Chemistry of 6*H*-pyrido[4,3-*b*]carbazoles. Part 9.[1] An Efficient Route to 3-[1-(3-Ethylpyridyl)]indoles and the Synthesis of Some New Ellipticines [2]

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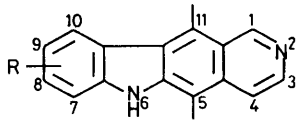
A new and efficient route to 3-[1-(3-ethylpyridyl)]indoles has been developed which requires the Fischer indolisation of 3-(3-pyridyl)butanal with arylhydrazines. The ethylpyridylindoles can be converted into 6*H*-pyrido[4,3-*b*]carbazoles by a known procedure, leading to the first syntheses of 7-chloro-, 7-fluoro-, 7-methyl-, 8-methoxy-, and 8-hydroxy-ellipticines. The last-named compound is identical with a minor metabolite of ellipticine in *Aspergillus alliaceus*.

We have described previously a mild and effective synthesis of 6*H*-pyrido[4,3-*b*]carbazoles (1) from (ethylpyridyl)indoles (2).[3] Unfortunately, preparations of the latter from indolyl magnesium halides and 3-(1-chloroethyl)pyridine are inefficient, and we have not been able to extend Kubo and Nakai's synthesis of the parent compound [4] to derivatives bearing methoxy and other substituents in the benzenoid ring. Consequently we decided to synthesise 3-(3-pyridyl)butanal (7), which



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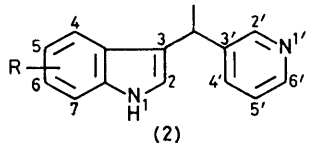

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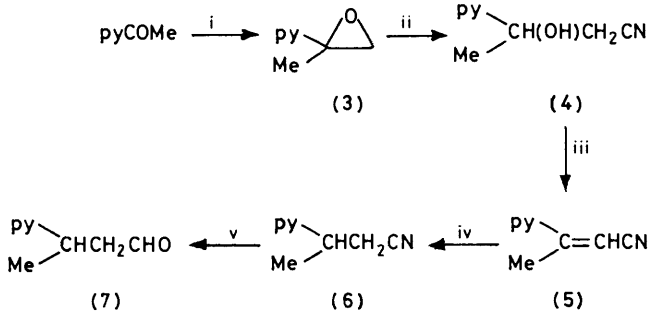
through Fischer indolisation we expected to provide a more direct and versatile approach to the required starting materials. Our first route to the aldehyde is shown in Scheme 1.



Scheme 1 A synthesis of 3-(3-pyridyl)butanal (py = 3-pyridyl) *Reagents*: i, Me_2SCH_2Na; ii, $MgSO_4$, KCN, H_2O; iii, H^+; iv, $NaBH_4$; v, Bu^i_2AlH

Reaction of 3-acetylpyridine with dimethylsulphonium methylide gave the oxiran (3) in high yield, and when this is added to a solution containing magnesium sulphate and potassium cyanide, exclusive ring-opening to the required alcohol (4) occurs. If magnesium sulphate is omitted no reaction takes place, but should potassium cyanide solution be added to a mixture of the oxiran and magnesium sulphate, the alternative alcohol (8) is the major product.

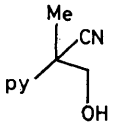
Thus the order in which the reagents are added is critical.[5] We suppose that in the first case a co-ordination complex between magnesium and cyanide ions and the oxygen atom of the oxiran is built up which delivers the nucleophile intramolecularly to the least hindered β-carbon atom of the epoxide ring. When the addition of cyanide ion is delayed, a similar complex is formed containing magnesium bonded directly to oxygen atoms only. Attack by cyanide ion then occurs intermolecularly, and although the α-site is less favoured sterically it is the more electrophilic. As a result a mixture of ring-opened products is formed.

Attempts to dehydrate the alcohol (4) with acids, and to form *O*-mesyl and *O*-tosyl derivatives, were unsuccessful, but a reaction with phosphorus tribromide, followed by work-up in the presence of aqueous alkali, afforded a mixture of *E*- (5a) and *Z*- (5b) alkenes in the molar ratio 4 : 3. This ratio was increased to 18 : 1 when thionyl chloride was substituted for phosphorus tribromide (stereochemical assignments rest on n.m.r. chemical shifts, coupling constants and nuclear Overhauser effect data; see Experimental section). Without supporting kinetic evidence it is not possible to define the mechanisms which operate in these reactions, although it does appear that in the case of thionyl chloride, rather than *E*1 or *E*2 processes, an internal *syn*-elimination reaction may occur. The major product, the *E*-isomer, would then form by loss of sulphur dioxide and hydrogen chloride from the 'best' staggered conformer (9). Reduction of the mixed alkenes by sodium borohydride afforded the nitrile (6) in quantitative yield, and this was further reduced with di-isobutylaluminium hydride (DIBAL) to the aldehyde (7). The yield in this last step was only 40% and we were unable to improve upon it by varying the conditions of the reaction or the reagent employed. Other workers [6] have noted similar problems in attempts to reduce nitriles selectively, and in view of this we sought

to prepare and reduce the corresponding ester (10) instead.

Sugasawa and Matsuo [7] have synthesised the α,β-unsaturated ester (11) by a Wittig reaction between 3-acetylpyridine and ethoxycarbonylmethyltriphenylphosphonium bromide. The yield in this case was 80%, but we find that by using triethylphosphonoacetate in place of the bromide a yield of 94% is obtained.

Hydrogenation of the α,β-unsaturated ester over palladium–charcoal then afforded the ester (10) in 98% yield, and its reduction to the aldehyde (7) was effected with DIBAL, with 93% efficiency.



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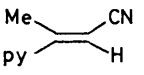
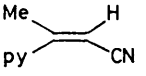


(5a)



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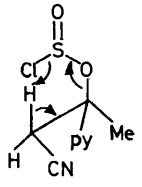

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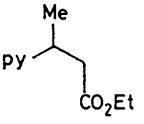

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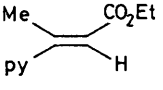

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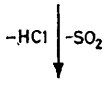

(5a)

This aldehyde was then treated with a number of arylhydrazines in methanolic hydrogen chloride, and from these reactions the corresponding indolylpyridylethanes (2; R = 7-Cl, 7-F, or 7-Me) were obtained in yields ranging from 45 to 56% (see Experimental section). The products were then converted into the tetracyclic systems by the usual route,[3] and in this way 7-chloro-, 7-fluoro-, and 7-methyl-ellipticines were made for the first time.

When 3-substituted arylhydrazines are employed a mixture of 4- and 6-substituted indolylpyridylethanes is obtained, typically in the molar ratio 3 : 1. These isomers can be isolated by chromatography and may be then employed in the construction of 8- and 10-substituted ellipticines; thus, for example, the ethylpyridylindole (2; R = 6-MeO), obtained by the reaction of 3-methoxyphenylhydrazine with the butanal (7) was converted into 8-methoxyellipticine (1; R = 8-MeO). De-*O*-methylation of this product with pyridinium chloride afforded 8-hydroxyellipticines,[1] which is identical with one of the metabolites of ellipticine in the micro-organism *Aspergillus alliaceus*.[8]

As a further illustration of the utility of this synthesis, the alkaloid 9-methoxyellipticine [9] was prepared in 40% yield from 4-methoxyphenylhydrazine.

EXPERIMENTAL

U.v. spectra were recorded for solutions in aqueous 98% 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.

1-*Methyl*-1-(3-*pyridyl*)*oxiran* (3).—A solution of trimethylsulphonium iodide (20.3 g) in dry dimethyl sulphoxide (90 cm^3) was added to sodium hydride (4.8 g), dimethyl sulphoxide (10 cm^3), and tetrahydrofuran (100 cm^3) under nitrogen. The mixture was cooled to −10 °C and 3-acetylpyridine (10 g) was then introduced. After 1 h the mixture was allowed to warm to room temperature, then poured into ice–water (600 cm^3) and washed with light petroleum (b.p. 60—80 °C) (3 × 50 cm^3). The aqueous phase was then extracted with dichloromethane (3 × 150 cm^3) and the dry combined extracts were evaporated to yield the oxiran as an oil (10.6 g), $\lambda_{max.}$ 260 and 273 nm; δ ($CDCl_3$) 8.6 (1 H, d, *J* 2 Hz, H-2′), 8.55 (1 H, dd, J_1 8, J_2 2 Hz, H-6′), 7.60 (1 H, m, H-4′), 7.18 (1 H, dd, $J_1 = J_2 = 8$ Hz, H-5′), 2.85 (2 H, dd, $J_1 = J_2 = 6$ Hz, oxiran CH_2), and 1.7 (3 H, s, CH_3).

3-*Hydroxy*-3-(3-*pyridyl*)*butanonitrile* (4).—Potassium cyanide (9.6 g) was added in portions to magnesium sulphate (18 g) in water (100 cm^3). After 1 h, the oxiran (3) (10 g) was introduced and the mixture was stirred for 48 h, before it was poured into water (250 cm^3) and extracted with ethyl acetate (10 × 75 cm^3). The dry combined extracts when evaporated gave the nitrile as a brown oil (11 g), $\lambda_{max.}$ 255 and 266 nm; $\nu_{max.}$ 3 200, 2 250, and 1 595 cm^{-1}; δ ($CDCl_3$) 8.75 (1 H, d, *J* 2 Hz, H-2′), 8.45 (1 H, br, d, *J* 6 Hz, H-6′), 7.95 (1 H, br, d, *J* 8 Hz, H-4′), 7.35 (1 H, dd, $J_1 = J_2 = 8$ Hz, H-3′), 6.32 (1 H, br, s, OH), 2.9 (2 H, s, CH_2), and 1.75 (3 H, s, CH_3).

(E)- *and* (Z)-3-(3′-*Pyridyl*)*but*-2-*enonitrile* (5a *and* b).—Phosphorus tribromide (5 cm^3) was added to a solution of the nitrile (4) (1 g) in dry dichloromethane (10 cm^3), which was then stirred at room temperature for 5 h. The excess of solvent and reagent were evaporated off and the residue was dissolved in ice–water (50 cm^3), basified with potassium hydroxide, and extracted with dichloromethane (3 × 50 cm^3) to give an oil (0.8 g). This product was a mixture of *E*- and *Z*-isomers of the title compound in the ratio 1 : 0.81 (by ^{1}H n.m.r.): *E*-isomer δ ($CDCl_3$) 5.76 (1 H, q, *J* 1.1 Hz, H-2) and 2.42 (3 H, d, *J* 1.1 Hz, H-4) (irradiation at δ 2.42 causes no change in integral of signal at δ 5.76); *Z*-isomer δ($CDCl_3$) 5.58 (1 H, q, *J* 1.3 Hz, H-2) and 2.30 (3 H, d, *J* 1.3 Hz, H-4) (irradiation at δ 2.30 causes an 18.5% enhancement of the signal at δ 5.58); remainder of ^{1}H n.m.r. spectrum: 8.72 (1 H, d, *J* 2 Hz, H-2′), 8.59 (1 H, dd, J_1 8, J_2 2 Hz, H-6′), 7.83 (1 H, m, H-4′), and 7.38 (1 H, dd, $J_1 = J_2 = 8$ Hz, H-5′).

When thionyl chloride is used in place of phosphorus tribromide the crude mixture contains the *E*- and *Z*-isomers in the ratio 18 : 1. Trituration with methanol causes the pure *E*-isomer to crystallise as prisms, m.p. 49—50° (from methanol) (Found: C, 74.9; H, 5.4; N, 18.9. $C_9H_8N_2$ requires C, 75.0; H, 5.6; N, 19.4%).

3-(3-*Pyridyl*)*butanonitrile* (6).—The mixed nitriles (5a and b) (1 g) when added to sodium borohydride (2 g) in ethanol (25 cm^3) and heated at 60 °C for 1 h, gave the nitrile (6) as an oil (0.9 g), $\nu_{max.}$ 2 224 cm^{-1}; δ ($CDCl_3$) 8.55 (1 H, d, *J* 2 Hz, H-2′), 8.48 (1 H, dd, J_1 8, J_2 2 Hz, H-6′),

7.65 (1 H, m, H-4′), 7.26 (1 H, dd, $J_1 = J_2 = 8$ Hz, H-5′), 3.24 (1 H, m, H-3), 2.69 (2 H, d, J 8 Hz, H-2), and 1.45 (3 H, d, J 10 Hz, H-4).

Ethyl 3-(3-Pyridyl)but-2-enoate (11).[7]—Triethylphosphonoacetate (41 g) was added dropwise to a cold (0 °C) suspension of sodium hydride (9 g) in tetrahydrofuran (75 cm³) under nitrogen. After gas evolution had ceased, 3-acetylpyridine (15 g) was introduced and the mixture set aside for 48 h. The product was poured onto ice (300 g) and extracted with dichloromethane (5 × 100 cm³) to give the title ester as an amber oil (22 g, 94%), $\nu_{max.}$ 1 715 and 1 630 cm⁻¹; δ ($CDCl_3$) 8.75 (1 H, d, J 2 Hz, H-2′), 8.61 (1 H, br, d, J 6 Hz, H-6′), 7.80 (1 H, m, H-4′), 7.31 (1 H, dd, $J_1 = J_2 =$ 6 Hz, H-3′), 6.16 (1 H, q, J 1 Hz, H-2), 4.23 (2 H, q, $J = 8$ Hz, OCH_2CH_3), 2.60 (3 H, d, J 1 Hz, H-4), and 1.32 (3 H, t, J 8 Hz, OCH_2CH_3).

Ethyl 3-(3-Pyridyl)butanoate (10).—A solution of the ester (10 g) from the previous experiment in ethanol (100 cm³) was hydrogenated at 100 lb in⁻² over 10% palladium–carbon (1 g) during 15 h, to yield an oil (10 g, 98%); $\nu_{max.}$ 1 738 cm⁻¹; δ ($CDCl_3$) 8.5 (1 H, d, J 2 Hz, H-2′), 8.45 (1 H, dd, J_1 6, J_2 2 Hz, H-6′), 7.55 (1 H, m, H-4′), 7.20 (1 H, dd, $J_1 = J_2 = 6$ Hz, H-5′), 4.1 (2 H, q, J 8 Hz, OCH_2CH_3), 3.3 (1 H, m, H-3), 2.58 (2 H, d, J 7 Hz, H_2-2′), 1.3 (3 H, d, $J = 8$ Hz, H_3-4), and 1.15 (3 H, t, J 8 Hz, OCH_2CH_3).

3-(3-Pyridyl)butanal (7).—A solution of di-isobutylaluminium hydride in toluene (1.2M; 65 cm³) was added dropwise to a solution of ethyl 3-(3-pyridyl)butanoate (10 g) in toluene (20 cm³) maintained at −78 °C under nitrogen. After 2 h, the mixture was treated cautiously with water (20 cm³) and then extracted with dichloromethane (7 × 150 cm³) to give the aldehyde as a pale yellow oil, which was purified by chromatography on alumina (elution with diethyl ether); yield 7.2 g (93%); $\nu_{max.}$ 2 720 and 1 720 cm⁻¹; δ ($CDCl_3$) 9.60 (1 H, d, J 1 Hz, H-1), 8.46 (1 H, d, J 2 Hz, H-2′), 8.40 (1 H, dd, J_1 6, J_2 2 Hz, H-6′), 7.49 (1 H, m, H-4′), 7.16 (1 H, dd, $J_1 = J_2 = 6$ Hz, H-5′), 3.32 (1 H, m, H-3), 2.68 (2 H, br, d, $J = 8$ Hz, H-2), and 1.26 (3 H, d, $J = 6$ Hz, H-4).

Synthesis of 3-[1-(3-Pyridyl)ethyl]indoles (2).—(a) *From indolylmagnesium bromides; standard procedure.* The indole in dry tetrahydrofuran was added slowly to ethylmagnesium bromide (1.7 mol equiv.) in the same solvent under nitrogen. The mixture was then stirred for 1 h, and 3-(1-chloroethyl)pyridine (1 mol equiv.) was then introduced. An exothermic reaction occurred, after which the vessel was sealed and set aside for 2 days. The solvent was then removed and the residue worked up for bases by extraction with 2N-hydrochloric acid. The product was purified by chromatography on silica with diethyl ether as eluant prior to recrystallisation.

3-[1-(3-Pyridyl)ethyl]-5-methoxyindole, yield 30%, had m.p. 136—137° (MeOH); $\lambda_{max.}$ 220 (ε 25 940), 268 (7 660), 297 (5 360), and 308 nm (3 890); δ [$(CD_3)_2SO$] 10.80 (1 H, br, s, NH), 8.61 (1 H, d, J 2 Hz, H-2′), 8.38 (1 H, dd, J_1 6, J_2 2 Hz, H-6′), 7.66 (1 H, m, H-4′), 7.28 (3 H, m, H-4, H-6, H-7), 6.83—6.65 (2 H, m, H-2, H-5′), 4.36 (1 H, q, J 8 Hz, $CHCH_3$), 3.66 (3 H, s, CH_3O), and 1.68 (3 H, d, J 8 Hz, $CHCH_3$) (Found: C, 76.1; H, 6.3; N, 12.0. $C_{16}H_{16}N_2O$ requires C, 76.2; H, 6.4; N, 11.1%).

3-[1-(3-Pyridyl)ethyl]-6-methoxyindole, yield 40%, had m.p. 166—167° (EtOH); $\lambda_{max.}$ 221 (ε 21 600), 251 (4 300), 260 (6 300), 272 (3 800), and 281 nm (2 400); δ [$(CD_3)_2SO$] 1.80 (1 H, br, s, NH), 8.55 (1 H, d, J 2 Hz, H-2′), 8.15 (1 H, dd, J_1 6, J_2 2 Hz, H-6′), 7.60 (1 H, dd, J_3 6, J_4 2 Hz, H-4′), 7.4—7.1 (3 H, m, H-2, H-4, H-5′), 6.70 (2 H, m, H-5, H-7), 4.35 (1 H, q, J 8 Hz, $CHCH_3$), 3.80 (3 H, s, OCH_3), and 1.62 (3 H, d, J 8 Hz, $CHCH_3$) (Found: C, 76.2; H, 6.3; N, 11.2. $C_{16}H_{16}N_2O$ requires C, 76.2; H, 6.4; N, 11.1%).

(b) *From 3-(3-Pyridyl)butanal.* The arylhydrazine hydrochloride and 3-(3-pyridyl)butanal (1 mol equiv.) in methanol were heated at reflux for 4 h, then cooled. The solvent was removed and the residue heated with methanol previously saturated with hydrogen chloride for 1.5 h; then the solvent was again removed. Water was added and the mixture made basic with dilute aqueous ammonium hydroxide. Extraction with dichloromethane afforded the product pyridylethylindole.

3-[1-(3-Pyridyl)ethyl]indole, yield 56%, had m.p. 172° (lit.,[3] 173°) (Found: C, 82.0; H, 6.3; N, 12.4. Calc. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.6%).

3-[1-(3-Pyridyl)ethyl]-5-methoxyindole was obtained in 45% yield.

3-[1-(3-Pyridyl)ethyl]-7-methylindole, yield 50%, had m.p. 168—169° (EtOH); $\lambda_{max.}$ 219 (ε 47 290), 260 (16 290), 266 (16 110), 280 (13 830), 290 (10 970), and 341 nm (4 060); δ [$(CD_3)_2SO$] 10.82 (1 H, br, s, NH), 8.52 (1 H, d, J 2 Hz, H-2′), 8.32 (1 H, dd, J_1 6, J_2 2 Hz, H-6′), 7.60 (1 H, m, H-4′), 7.28—6.73 (5 H, m, H-2, H-4, H-5, H-5′, H-6), 4.36 (1 H, *q*, J 8 Hz, $CHCH_3$), 2.45 (3 H, s, CH_3), and 1.68 (3 H, d, J 8 Hz, $CHCH_3$) (Found: C, 81.0; H, 6.5; N, 12.0. $C_{16}H_{16}N_2$ requires C, 81.35; H, 6.8; N, 11.9%).

3-[1-(3-Pyridyl)ethyl]-7-fluoroindole, yield 52%, had m.p. 162° (EtOH); $\lambda_{max.}$ 215 (ε 51 490), 262 (11 840), and 287 nm (5 840); δ [$(CD_3)_2SO$] 12.4 (1 H, br, s, NH), 8.55 (1 H, d, J 2 Hz, H-2′), 8.33 (1 H, dd, J_1 6, J_2 2 Hz, H-6′), 7.60 (1 H, m, H-4′), 7.75—7.33 (5 H, m, H-2, H-4, H-5, H-5′, H-6), 4.35 (1 H, q, J 8 Hz, $CHCH_3$), and 1.66 (3 H, d, J 8 Hz, $CHCH_3$) (Found: C, 75.1; H, 5.4; N, 11.4. $C_{15}H_{13}FN_2$ requires C, 75.0; H, 5.45; N, 11.7%).

3-[1-(3-Pyridyl)ethyl]-7-chloroindole, yield 50%, had m.p. 156—157° (EtOH–H_2O); $\lambda_{max.}$ 221 (ε 56 200), 270 (13 700), 285 (12 050), and 296 nm (9 760); δ[$(CD_3)_2SO$] 11.2 (1 H, br, s, NH), 8.60 (1 H, d, J 2 Hz, H-2′), 8.39 (1 H, dd, J_1 6, J_2 2 Hz, H-6′), 7.65 (1 H, m, H-4′), 7.4—6.8 (5 H, m, H-4, H-5, H-5′, H-6), 4.40 (1 H, q, J 8 Hz, $CHCH_3$), and 1.70 (3 H, d, J 8 Hz, $CHCH_3$) (Found: C, 70.0; H, 5.0; N, 11.1. $C_{15}H_{13}ClN_2$ requires C, 70.2; H, 5.1; N, 10.9%).

In the case of 3-substituted arylhydrazines, mixtures of pyridylethylindoles were formed, *e.g.* 3-fluorophenylhydrazone gave a 3.2 : 1 ratio of 3-[1-(3-pyridyl)ethyl]-4- and -6-fluoroindoles, 3-methylphenylhydrazine yielded 3-[1-(3-pyridyl)ethyl]-4- and -6-methylindoles (3 : 1), and 3-methoxyphenylhydrazine afforded 3-[1-(3-pyridyl)ethyl]-4- and -6-methoxyindoles (3.1 : 1). Only the last mixture has been separated [flash chromatography; SiO_2; chloroform–light petroleum (b.p. 60—80 °C)] giving the 6-methoxyindole in 25% yield.

1-Acetyl-3-{1-[3-(4-cyanopyridyl)]ethyl}indoles; General Procedure.—The pyridylethylindole (1.5 g), acetic anhydride (20 cm³), and triethylamine (0.2 g) were heated at reflux for 0.5 h. The solvent was then removed and the residue treated with crushed ice (100 g). After basification with ammonium hydroxide, extraction with dichloromethane gave the 1-acetyl derivative of the parent pyridylethylindole (2). (These products can be re-crystallised from methanol, but are normally pure enough for use in the next stage.) A solution of *O*-mesityl sulphonylhydroxylamine (1.55 g) in dichloromethane (5 cm³) was added to the acetylindole, also dissolved in this solvent (15 cm³), and the mixture was

stirred at −10 °C for 0.5 h. After this the contents of the flask were poured into diethyl ether (250 cm³) and the colourless solid which separated out was collected by filtration. This was dissolved in water (25 cm³) and stirred with acetic anhydride (25 cm³) at room temperature for 0.5 h. After basification with ammonium hydroxide the mixture was extracted with dichloromethane (5 × 100 cm³) and the dry combined extracts were evaporated. The oily residue was taken up in acetone (50 cm³) and treated with methyl iodide (25 cm³) at reflux for 0.75 h. As the mixture cooled a yellow solid separated. This was collected, dissolved in water (50 cm³) containing ammonium chloride (1.3 g), and treated with potassium cyanide (1.5 g) in water (20 cm³). After 1 h, the suspension which had formed was extracted with dichloromethane (5 × 100 cm³) to give an oil which was dissolved in ethanol (100 cm³) and irradiated with u.v. light from a low pressure source. The ethanol was then removed and the appropriate nitrile separated from *N*-methylacetamide by chromatography on silica using diethyl ether as eluant.

As an example the 5-methoxy-derivative was fully characterised, but in general the products are suitable for direct conversion into the corresponding ellipticines.

1-*Acetyl*-3-{1-[3-(4-*cyanopyridyl*)]*ethyl*}-5-*methoxyindole*, yield 85%, had m.p. 95—96°; δ [$(CD_3)_2SO$] 8.65 (1 H, s, H-2′), 8.62 (1 H, d, *J* 6 Hz, H-6′), 8.3 (1 H, d, *J* 10 Hz, H-7), 7.5 (1 H, d, *J* 6 Hz, H-5′), 7.41 (1 H, s, H-2), 6.90 (1 H, dd, J_1 10, J_2 2 Hz, H-6), 6.64 (1 H, d, *J* 2 Hz, H-4), 4.64 (1 H, q, *J* 8 Hz, C*H*CH_3), 3.75 (3 H, s, CH_2O), 2.65 (3 H, s, CH_3CO), and 1.85 (3 H, d, *J* 8 Hz, CHCH_3) (Found: C, 71.2; H, 5.6; N, 13.0. $C_{19}H_{17}N_3O_2$ requires C, 71.45; H, 5.4; N, 13.2%).

Synthesis of Ellipticines; General Procedure.—A solution of the nitrile (500 mg) in dry tetrahydrofuran (5 cm³) was added dropwise to a cold (−78 °C) solution of methyllithium (4 mol equiv.) in dry tetrahydrofuran under nitrogen, and the mixture was vigorously stirred for 0.5 h. It was then allowed to warm to room temperature and poured onto ice and 20% acetic acid (50 cm³). After heating on a steam-bath for 1 h the mixture was cooled, basified with ammonium hydroxide, and extracted with dichloromethane or ethyl acetate (8 × 15 cm³). Evaporation of the dry, combined extracts afforded the appropriate ellipticine (1).

9-Methoxyellipticine, yield 94%, had m.p. 268—269° (methanol) (lit.,[15] 270°); $\lambda_{max.}$ 245 (ε 21 380), 276 (36 170), 292 (42 640), 305 (26 190), 336 (5 280), and 353 nm (2 870); δ [$(CD_3)_2SO$] 11.89 (1 H, br, s, NH), 9.68 (1 H, br, s, H-1), 8.42 (1 H, br, d, *J* 6 Hz, H-3), 7.85 (1 H, br, d, *J* 6 Hz, H-4), 7.84 (1 H, br, d, *J* 2 Hz, H-10), 7.50 (1 H, d, *J* 10 Hz, H-7), 7.20 (1 H, dd, J_1 10, J_2 2 Hz, H-8), 3.91 (3 H, s, CH_3O), 3.20 (3 H, s, 11-CH_3), and 2.75 (3 H, s, 5-CH_3) (Found: C, 78.0; H, 5.8; N, 10.2. Calc. for $C_{18}H_{16}N_2O$: C, 78.2; H, 5.8; N, 10.1%).

7-*Fluoroellipticine*, yield 86%, had m.p. 244—245° (decomp.) (ethanol); $\lambda_{max.}$ 242 (ε 28 490), 276 (42 110), 284 (59 050), 360 (39 200), and 353 nm (4 030); δ [$(CD_3)_2SO$] 12.61 (1 H, br, s, NH), 9.65 (1 H, s, H-1), 8.28 (1 H, d, *J* 6 Hz, H-3), 8.10 (1 H, d, *J* 6 Hz, H-4), 7.85 (1 H, br, d, *J* 8 Hz, H-10), 7.4—7.0 (2 H, m, H-9, H-8), 2.96 (3 H, s, 11-CH_3), and 2.60 (3 H, s, 5-CH_3) (Found: C, 77.4; H, 5.0; N, 10.5. $C_{17}H_{13}N_2F$ requires C, 77.25; H, 5.0; N, 10.6%).

7-*Chloroellipticine*, yield 93%, had m.p. 315—320° (ethanol); $\lambda_{max.}$ 238 (ε 29 340), 266 (40 040), 276 (62 660), 286 (69 200), 330 (6 120), 345 (4 850), and 378 nm (4 180); δ [$(CD_3)_2SO$–CF_3CO_2D] 9.66 (1 H, s, H-1), 8.32 (1 H, d, *J* 6 Hz, H-3), 8.08 (1 H, d, *J* 6 Hz, H-4), 7.92 (1 H, d, *J* 8 Hz, H-10), 7.40 (1 H, d, *J* 8 Hz, H-8), 7.08 (1 H, dd, J_1 10, J_2 10 Hz, H-9), 2.92 (3 H, s, 11-CH_3), and 2.60 (3 H, s, 5-CH_3) (Found: C, 73.0; H, 4.7; N, 9.8. $C_{17}H_{13}ClN_2$ requires C, 72.7; H, 4.7; N, 10.0%).

7-*Methylellipticine*, yield 86%, had m.p. 298—300° (ethanol); $\lambda_{max.}$ 239 (ε 28 410), 280 (58 410), 287 (63 600), and 332 nm (5 090); δ [$(CD_3)_2SO$–CF_3CO_2D] 9.58 (1 H, s, H-1), 8.25 (1 H, d, *J* 6 Hz, H-3), 8.06 (1 H, d, *J* 6 Hz, H-4), 7.88 (1 H, d, *J* 8 Hz, H-10), 7.30—7.03 (2 H, m, H-8, H-9), 2.90 (3 H, s, 11-CH_3), 2.60 (3 H, s, 5-CH_3), and 2.48 (3 H, s, 7-CH_3) (Found: C, 83.1; H, 6.2; N, 10.8. $C_{18}H_{16}N_2$ requires C, 83.0; H, 6.2; N, 10.8%).

8-*Methoxyellipticine*, yield 93%, had m.p. 280—281° (ethanol–H_2O); $\lambda_{max.}$ 248 (ε 21 600), 280 (39 100), 300 (47 400), 310 (27 200), 340 (5 800), and 360 nm (2 600); δ [$(CD_3)_2SO$] 10.95 (1 H, br, s, NH), 9.70 (1 H, s, H-1), 8.35 (2 H, m, H-4, H-3), 7.90 (1 H, d, *J* 2 Hz, H-7), 7.50 (1 H, d, *J* 8 Hz, 10-H), 7.25 (1 H, dd, J_1 8, J_2 2 Hz, 9-H), 3.92 (3 H, s, OCH_3), 3.20 (3 H, s, 11-CH_3), and 2.76 (3 H, s, 5-CH_3) (Found: C, 78.2; H, 5.7; N, 10.1. $C_{18}H_{16}N_2O$ requires C, 78.2; H, 5.2; N, 10.1%).

8-*Hydroxyellipticine*.—8-Methoxyellipticine (100 mg) and pyridine hydrochloride (3.5 g) were mixed and heated to 215 °C in a thermostatically controlled oil-bath. After 1 h, the mixture was cooled and water (5 cm³) added. The pH was adjusted to 10 with ammonium hydroxide and the solid which separated was collected and chromatographed (thick-layer chromatography) on silica [eluant benzene–ethyl acetate–ethanol–concentrated ammonium hydroxide (21 : 6 : 4 : 5)]. A band showing strong green fluorescence under u.v. light was collected and extracted with hot methanol to give 8-hydroxyellipticine as yellow prisms (30%), m.p. 268—270° (decomp.) (methanol–ethyl acetate, 1 : 1) (lit.,[8] 268°), mixed m.p. with authentic 8-hydroxyellipticine 268—270°, showing identical t.l.c. behaviour in $CHCl_3$–EtOH–HOAC (70 : 30 : 2) (R_F 0.36), $CHCl_3$–MeOH–Et_2NH (40 : 5 : 2) (R_F 0.17), and $CHCl_3$–MeOH (4 : 1) (R_F 0.34); $\lambda_{max.}$ 228 (ε 32 400), 273 (37 200), 281 (41 700), 302 (72 400), 340 (42 700), and 370 nm (32 400); δ [$(CD_3)_2SO$] 11.12 (1 H, s, NH), 9.75 (1 H, s, H-1), 8.38 (1 H, d, *J* 6 Hz, H-4), 8.15 (1 H, d, *J* 8 Hz, 10-H), 7.85 (1 H, d, *J* 6 Hz, H-3), 6.94 (1 H, d, *J* 2 Hz, 7-H), 6.71 (1 H, dd, J_1 8, J_2 2 Hz, H-9), 3.17 (3 H, s, 11-CH_3), and 2.75 (3 H, s, 5-CH_3) (Found: C, 77.8; H, 5.4; N, 10.6. Calc. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.4; N, 10.7%).

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