoellipticine was prepared; the yield in the final step was 65%.

9-Aminoellipticine shows activity comparable to that

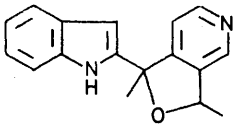
of 9-methoxyellipticine against the leukaemic mouse, whereas 9-phenylellipticine is inactive. The latter observation supports the view [15] that the anticancer activity of 6*H*-pyrido[4,3-*b*]carbazoles depends upon their intercalation between the base pairs of doubly



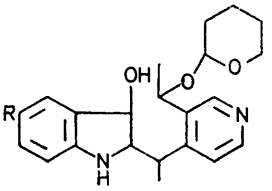
(43) R = H
(44) R = NHAc
only *E*-isomers shown



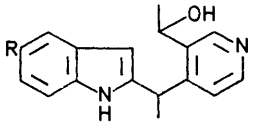
(45)



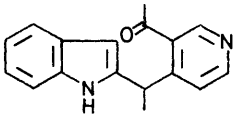
(46)



(47) R = H
(48) R = NHAc



(49) R = H
(50) R = NHAc



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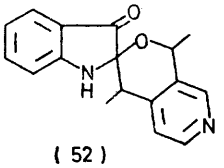

(52)

stranded DNA. From a consideration of models, 9-phenylellipticine may not readily form such an intercalation complex and thus should be comparatively inactive.

EXPERIMENTAL

U.v. spectra were recorded for solutions in 95% aqueous ethanol, and i.r. spectral data refer to Nujol mulls. ^{1}H N.m.r. spectra were recorded at either 60 or 100 MHz with tetramethylsilane as internal standard.

4-Acetamidobiphenyl-3-carbonitrile.— 4-Acetamido-3-bromobiphenyl [16] (72·5 g) and copper(I) cyanide (26·7 g) in dimethylformamide were heated under reflux for 6 h. After partial cooling the mixture was poured slowly into a warm solution of sodium cyanide (50 g) in water (250 cm^3); this was stirred vigorously for 2 h and then extracted with chloroform (500 cm^3). The organic phase was washed with aqueous 10% sodium cyanide (100 cm^3), then with water, dried, and evaporated to give the *nitrile* as needles, m.p. 161—162° (46 g, 79%), *m/e* 236 (base, M^+), 213, 195, 167, and 139; $\nu_{max.}$ 3320 (NH), 2240 (CN), and 1680 cm^{-1} (CONH); δ [$(CD_3)_2SO$] 8·62 (1H, d, *J* 9 Hz, 5-H), 7·95 (2H, m, 2- and 6-H), 7·65 (5H, m, 1-Ph), and 2·45 (3H, s, Ac) (Found: C, 76·25; H, 5·1; N, 6·8. $C_{15}H_{12}N_2O$ requires C, 76·25; H, 5·1; N, 6·8%).

4-Aminobiphenyl-3-carbonitrile.—Hydrolysis of 4-acetamido-3-bromobiphenyl [16] with 50% aqueous sulphuric acid followed by treatment of the free base in the manner described in the previous experiment gave the *nitrile* as pale brown prisms (45%), m.p. 143—144° (from ethanol), *m/e* 194 (M^+, base), 166, and 139; $\nu_{max.}$ 3460, 3360 (NH_2), and 2205 cm^{-1} (CN) (Found: C, 80·1; H, 5·1; N, 14·6. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·2; N, 14·4%).

5-Phenylanthranilic Acid.—(a) *From 4-aminobiphenyl-3-carbonitrile.* The nitrile was heated under reflux with aqueous 30% potassium hydroxide and an equal volume of ethanol until evolution of ammonia ceased (*ca.* 24 h). The ethanol was then distilled off and the residual solution acidified with concentrated hydrochloric acid to pH 3. After cooling, the precipitated acid was filtered off and crystallized from methanol to give prisms (85%), m.p. 200—201° (lit.,[17] 200—202°) (Found: C, 73·0; H, 5·4; N, 6·5. Calc. for $C_{13}H_{11}NO_2$: C, 73·2; H, 5·2; N, 6·6%).

(b) *From 4-acetamidobiphenyl-3-carbonitrile.* Hydrolysis of this compound under the same conditions as in method (a) was extremely slow; heating for 1 week was required before the evolution of ammonia stopped. The mixture was worked up as before (yield 80—86%).

N-(3-Carboxybiphenyl-4-yl)glycine.— 5-Phenylanthranilic acid (213 mg), chloroacetic acid (0·94 g), sodium carbonate (1·5 g), copper powder (0·1 g), and water (8 cm^3) were heated under reflux for 2 h. The hot mixture was filtered and the filtrate cooled and acidified to pH 3 with concentrated hydrochloric acid. After further cooling the product was collected, washed with water, and dried. Recrystallization from aqueous ethanol gave pale yellow *crystals* (65%), m.p. 211—213°, $\nu_{max.}$ 3380, 2900, 1720, 1670, and 1230 cm^{-1} (Found: C, 62·5; H, 5·2; N, 4·65. $C_{15}H_{13}NO_4,H_2O$ requires C, 62·3; H, 5·2; N, 4·8%).

1,3-Diacetyl-5-phenylindoxyl (4; R = Ph). A mixture of acetic anhydride (5 cm^3) and triethylamine (1 cm^3) was treated with the foregoing glycine (1 g) by heating on a steam-bath until all the solid had dissolved. The solution was then heated under reflux for a further 20 min. The solvents were removed under reduced pressure and the residue was extracted with hot petroleum (b.p. 60—80°). The extracts were boiled with charcoal, filtered, and evaporated to give needles (40%), m.p. 138—139° (from ethanol), *m/e* 293 (M^+), 251 (base), 209, and 152; $\nu_{max.}$ 1760 (NAc) and 1700 cm^{-1} (OAc); δ ($CDCl_3$) 8·5 (1H, d, *J* 8 Hz, 7-H), 7·65 (7H, m, 5-Ph, 2- and 4-H), 7·4 (1H, d, *J* 8 Hz, 6-H), and 2·6 and 2·35 (2 × 3H, s, OAc and NAc) (Found: C, 73·5; H, 5·3; N, 4·7. $C_{18}H_{15}NO_3$ requires C, 73·7; H, 5·15; N, 4·8%).

2-{1-[3-(Methoxyethyl)-4-pyridyl]ethylidene}-5-phenylindolin-3-one (E *and* Z-*Isomers*) (5; R = Ph). 1,3-Diacetyl-5-phenylindoxyl (780 mg) and 4-acetyl-3-(1-methoxyethyl)-pyridine (540 mg) were dissolved in aqueous 50% methanol

[15] B. Festy, J. Poisson, and C. Paoletti, *F.E.B.S. Letters*, 1971, **17**, 321.

[16] D. J. Byron, G. W. Gray, A. Ibbotson, and B. M. Worral, *J. Chem. Soc.*, 1963, 2256.

[17] G. Kranzlein, P. Ochwat, and K. Moldaenke, U.S.P. 2,012,569/1935.

(9 cm³) containing potassium hydroxide (1·8 g). The mixture was set aside under nitrogen. Within the first 24 h some orange crystals separated, but later green prisms also formed. After 4 days the solids were collected and washed with cold 50% aqueous methanol (yield 965 mg, 98%). The green compound, which is more soluble in most organic solvents than the orange product, is the *E*-isomer; the latter compound is the *Z*-form.

The E-*isomer* had m.p. 222—224°; *m/e* 270 (M^+), 338, 323 (base), 311, 295, and 162; $\nu_{max.}$ 3120 (NH), 1690 (CO), and 1640 cm⁻¹ (C=C); δ [$CDCl_3$–5% $(CD_3)_2SO$] 8·8br (1H, s, NH), 8·74 (1H, s, 2′-H), 8·5 (1H, d, *J* 5 Hz, 6′-H), 7·0—8·75 (9H, m, 5-Ph, 4-, 5′-, 6-, and 7-H), 4·4 (1H, two superimposed quartets, *J* 7 Hz, C*H*·CH_3), 3·23 and 3·15 (3H, 2 × s, OCH_3), 2·26 and 2·11 (3H, 2 × s, CH_3C), and 1·43 and 1·28 (3H, 2 × d, *J* 7 Hz, CH_3·CH) (Found: C, 78·0; H, 6·1; N, 7·5. $C_{24}H_{22}N_2O_2$ requires C, 77·8; H, 6·0; N, 7·6%). The orange product was not obtained free from the green isomer; consequently complete physical data are not available. A carbonyl band at 1685 cm⁻¹ in the i.r. spectrum of the crude product and a chemical shift of δ 2·6 for the n.m.r. signal of an olefinic methyl group support the *Z*-assignment.

2-{1-[3-(1-*Methoxyethyl*)-4-*pyridyl*]*ethyl*}-5-*phenylindole* (7; R = Ph).—Compound (5; R = Ph) (*EZ*-mixture; 3·3 g) in aqueous 70% ethanol (300 cm³) was treated with sodium borohydride (*ca.* 10 g) while boiling under reflux. After *ca.* 1 h the solvents were evaporated off and the residue partitioned between chloroform and water. The chloroform layer was dried and evaporated to leave the indoline (6; R = Ph). This was dissolved in dry methanol and the solution saturated with hydrogen chloride gas; the solvent was removed and the residue extracted with a mixture of sodium hydrogen carbonate solution and chloroform. The organic layer was then separated, dried, and evaporated to give a solid which crystallized from ethanol as solvated *prisms*, m.p. 185—186°, *m/e* 356 (M^+), 324, 309 (base), and 294; $\nu_{max.}$ 3150 (NH) and 1605 cm⁻¹ (C=C); δ ($CDCl_3$) 8·63 and 8·54 (1H, 2 × s, 2′-H), 8·4 (1H, m, 6′-H), 8·3br (1H, s, NH), 7·1—7·8 (9H, m, 5-Ph, 4-, 5′-, 6-, and 7-H), 6·5 (1H, s, 3-H), 4·5—4·9 [2H, two superimposed quartets, C*H*·CH_3 and C*H*(OCH_3)·CH_3], 3·7 (2H, q, *J* 7 Hz, CH_3·C*H*$_2$·OH), 3·36 (3H, 2 × s, OCH_3), 1·4—1·8 [6H, m, C*H*$_3$·CH= and C*H*$_3$·CH(OCH_3)], and 1·1 (3H, t, *J* 7 Hz, C*H*$_3$·CH_2·OH) (Found: C, 77·5; H, 7·4; N, 7·0. $C_{24}H_{24}N_2O$,CH_3CH_2OH requires C, 77·6; H, 7·5; N, 7·0%).

9-*Phenylellipticine* (9; R = Ph).—The indole (7; R = Ph) (1 g) in aqueous 60% hydrobromic acid (20 cm³) was heated under reflux until no further change was observed in the u.v. spectrum (*ca.* 5 h). The solution was then cooled and the solid which had separated collected, washed with 60% hydrobromic acid, and dried. The free base was liberated from this salt by treatment with aqueous sodium carbonate and extracted into chloroform.

The chloroform extracts yielded 9-phenylellipticine as yellow prisms (423 mg, 47%), m.p. 307—308°, *m/e* 322 (base), 307, and 162; $\nu_{max.}$ 3120 (NH) and 1600 cm⁻¹ (C=C); $\lambda_{max.}$ 231 (ε 33,810), 265sh (41,860), 275sh (46,150), 299 (66,545), 349 (11,810), and 354 nm (8590) δ (CF_3·CO_2H) 9·3 (1H, m, 1-H), 8·0 (3H, m, 3-, 4-, and 10-H), 7·4 (7H, m, 9-Ph, 7- and 8-H), 292 (3H, s, 11-Me), and 2·63 (3H, s, 5-Me) (Found: C, 85·5; H, 5·7; N, 8·3%; M^+, 322·1465. $C_{23}H_{18}N_2$ requires C, 85·7; H, 5·6; N, 8·7%; *M*, 322·1470).

1,3-*Diacetyl*-5-*bromoindoxyl* (4; R = Br).—5-Bromoanthranilic acid was converted into 2-carboxy-4-bromophenylglycine by the method of Holt *et al.*[18] This compound was transformed into (4; R = Br) as described above for the phenyl analogue (4; R = Ph); yield 52%; m.p. 121—122° (lit.,[10] 123°); δ ($CDCl_3$) 8·25 (1H, d, *J* 7 Hz, 7-H), 7·61 (1H, s, 2-H), 7·58 (1H, d, *J* 2 Hz, 4-H), 7·35 (1H, 2 × d, *J* 7 and 2 Hz, 6-H), and 2·50 and 2·27 (2 × 3H, 2 × s, OAc and NAc).

5-*Bromo*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethylidene*}*indoline*-3-*one* (5; R = Br).—1,3-Diacetyl-5-bromoindoxyl was combined with the acetylpyridine (2) as described for the preparation of (5; R = Ph). At the end of 4 days, however, no solid had separated so the mixture was poured on to water containing sufficient dilute hydrochloric acid to adjust the pH to *ca.* 7. Extraction with dichloromethane afforded, after removal of the solvent, a dark coloured solid (80%), which crystallized from aqueous ethanol as dark brown rosettes, m.p. 207—208°. This compound was the *Z*-isomer; the *E*-isomer was not obtained pure.

The *Z*-*isomer* showed *m/e* 372/374, 340/342, 325/327 (base), 313/315, 246, and 218; $\nu_{max.}$ 1685 (CO) and 1630 cm⁻¹ (C=C); δ ($CDCl_3$) 8·6 (1H, d, *J* 3 Hz, 2′-H), 8·18 (1H, 2 × d, *J* 5 and 3 Hz, 6′-H), 7·8 (1H, d, *J* 1·5 Hz, 4-H), 7·44 (1H, 2 × d, *J* 8 and 1·5 Hz, 6-H), 6·7 (1H, d, *J* 8 Hz, 7-H), 4·4 [1H, q, *J* 7 Hz, CH_3·C*H*(OCH_3)] 3·3 and 3·25 (3H, 2 × s, O*CH*$_3$), 2·70 and 2·65 (3H, 2 × s, C*H*$_3$·C=), and 1·45br and 1·40br (3H, d, *J* 7 Hz, C*H*$_3$CH(OCH_3)] (Found: C, 58·0; H, 4·5; N, 7·4. $C_{18}H_{17}BrN_2O_2$ requires C, 57·9; H, 4·6; N, 7·5%).

5-*Bromo*-2-{1-[3-(1-*methoxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (7; R = Br).—The indolin-3-one (5; R = Br) was treated with sodium borohydride in the usual way; the product reacted with hydrogen chloride to give *compound* (7; R = Br) (38%), m.p. 166—167° (from methanol), *m/e* 358/360 (M^+), 326/328, 311/313, (base) 296/298, 247, and 232; $\nu_{max.}$ 3150 (NH) and 1605 cm⁻¹ (C=C); δ ($CDCl_3$) 8·45 (1H, d, *J* 9 Hz, 7-H), 8·3 (1H, d, *J* 5 Hz, 6′-H), 7·6br (1H, s, 2′-H), 7·2 (3H, m, 4-, 5′-, and 6-H), 6·3br (1H, s, 3-H), 4·6 [2H, two superimposed quartets, C*H*·CH_3 and C*H*(OCH_3)CH_3], 3·3 (3H, 2 × s, OCH_3), and 1·75 and 1·45 [6H, m, C*H*$_3$·CH= and C*H*$_3$·CH(OCH_3)] (Found: C, 59·8; H, 5·4; N, 7·6. $C_{18}H_{19}BrN_2O$ requires C, 60·2; H, 5·3; N, 7·8%).

9-*Bromoellipticine* (9; R = Br).—The indole (7; R = Br) (250 mg) was dissolved in aqueous 60% hydrobromic acid (25 cm³) and heated under reflux for 1 h. The solution was cooled and neutralized with sodium carbonate. Extraction with chloroform and evaporation of the extract left a residue which crystallized when triturated with chloroform to yield a product (185 mg) which was principally ellipticine. The mass spectrum showed molecular ions corresponding to ellipticine, *m/e* 246·1155 (calc. for $C_{17}H_{14}N_2$: 246·1157); 9-bromoellipticine, *m/e* 324·0260 (calc. for $C_{17}H_{13}BrN_2$: 324·0263); 5- or 11-demethylellipticine, *m/e* 232·0008 (calc. for $C_{16}H_{12}N_2$: 232·1000); and 5- or 11-demethyl-9-bromoellipticine, *m/e* 310·0094 (calc. for $C_{16}H_{11}BrN_2$: 310·0106). Repeated sublimation and recrystallization afforded, eventually, pure ellipticine, identical (m.p. and i.r. and u.v. spectra) with an authentic sample, but despite numerous attempts using various solvent mixtures and adsorbents we were unable to obtain satisfactory separations of the other components by column or thin-layer chromatography.

3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* 1-*Oxide* (12).—3-Acetylpyridine 1-oxide [19] (4·9 g) was heated with toluene-*p*-sulphonic acid (1·1 mol. equiv.) in ethylene glycol (20 cm³) and dry benzene (400 cm³) in a Dean-Stark apparatus for 6 h. The mixture was then cooled and the benzene layer separated

[18] S. J. Holt and P. W. Sadler, *Proc. Roy. Soc.*, 1958, **148**, 481.
[19] S. Kanno, *J. Pharm. Soc.* (*Japan*), 1952, **73**, 120.

and evaporated to give the acetal (12) as an oil. More product was isolated from the ethylene glycol layer by dilution with water and extraction with chloroform. The combined product was distilled (oil-bath temperature 200—230°) to give an oil which slowly crystallized to afford a hygroscopic solid with indefinite m.p.; $\nu_{max.}$ 2980, 2880, and 2030 cm^{-1}; δ ($CDCl_3$) 3·95 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$) and 1·65 (3H, s, CCH_3).

The hydrochloride of this compound was prepared by treatment with chloroform saturated with hydrogen chloride, followed by removal of the solvent.

Reaction of the Acetal (12) *with Phosphoric Trichloride.*—The hydrochloride of (12) (1·66 g) was heated with phosphoric trichloride (6 cm^3) at 120° for 2 h. After cooling, the solution was poured onto aqueous 2N-potassium carbonate and ice; extraction with ether then afforded an oil (1·48 g) which partially crystallized. The mass spectrum of this product showed a molecular ion cluster (*m/e* 217/219/221; $C_9H_9Cl_2NO$) presumed to be due to compound (17); a group of ions corresponding to $C_9H_{10}ClNO_2$, probably (14) and (15); and a further cluster, *m/e* 311/413/415 ($C_{21}H_{12}Cl_3N_3$) due to the tetracycle (16).

The oil was warmed with 6N-hydrochloric acid on a water-bath for 10 min and the solution then extracted with chloroform.* The organic phase was washed with 5% sodium carbonate solution, dried, and evaporated to give an oil which crystallized on trituration with ether affording *tris*-(6-*chloro*-3-*pyridyl*)*benzene* (16) as pale yellow plates (80 mg), m.p. 264—266° (from acetone); $\nu_{max.}$ 1600, 1580, 1560, and 1205 cm^{-1}, $\lambda_{max.}$ 257 (ε 39,640) and 278sh nm (25,280), δ ($CDCl_3$) 8·7 (3H, d, *J* 2 Hz, 3 × 6′-H), 7·95 (3H, 2 × d, *J* 8 and 2 Hz, 3 × 4′-H), 7·75 (3H, s, benzenoid), and 7·5 (3H, d, *J* 8 Hz, 3 × 5′-H) (Found: C, 61·0; H, 3·0; N, 10·1. $C_{21}H_{12}Cl_3N_3$ requires C, 61·1; H, 2·9; N, 10·2%).

Action of Dimethylcadmium on 4-*Chloropyridine*-3-*carbonyl Chloride.*—4-Chloropyridine-3-carboxylic acid (5·3 g) was heated under reflux with thionyl chloride (80 cm^3) for 3 h. The excess of reagent was then distilled off, and last traces were removed by addition of benzene and evaporation under reduced pressure. The residue was covered with dry ether and treated with dry triethylamine after stirring for 10 h. The precipitate of triethylamine hydrochloride was removed and the filtrate treated at room temperature with an excess of dimethylcadmium in ether. The mixture was then heated under reflux for a further 3 h. After cooling, sufficient aqueous 15% ammonium chloride was added to decompose the complex and the excess of dimethylcadmium, the ether layer was separated, and the aqueous phase was extracted with ether. The combined ether layers were washed with sodium carbonate solution, dried, and evaporated to give an orange gum. This was dissolved in chloroform † and extracted with 2N-sulphuric acid. The acid extract was then basified to yield 4-chloro-*NN*-diethylpyridine-3-carboxamide (20) as an oil (400 mg), M^+ 212/214; $\nu_{max.}$ 1635 cm^{-1}; δ ($CDCl_3$) 1·08 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 1·26 (3H, t, *J* 7 Hz, CH_2CH_3), 3·14 (2H, q, *J* 7 Hz, $CH_2{\cdot}CH_3$), 3·60 (2H, q, *J* 7 Hz, $CH_2{\cdot}CH_3$), 7·35 (1H, d, *J* 5 Hz, 5-H), 8·45 (1H, s, 2-H), and 8·50 (1H, d, *J* 5 Hz, 6-H). The oil decomposed when attempts were made to distil it.

1,1-*Dimethylfuro*[3,4-c]*pyridin*-3(1H)-*one* (22).—Pyridine-3,4-dicarboxylic acid (3·8 g) was treated with thionyl chloride (20 cm^3) in dimethylformamide (2 g) and the mixture was heated under reflux for 2½ h, then set aside at room temperature overnight. Solvent and reagent were removed and the residue was treated with a five-fold excess of dimethylcadmium in ether. Benzene was then introduced, the ether was distilled off, and the mixture was kept at 36—38° for 3½ h. After cooling, ammonium chloride (20 g) in water (100 cm^3) and concentrated hydrochloric acid (20 cm^3) was added slowly; the aqueous layer was then separated, basified with sodium carbonate, and extracted with chloroform. Removal of the chloroform yielded crude (22) as a red oil which gradually crystallized on trituration with ether. The product (200 mg) crystallized from ether as yellow needles, m.p. 152—155° (lit.,[10] 160—161°); $\nu_{max.}$ 1760, 1608, 1300, and 1040 cm^{-1}; δ ($CDCl_3$) 9·10 (1H, s, 4-H), 8·84 (1H, d, *J* 6 Hz, 6-H), 7·40 (1H, d, *J* 6 Hz, 7-H), and 1·65 (6H, s, CMe_2) (Found: C, 66·0; H, 5·7. Calc. for $C_9H_9NO_2$: C, 66·2; H, 5·6%).

3-*Acetyl*-1,4-*dihydro*-1-(4-*nitrobenzyl*)*pyridine*-4-*carbonitrile* (27).—3-Acetyl-1-(4-nitrobenzyl)pyridinium bromide (3 g) in water (80 cm) was added dropwise during 30 min to a vigorously stirred solution of potassium cyanide (5·8 g) in water (20 cm^3). After a further 30 min, an unstable yellow solid formed; this was filtered off; m.p. 110—130° (decomp.); $\nu_{max.}$ 2230, 1680, 1640, 1580, 1520, and 1340 cm^{-1}; δ [$(CD_3)_2SO$] 8·65 (2H, d, *J* 9 Hz, 3′- and 5′-H), 8·24 (1H, s, 2-H), 7·96 (2H, d, *J* 9 Hz, 2′- and 6′-H), 6·70 (1H, d, *J* 8 Hz, 6-H), 5·25 (1H, 2 × d, *J* 8 and 5 Hz, 5-H), 5·02 (2H, s, CH_2Ar), 4·72 (1H, d, *J* 5 Hz, 4-H), and 2·32 (3H, s, Ac)

Reaction of the Nitrile (27) *with Hydrochloric Acid.* The dihydropyridine (27) (114 mg) in chloroform (7 cm^3) was treated with aqueous 2N-hydrochloric acid (10 cm^3) and the mixture heated at 55—69° for 1 h. The aqueous phase was separated, neutralized with sodium carbonate, and extracted with chloroform to yield a gum which crystallized from ethanol to give 5-*acetyl*-1,2,3,4-*tetrahydro*-2-*hydroxy*-1-(4-*nitrobenzyl*)*pyridine*-4-*carboxamide* (28) as pale yellow prisms, m.p. 179—180° (90·6 mg), *m/e* 319 (M^+) and 275 (base); $\nu_{max.}$ 3300, 1660, 1620, 1570, 1510, 1345, and 1060 cm^{-1}; δ [$(CD_3)_2SO$] 8·22 (2H, d, *J* 8 Hz, 3′- and 5′-H), 7·85 (1H, s, 6-H), 7·58 (2H, d, *J* 8 Hz, 2′- and 6′-H), 7·5br (1H, s, OH), 7·36br (2H, d, *J* 14 Hz, $CONH_2$), 4·76 (2H, s, CH_2Ar), 4·52 (1H, d, *J* 10 Hz, CHOH), 3·65 (1H, 2 × d, *J* 6 and 2 Hz, 4-H), 2·20 and 1·82 (2H, m, $3\text{-}H_2$), and 2·12 (3H, s, Ac) (Found: C, 56·3; H, 5·4; N, 13·0. $C_{15}H_{17}N_3O_5$ requires C, 56·4; H, 5·4; N, 13·2%).

Reaction between 3-*Acetylpyridine and Hydroxylamine*-O-*sulphonic Acid.*—3-Acetylpyridine (1·94 g) in water (4 cm^3) was added to a solution of hydroxylamine-*O*-sulphonic acid (3·62 g) and potassium hydroxide (1·79 g) in water (6·4 cm^3) maintained below 0°. The temperature was raised to 70° for 4 h, and the solution was then cooled and basified with sodium carbonate (2·2 g) in water (3·3 cm^3). After ½ h the

* The aqueous phase was basified and extracted with chloroform to give an oil (30 mg), the ^1H n.m.r. spectrum of which showed it to be 3-acetyl-2-chloropyridine [δ ($CDCl_3$) 8·50 (1H, m, 6-H), 7·92 (1H, m, 5-H), 7·35 (1H, m, 4-H), and 2·70 (3H, s, Ac)] contaminated with *ca.* 5% of the 6-chloro-isomer. Assignment of this latter structure rests upon the fact that only one α-pyridine proton signal is observed [δ 8·95 (d *J* 2 Hz)]; the remainder of the spectrum is difficult to assign because of the low intensity of the signals, apart from that due to the acetyl protons which appears as a singlet (δ 2·62).

† The chloroform layer was dried and evaporated to give, as a yellow solid, 1,3-*bis*-(4-*chloro*-3-*pyridyl*)-3-*hydroxyprop*-2-*en*-1-*one* (21), which crystallized on trituration with acetone as yellow plates, m.p. 239—241° (from acetone), M^+ 294/296/298, $\nu_{max.}$ 3160, 1580, 1105, and 1010 cm^{-1}; δ ($CF_3{\cdot}CO_2H$) 9·42 (2H, d, *J* 2 Hz, 2 × 2′-H), 9·16 (2H, 2 × d, *J* 8 and 2 Hz, 2 × 6′-H), 8·2 (2H, d, *J* 8 Hz, 2 × 5′-H), and 7·34 (1H, s, =CH–) (Found: C, 53·0; H, 3·0; N, 9·4 $C_{13}H_8Cl_2N_2O_2$ requires C, 52·9; H, 2·7; N, 9·5%).

mixture was acidified with concentrated hydrochloric acid and filtered, and the filtrate was evaporated. The residue was treated with methanol and the mixture filtered. On concentration, the methanolic filtrate yielded a crystalline solid. Without purification, this was treated with acetic anhydride (16 cm^3) during 5 h; the excess of reagent was then removed under reduced pressure to afford a brown oil which was chromatographed on neutral aluminia (100 g) with 2% methanol in dichloromethane as eluant. Fifty fractions (30 cm^3) were collected: t.l.c. indicated that fractions 3—34 contained the same material and on combination and evaporation these yielded a solid which crystallized from di-isopropyl ether–petroleum (b.p. 60—80°) as pale yellow prisms (0·99 g), m.p. 116—117°. This material was identical with the authentic oxime of 3-acetylpyridine (lit.,[20] m.p. 113°) (from di-isopropyl ether), but was contaminated with a trace of its *O*-acetate.

The remaining fractions were combined and evaporated to yield 3-(1-*hydroxyiminoethyl*)*pyridine* N-*acetylimidine* (31) (30 mg), m.p. 188—190° (from acetone), M^+ 193, $\nu_{max.}$ 3400—2500, 1560, and 1030 cm^{-1}, δ [$(CD_3)_2SO$] 8·90 (1H, d, *J* 2 Hz, 2-H), 8·70 (1H, m, 6-H), 8·38 (1H, m, 4-H), 7·9 (1H, m, 5-H), 2·20 (3H, s, Ac), and 1·85 (3H, s, CH_3C) (Found: C, 56·0; H, 6·1; N, 22·05. $C_9H_{11}N_3O_2$ requires C, 55·95; H, 5·7; N, 21·75%).

1-*Amino*-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*pyridinium Mesitylenesulphonate*.— 3-(2-Methyl-1,3-dioxolan-2-yl)pyridine (15·6 g) in dichloromethane (42 cm^3) was cooled to 0° and *O*-mesitylsulphonylhydroxylamine (20·4 g) in dichloromethane (40 cm^3) was added. After stirring at room temperature for 30 min, the solution was diluted with diethyl ether (800 cm^3) and again cooled to 0°. After a few minutes, the crystalline product was collected (33·8 g, 94·0%); m.p. 118—119°; $\nu_{max.}$ 3210, 3130, and 1190 cm^{-1}; δ [$(CD_3)_2SO$] 9·15 (1H, s, 2-H), 9·10 (1H, d, *J* 8 Hz, 6-H), 8·95br (2H, s, NH_2), 8·50 (1H, d, *J* 9 Hz, 4-H), 8·35 (1H, q, *J* 8 and 9 Hz, 5-H), 7·03 (2H, s, benzenoid), 4·3—3·8 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 2·50 (6H, s, 2 × CH_3), 2·49 (3H, s, CH_3), and 1·70 (3H, s, CH_3).

3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* N-*Acetylimide* (32).—The product from the previous reaction was dissolved in water (100 cm^3) and treated with acetic anhydride (200 cm^3), previously cooled to 5°, and then dropwise with aqueous 30% sodium hydroxide (150 cm^3). The mixture was then poured into aqueous potassium carbonate (100 g in 900 cm^3) and stirred with chloroform (100 cm^3). A colourless precipitate was removed and the aqueous phase separated and extracted with chloroform (100 cm^3). The chloroform layers were combined, dried, and evaporated to give (32) as an amber-coloured oil which slowly crystallized to afford a hygroscopic solid (19·2 g, 98%), *m/e* 222 (M^+) and 207 (base); $\nu_{max.}$ 1570 cm, δ ($CDCl_4$) 9·0 (2H, m, 2- and 6-H), 8·35 (1H, d, *J* 8 Hz, 4-H), 7·95 (1H, q, *J* 8 and 7 Hz, 5-H), 4·40—3·90 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 2·13 (3H, s, Ac), and 1·72 (3H, s, CH_3).

1-(N-*Methylacetamido*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-*pyridinium Iodide* (33).—The pyridine (32) (15·1 g) was treated with methyl iodide (150 cm^3) at reflux during 45 min. Removal of the excess of reagent afforded a yellow solid (98%), m.p. 176—177° (from ethanol).

3-(2-*Methyl*-1,3-*dioxolan*-2-*yl*)*pyridine*-4-*carbonitrile* (34).—The salt (33) (24 g) in water (56 cm^3) was warmed to 20—22° and treated with ammonium chloride (7·0 g) and potassium cyanide (5·6 g) in water (10 cm^3). After 1 h the mixture was extracted with chloroform to yield an oil, which was stirred in ethanol solution and irradiated with 'soft' u.v. light for 15 min. The solvent was removed under reduced pressure to give (34) as a solid which crystallized from ethyl acetate as *needles* (10·2 g, 81·5%), m.p. 68—69°, *m/e* 190 (M^+), 175 (base), 131, and 87, δ [$(CD_3)_2SO$] 1·70 (3H, s, CH_3C), 3·9 (4H, m, $CH_2{\cdot}CH_2$), 7·8 (1H, d, *J* 5 Hz, 5-H), 8·7 (1H, d, *J* 5 Hz, 6-H), and 8·8 (1H, s, 2-H) (Found: C, 63·2; H, 5·3; N, 14·7. $C_{10}H_{10}N_2O_2$ requires C, 63·15; H, 5·3; N, 14·7%).

4-*Acetyl*-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* (36).—The nitrile (34) (1·0 g) in ether (30 cm^3) was added slowly to a solution of methyl-lithium (1·2 mol. equiv.) in ether at −10 to −15° under nitrogen. Stirring was maintained for a further 30 min, and then ice–water (40 cm^3) was introduced followed by ammonium chloride (1·0 g) in water (10 cm^3). The ethereal layer was removed, dried, and evaporated to give a small amount of starting material. Extraction of the aqueous phase with chloroform gave an oil which slowly crystallized to afford prisms of 4-(1-*iminoethyl*)-3-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*pyridine* (35), m.p. 85—86° (from ether) (0·97 g, 89·5%); $\nu_{max.}$ 1640 and 1590 cm^{-1}; δ ($CDCl_3$) 1·8 (3H, s, CH_3C), 2·40 (3H, s, $CH_3{\cdot}C{=}N$), 3·7—4·1 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 7·01 (1H, d, *J* 5·5 Hz, 5-H), 8·55 (1H, d, *J* 5·5 Hz, 6-H), and 8·82 (1H, s, 2-H) (Found: C, 64·0; H, 6·7; N, 13·3. $C_{11}H_{14}N_2O_2$ requires C, 64·1; H, 6·8; N, 13·6%).

Treatment of the imine (5·7 g) with aqueous 20% acetic acid (160 cm^3) on a steam-bath for 30 min, followed by basification (K_2CO_3) and extraction with chloroform afforded the 4-acetyl derivative (36) as prisms (5·3 g, 94·5%), m.p. 49—50° [from petroleum (b.p. 60—80°)]; $\nu_{max.}$ 2980, 2890, 1705, and 1030 cm^{-1}; $\lambda_{max.}$ 263 nm (ε 2490); δ ($CDCl_3$) 1·8 (3H, s, CH_3C), 2·5 (3H, s, CH_3CO), 3·8 (4H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 7·0 (1H, d, *J* 5 Hz, 5-H), 8·55 (1H, d, *J* 5 Hz, 6-H), and 8·75 (1H, s, 2-H) (Found: C, 63·7; H, 6·4; N, 6·7. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·8%).

3,4-*Diacetylpyridine* (10).—Hydrolysis of the imine (35), this time with aqueous 20% hydrochloric acid at 100° for 30 min, gave 3,4-*diacetylpyridine* (96%), m.p. 42—44° [from petroleum (b.p. 40—60°)], $\lambda_{max.}$ 227 (ε 5740) and 275 nm (2420); $\nu_{max.}$ 1710br and 1590 cm^{-1}; δ ($CDCl_3$) 2·50 (3H, s, Ac), 2·64 (3H, s, Ac), 7·32 (1H, d, *J* 6 Hz, 5-H), 8·85 (1H, d, *J* 6 Hz, 6-H), and 9·05 (1H, s, 2-H) (Found: C, 66·0; H, 5·7; N, 8·9. $C_9H_9NO_2$ requires C, 66·2; H, 5·6; N, 8·6%).

Reaction between 3,4-*Diacetylpyridine and Ethane*-1,2-*diol*.—3,4-Diacetylpyridine (1·6 g) in dry benzene (50 cm^3) containing toluene-*p*-sulphonic acid (1·15 mol. excess) and ethane-1,2-diol (5 cm^3) was heated in a Dean-Stark apparatus for 12 h. Removal of the solvents gave a red oil which was chromatographed upon basic alumina (50 g), with ether as eluant. Thirty fractions (50 cm^3) were collected. Fractions 1—7 yielded a white crystalline solid (64 mg), m.p. 141—142 [from petroleum (b.p. 60—80°)], identified as 5,7,8,10-*tetrahydro*-5,10-*dimethyl*-5,10-*epoxy*[1,4]*dioxepino*-[6,7-c]*pyridine* (37), $\lambda_{max.}$ 260 (ε 1750) and 265sh nm (1520); δ ($CDCl_3$) 1·80 (3H, s, CH_3C), 1·83 (3H, s, CH_3C), 3·3 and 3·85 (2 × 2H, m, $O{\cdot}CH_2{\cdot}CH_2{\cdot}O$), 7·25 (1H, m, 4-H), and 8·62 (2H, m, 1- and 3-H), *m/e* 207 (M^+) and 147 (base) (Found: C, 63·8; H, 6·8; N, 7·2. $C_{11}H_{13}NO_3$ requires C, 63·75; H, 6·3; N, 6·8%). Fractions 23—30 gave an oil (70 mg) the ^1H n.m.r. spectrum of which indicated the presence of a mixture of the acetals (36) and (38) (*ca.* 3 : 1).

3-[1-(*Tetrahydropyran*-2-*yloxy*)*ethyl*]*pyridine*.—The hydrochloride of 3-(1-hydroxyethyl)pyridine (32·4 g) was treated with 2,3-dihydropyran (3 mol. equiv.) in dimethylformamide (200 cm^3), and dry hydrogen chloride was then bubbled

[20] F. B. La Forge, *J. Amer. Chem. Soc.*, 1928, **50**, 2477.

through the solution for 10 min. The mixture was set aside for 5 days. The solvent was removed under reduced pressure and the residue was treated with a mixture of ether and aqueous 10% sodium carbonate. The organic layer was then separated, washed with water, dried, and evaporated to give the required ether as an oil (37·8 g, 90·0%), b.p. 100—102° at 0·65 mmHg. This product was converted, by a series of steps similar to those described previously for (36), into 4-acetyl-3-[1-(tetrahydropyran-2-yloxy)ethyl]pyridine (39), obtained as an oil after chromatography upon alumina and elution with ether [yield from 3-(1-hydroxyethyl)-pyridine, 65%]; M^+ 249; $\nu_{max.}$ 1700, 1580, and 1255 cm^{-1}; δ ($CDCl_3$) 9·04 (1H, 2 × s, 2-H), 8·75 (1H, m, 6-H), 7·4 (1H, m, 5-H), 5·3 (1H, q, C*H*·CH_3), 3·96—3·31 (3H, m, CHO and CH_2O), 2·63 (3H, s, Ac), and 1·8—1·3 (9H, m, CH_2·CH_2·CH_2 and $CHCH_3$) (Found: C, 67·3; H, 7·5; N, 5·8. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6%).

1,3-*Dihydro*-1,3-*dimethylfuro*[3,4-c]*pyridin*-1-*ol* (41).—The 4-acetylpyridine (39) (1·4 g) in dilute hydrochloric acid (20 cm^3) was warmed on a steam-bath for 10 min. The solution was then basified with sodium carbonate and extracted with chloroform; removal of the solvent gave (41) as an *oil* (1·0 g). This was purified by repeated chromatography upon alumina (elution with ether); *m/e* 165 (M^+) and 150 (base); $\nu_{max.}$ (film) *ca.* 3300 and 1605 cm^{-1}; δ ($CDCl_3$) 8·44 (1H, two overlapping d, 4-H), 8·34 (1H, m, 6-H), 7·3 (1H, m, 7-H), 5·36 (1H, two overlapping q, C*H*CH_3), 1·78 and 1·78 (3H, two s, CH_3C), 1·50 (3H, two overlapping d, CH_3CH), and 4·92br (1H, s, OH); $\lambda_{max.}$ 255sh (ε 1130), 260 (1320), and 266sh nm (1130) (Found: C, 65·0; H, 6·3; N, 8·2. $C_9H_{11}NO_2$ requires C, 65·4; H, 6·7; N, 8·5%).

The isomeric 3-*ol* (42) was obtained by reduction of (36) with sodium borohydride to give 4-(1-hydroxyethyl)-3-(2-methyl-1,3-dioxolan-2-yl)pyridine [m.p. 84·6°; $\nu_{max.}$ 3400 cm^{-1}; δ ($CDCl_3$) 8·64 (1H, s, 2-H), 8·45 (1H, d, *J* 5 Hz, 6-H), 7·55 (1H, d, *J* 5 Hz, 5-H), 5·46 (1H, q, *J* 5 Hz, CH_3CH), 4·1—3·7 (4H, m, O·CH_2·CH_2·O), 1·65 (3H, s, Ac), and 1·42 (3H, d, *J* 5 Hz, CH_3CH)] followed by treatment of this with 6N-hydrochloric acid at 100° for 10 min. The product (42), an oil, *m/e* 165 (M^+), 150, and 147 (base); $\nu_{max.}$ (film) *ca.* 3300 cm^{-1}, was not completely characterized.

Reaction between 1,3-*Diacetylindoxyl and* 3,4-*Diacetylpyridine.*—1,3-Diacetylindoxyl (1·2 g) and 3,4-diacetylpyridine (0·89 g) in deoxygenated methanol (10 cm^3) were treated with potassium hydroxide (3·5 g) in deoxygenated water (10 cm^3) under nitrogen. After 3 days at room temperature, the solution was poured onto ice and aqueous 10% acetic acid; it was then basified with sodium carbonate and extracted with chloroform, and the extracts were evaporated to yield a deep red oil. This was chromatographed on alumina (elution with benzene–chloroform mixtures) and the major fraction (650 mg) was evaporated. The residue was triturated with ethanol to give 2-(3-*methylcyclopenta*[c]*pyridin*-1-*ylidene*)*indolin*-3-*one* (40) as red prisms. This product does not have a definite m.p., but begins to darken at *ca.* 290°; *m/e* 260 (M^+, base) and 245; $\lambda_{max.}$ 229 (ε 8230), 240 (8110), 290 (8790), 336 (6760), 356sh (4510), 542 (6310), and 612 nm (3610); $\nu_{max.}$ 1690, 1630, 1610, and 1600 cm^{-1}; δ (CF_3·CO_2H) 9·2 (1H, d, *J* 7 Hz), 8·6—8·45 (2H, m), 8·0—7·6 (4H, m), 7·4—7·1 (3H, m), and 2·46 (3H, s) (Found: C, 78·4; H, 4·6; N, 10·8. $C_{17}H_{12}O_2$ requires C, 78·4; H, 4·65; N, 10·8%).

(E)- *and* (Z)-2-{1-{3-[1-(*Tetrahydropyran*-2-*yloxy*)*ethyl*]-4-*pyridyl*}*ethylidene*}*indolin*-3-*one* [(43) *and isomer*].—1,3-Diacetylindoxyl (750 mg) and (39) (860 mg) in deoxygenated methanol (6·5 cm^3) were treated with potassium hydroxide (2·5 g) in deoxygenated water (6·5 cm^3) and the mixture was stored for 4 days under nitrogen. The solid product was collected under nitrogen to yield the mixed isomers (0·93 g, 74·5%), *m/e* 364 (M^+), 280, and 247 (base); $\lambda_{max.}$ 239 (ε 21,210), 264 (32,270), 296sh (14,440), and 463 nm (7447). This material was not purified further.

(E)- *and* (Z)-5-*Acetamido*-2-{1-{3-[1-(*tetrahydropyran*-2-*yloxy*)*ethyl*]-4-*pyridyl*}*ethylidene*}*indolin*-3-*one* [(44) *and isomer*].—5-Acetamido-1,3-diacetylindoxyl was treated with the acetylpyridine (39) as described in the previous experiment. However, in this case the mixture was stored at 15—16° for 7 days prior to work-up. The product was a mixture of the required isomers plus some unacetylated materials; consequently it was dissolved in ethanol and treated with an excess of acetic anhydride. After shaking at room temperature for 10 min, the excess of reagent was decomposed with ice–water and the mixture basified with potassium carbonate. Chloroform extraction gave (44) and its isomer as a red solid (80·0%), M^+ 421; $\lambda_{max.}$ 266 (ε 14,000) and 486 nm (4600).

2-{1-[3-(1-*Hydroxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (49).—The mixture of indolinone (43) and its *Z*-isomer (300 mg) in aqueous 20% ethanol (20 cm^3) was heated at reflux under nitrogen and treated with sodium borohydride (500 mg) in small portions. After 1 h the solvent was removed and the residue partitioned between chloroform and water. The organic phase was dried, treated with charcoal, and evaporated to give the indolin-3-ol (47) as a greenish gum; this was dissolved in chloroform and the solution saturated with hydrogen chloride, then washed with sodium carbonate solution, dried, and evaporated to yield (49) as a *solid* (217 mg, 72·2%), m.p. 208—210° (from ethanol); *m/e* 266 (M^+) and 233 (base); $\lambda_{max.}$ 221 (ε 50,210), 265sh (12,290), 270 (12,640), 284 (11,410), and 293 nm (9830); $\nu_{max.}$ 3330, 3100, and 1600 cm^{-1}; δ [$(CD_3)_2SO$] 8·52 (1H, s, 2′-H), 8·24 (1H, d, *J* 5 Hz, 6′-H), 7·4—6·8 (5H, m, 4-, 5-, 6-, 7-, and 5′-H), 6·12br (1H, s, 3-H), 5·3br (1H, s, OH), 5·15 (1H, m, CH_3CHO), 4·62 (1H, q, *J* 6 Hz, CH_3CH), 1·62 (3H, d, *J* 8 Hz, CH_3CHO), and 1·38 (3H, d, *J* 6 Hz, CH_3CH) (Found: C, 76·6; H, 6·8; N, 10·3. $C_{17}H_{18}N_2O$ requires C, 76·7; H, 6·8; N, 10·5%).

5-*Acetamido*-2-{1-[3-(1-*hydroxyethyl*)-4-*pyridyl*]*ethyl*}*indole* (50).—This product, pale yellow micro-crystals, m.p. 140—150°,* was obtained from (44) and its *Z*-isomer as described in the previous experiment; yield 75%; *m/e* 323 (M^+) and 290 (base); $\lambda_{max.}$ 242 (ε 22,200), 300 (4000), and 311sh nm (2600); $\nu_{max.}$ 3380br, 1660br, and 1600 cm^{-1}; δ [$(CD_3)_2SO$] 8·64br (1H, s, 2′-H), 8·35 (1H, m, 6′-H), 7·75 (1H, s, 4-H), *ca.* 7·2 (3H, m, 6-, 7-, and 5′-H), 6·1br (1H, s, 3-H), 5·33 (1H, m, OH), 5·2 (1H, m, CH_3CHO), 4·6 (1H, 2 × q, CH_3CH), 1·6 (3H, d, *J* 6 Hz, CH_3CHO), and 1·4 (3H, 2 × d, CH_3CH) (Found: C, 70·8; H, 6·5; N, 12·6. $C_{19}H_{21}N_3O_2$ requires C, 70·6; H, 6·6; N, 13·0%).

1,3-*Dihydro*-1-(*indol*-2-*yl*)-1,3-*dimethylfuro*[3,4-c]*pyridine* (46).—The mixed indolines [(43) and its *Z*-isomer] (300 mg) in aqueous 20% ethanol (20 cm^3) were treated with sodium borohydride (300 mg). The mixture was then warmed on a water bath for 30 min. The solvent was removed to afford a gum which was dissolved in methanol and saturated with hydrogen chloride. Removal of the solvent, basification of the residue with aqueous sodium carbonate, and extraction with chloroform gave a sticky solid; this was chromatographed on alumina [elution with 1 : 1 petroleum (b.p. 60—80°)–ether] to yield (46) as a cream-coloured *solid*, m.p. 178°

* Mixture of diastereoisomers.

(from benzene); *m/e* 264 (M^+) and 249 (base); $\lambda_{max.}$ 220 (ε 21,600), 268 (5800), 284 (4970), and 293 nm (4200); $\nu_{max.}$ 1595 cm^{-1}; δ ($CDCl_3$) 1·62 (3H, d, *J* 6 Hz, CH_3CH), 1·95 (CH, s, CH_3C), 5·4 (1H, q, *J* 6 Hz, CH_3CH), 6·20 (1H, d, *J* 2 Hz, 3′-H), 6·95—7·60 (5H, m, 4′-, 5′-, 6′-, 7′-, and 7-H), 8·35 (1H, s, 4-H), and 8·45 (1H, d, *J* 6 Hz, 6-H) (Found: C, 77·4; H, 5·9; N, 10·3. $C_{17}H_{16}N_2O$ requires C, 77·25; H, 6·1; N, 10·6%).

Ellipticine.—The indole (49) (207 mg) in dry dimethyl sulphoxide (1·75 cm^3) was treated with acetic anhydride (1·1 cm^3) and the solution stirred at room temperature for 2 days. The mixture was then poured into water (50 cm^3) and treated with an excess of potassium carbonate. A yellow solid which gradually formed was collected, dried, and washed with benzene to yield ellipticine (130 mg), m.p. and mixed m.p. 309—312° (lit.,[1] 309—313°) (Found: C, 83·0; H, 5·6; N, 11·2. Calc. for $C_{17}H_{14}N_2$: C, 82·9; H, 5·7; N, 11·4%).

When the indole (49) (30 mg) in dichloromethane (2 cm^3) was stirred with active manganese dioxide (300 mg) for 12 h, a yellow solution was obtained. Filtration and evaporaton gave mainly starting material, but extraction of the manganese dioxide with hot ethanol afforded a small quantity (3 mg) of ellipticine. Similarly, with boron trifluoride in ether at reflux for 1 h, (49) gave a yellow gum which contained traces of ellipticine. Repetition of this reaction, but for longer periods, gave complex mixtures; at room temperature only starting material was obtained.

With phosphoric trichloride in pyridine at room temperature, (49) gave 5,11-dihydroellipticine. Particularly in the presence of aqueous acid or during chromatography on silica, this material was gradually oxidized to ellipticine. The total yield of the latter product, however, was poor (15—20%) and we were unable to obtain satisfactory analytical data for the dihydro-compound.

9-Acetamidoellipticine (9; R = NHAc).—When the indole (50) was treated with dimethyl sulphoxide and acetic anhydride as in the previous experiment, 9-acetamidoellipticine, m.p. 245—250° (decomp.) (yellow needles from ethanol), was obtained (65·2%); *m/e* 303 (M^+, base) and 261; $\lambda_{max.}$ 225 (ε 6460), 257 (10,200), 268sh (10,920), 277 (13,040), 298 (18,620), 308sh (12,040), 339 (2480), 354 (1990), and 412 nm (1650); $\nu_{max.}$ 1660 and 1600 cm^{-1}; δ ($CF_3{\cdot}CO_2H$) 9·75br (2H, s, 1- and 3-H), 8·65—8·2 (3H, m, 7-, 8-, and 10-H), 7·75 (1H, s, 4-H), 3·40 (3H, s, 11-CH_3), 29·5 (3H, s, 5-CH_3), and 2·68 (3H, s, NHAc) (Found: C, 75·0; H, 5·6; N, 13·9. $C_{19}H_{17}N_3O$ requires C, 75·2; H, 5·65; N, 13·85%).

1′,4′-Dihydro-1′,4′-dimethylspiro{indoline-2,3′-pyrano[3,4-c]pyridin}-3-one (52).—The indole (49) (50 mg) in glacial acetic acid (1 cm^3) containing potassium dichromate (40 mg) and water (0·5 cm^3) was heated at 100° for 1 h and then poured onto 2N-sodium carbonate solution to yield a gum. This was extracted into chloroform; the extract was washed with water, dried, and evaporated and the product crystallized on trituration with acetone as pale yellow *needles* (5 mg), m.p. 244—246° (from acetone); *m/e* 280 (M^+) and 252 (base); $\nu_{max.}$ 1710 cm^{-1}; $\lambda_{max.}$ 236 (ε 18,500), 262 (5650), and 410 nm (2330); δ [$(CD_3)_2SO$] 0·98 (3H, d, *J* 3·5 Hz, CH_3CH), 1·55 (3H, d, *J* 3·7 Hz, CH_3CHO), 3·4 (1H, q, *J* 3·5 Hz, CH_3CH), 5·1 (1H, q, *J* 3·7 Hz, CH_3CHO), *ca.* 6·8—7·2 (5H, m, 5′-H and benzenoid protons), 7·8 (1H, s, NH), and 8·5br (2H, s, 6′- and 8′-H) (Found: C, 72·6; H, 5·9; N, 9·8. $C_{17}H_{16}N_2O_2$ requires C, 72·8; H, 5·75; N, 10·0%).

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