Synthesis of 5-Ethyl-11*H*-pyrido[3,4-*a*]carbazole by Two Routes and Conversion of Uleine into 5-Ethyl-1,2,3,4-tetrahydro-2-methyl-11*H*-pyrido[3,4-*a*]carbazole

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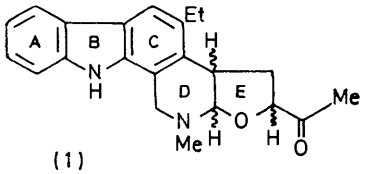
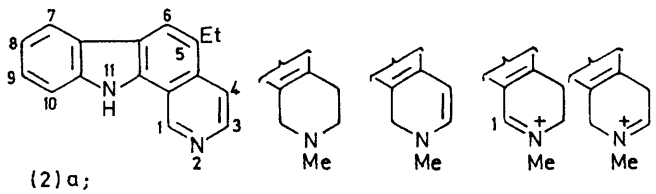
Syntheses of 5-ethyl-11*H*-pyrido[3,4-*a*]carbazole and derivatives as potential intermediates for a synthesis of the furopyridocarbazole alkaloid subincanine are described. In one approach 5-ethylisoquinoline was prepared and the indole ring was built up *via* 5-ethyl-8-hydrazinoisoquinoline. An alternative approach utilised the oxidative photocyclisation of a 1-(indol-3-yl)-2-(4-pyridyl)but-1-ene. Finally, the conversion of the 1,5-methanoazocino-[4,3-*b*]indole uleine into 5-ethyl-1,2,3,4-tetrahydro-2-methyl-11*H*-pyrido[3,4-*a*]carbazole is described.

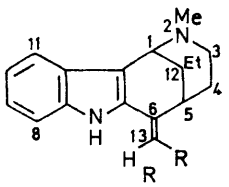
SUBINCANINE is an alkaloid obtained from *Aspidosperma subincanum*, to which we assigned [1] the provisional structure (1). Since lack of material precluded further



(1)



(2) a;
b; 7,8,9,10-tetrahydro (3) (4) (5) (6)

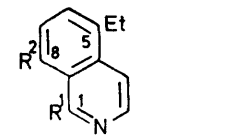


(7) a; H
b; Br

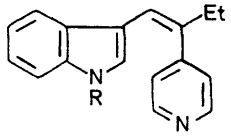
structural investigations we are pursuing a total synthesis as a means of settling remaining uncertainties. In order to leave flexible the construction of that part of the molecule (ring E, its mode of attachment, and the position of its acetyl substituent) which is least certain, our synthetic plans centre on the use of a tetracyclic intermediate such as (2a) comprising rings A to D. We report here two routes for the total synthesis of (2a), the transformation of uleine (7) into (3), and the preparation of the potentially useful enamine (4) and iminium salts (5) and (6).

The first route to (2a) which we have employed is patterned on that [2] developed by Manske and later used by Govindachari [3] in syntheses of its desethyl analogue. 5-Bromoisoquinoline [4] was converted into 5-cyanoisoquinoline by the action of copper(I) cyanide in dimethyl sulphoxide, this being an improvement on an earlier method [5] which used no solvent. Reaction of the nitrile with methylmagnesium iodide and subsequent Wolff–Kishner reduction then gave 5-ethylisoquinoline. However, it was not found possible to achieve selectivity in the Grignard addition and an appreciable quantity of 5-acetyl-1-methylisoquinoline, resulting from attack at C-1 as well as at the nitrile function, was always present in the total ketonic product. Separation of the mixture was deferred until after reduction and subsequent nitration when the desired 5-ethyl-8-nitroisoquinoline (8a) could be easily separated by chromatography from its homologue 5-ethyl-1-methyl-8-nitroisoquinoline (8b).

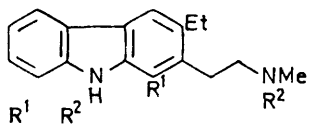
The structures of the two nitro-compounds are supported by their spectra: thus the lower homologue (8a) had u.v. absorption, in neutral and acidic media, which was very similar to that of 8-nitroisoquinoline itself; [6] the 1-methyl derivative however had a spectrum (see Experimental section and below) closer to that of isoquinoline, especially in acidic solution.



	R^1	R^2
(8) a;	H	NO_2
b;	Me	NO_2
c;	H	$NH{\cdot}NH_2$
d;	H	$NH{\cdot}N{:}C_6H_{10}$



	R
(9) a;	H
b;	Ac



	R^1	R^2
(10) a;	Me	Me
b;	Me	Ac
c;	CH_2Br	Ac
d;	CH_2OMe	H

The n.m.r. spectrum of (8a) showed a singlet at τ −0·05 due to the C-1 proton which was replaced by a

[1] A. J. Gaskell and J. A. Joule, *Tetrahedron Letters*, 1970, 77.
[2] R. H. F. Manske and M. Kulka, *Canad. J. Res.*, 1949, **27B**, 161, 291.
[3] T. R. Govindachari and V. Sudarsanam, *Indian J. Chem.*, 1971, **9**, 402.
[4] M. Gordon and D. E. Pearson, *J. Org. Chem.*, 1964, **29**, 329.
[5] F. T. Dyson, *J. Amer. Chem. Soc.*, 1939, **61**, 183.
[6] M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 1957, 2521.

C-1 methyl singlet at τ 7·2 in the spectrum of the higher homologue. Both compounds gave two sets of AB signals for the two pairs of aromatic protons and signals typical of an ethyl group. Interestingly the C-7 proton signal was at lower field (τ 1·75) in the spectrum of (8a) than in that of (8b) (τ 2·28); in the latter case the τ value was only slightly lower than that (2·48) of the C-6 proton. This difference can be ascribed to a steric interaction between the 8-nitro-group and the 1-methyl group, which must alter the degree of mesomeric interaction between the aromatic ring and the nitro-group and thus reduce the effect of the latter on the chemical shift of the *ortho*-proton. This same interaction must also account for the difference between the u.v. absorptions of (8a) and 8-nitroisoquinoline on the one hand and (8b) on the other.

The proximity of methyl and nitro-substituents in (8b) was also evidenced by a comparison of the mass spectral fragmentation of the two compounds. Thus, whereas the spectrum of 5-ethyl-8-nitroisoquinoline was typical of aromatic nitro-compounds, being dominated by successive losses of NO and CO, that of its 1-methyl derivative had the ion $M^+ - OH$ as base peak, presumably owing to interaction between the *peri*-nitro- and -methyl groups in a manner similar to that observed for *o*-nitrotoluene.[7]

The synthesis continued following the earlier pattern;[2,3] thus catalytic reduction, diazotisation, and reduction with tin(II) chloride converted (8a) into 5-ethyl-8-hydrazinoisoquinoline (8c), isolated as its dihydrochloride. This was then treated with cyclohexanone in anticipation of obtaining the corresponding hydrazone (8d), but even the mild conditions employed were sufficient to effect Fischer indolisation and 5-ethyl-7,8,9,10-tetrahydro-11*H*-pyrido[3,4-*a*]carbazole (2b) was obtained directly. Palladium-catalysed dehydrogenation then gave the desired compound (2a). Its u.v. absorption was identical with that reported[3,8] for its desethyl analogue and the material was identical with that obtained by a totally different route (see below) and independently[8] by photocyclisation. The overall yield in the nine-step sequence from isoquinoline was 0·006%.

The second route to (2a) was inspired by reports[9] that pyrido[*c*]carbazoles could be synthesised by oxidative photocyclisation * of 1-(indol-2-yl)-2-pyridylethylenes. The photosubstrate required for an analogous synthesis of (2a) was a trisubstituted ethylene of the type (9a), and this compound † was conveniently prepared by the condensation[11] of 3-formylindole and 4-n-propylpyridine to give (9b), followed by alkaline hydrolysis. Irradiation of (9a) in 95% ethanol at a concentration of 1 mg ml^{-1} and in the presence of iodine and air gave (2a) in 36% yield. It was later found not only that the separate hydrolysis step could be avoided but that a better cyclisation yield could be obtained by irradiating the *N*-acetyl condensation product directly in the presence of iodine and oxygen. Both ring closure and photocatalysed hydrolysis of the *N*-acetyl group took place and (2a) was obtained in 64% yield. Thus the tetracycle became available by a two-step procedure from commercial materials in an overall yield of 16%, but with the disadvantage that the high dilution necessary for the photocyclisation restricted the scale on which this step could be conveniently carried out.

The co-occurrence of subincanine and uleine in *A. subincanum* was adduced[1] as circumstantial evidence that the ABCD-ring system of the new alkaloid has a carbon skeleton identical with that of uleine. This suggested the possibility of transforming uleine chemically into a compound having the subincanine ABCD-ring system. It was recognised that in order to do this it would be necessary to break the C(1)–N(2) bond and make a C(13)–N(2) bond [see formula (7) for numbering system].

Since the earliest work[12] on uleine it has been known that the alkaloid methiodide undergoes a relatively easy Hofmann degradation giving the carbazole (10a) by migration of the exocyclic double bond into the ring. Later[13] it was discovered that treatment of uleine with acetic anhydride–pyridine and then acid gives the carbazole (10b). The transformation necessary for the present purpose required analogous ring opening and ring C aromatisation, but that these be carried out in such a way as to provide also a functionalised C-13 to allow subsequent closure of ring D.

To this end uleine (7a) was treated with 1 mol. equiv. of bromine at 0 °C. A crystalline hydrobromide was isolated in quantitative yield, and the corresponding base can be assigned structure (7b). Its u.v. absorption [only a small (6 nm) hypsochronic shift] was similar to that of the starting material; its mass spectrum and the results of combustion analysis of the salt showed the product to have been formed by the substitution of one bromine for a hydrogen atom. The n.m.r. spectrum of the free base was virtually identical with that of uleine except for two features: only one vinyl proton signal was present, at lower field (τ 4·33) than either of the two

* The use of a photocyclisation for the synthesis of pyrido[*a*]-carbazoles was independently developed by Snieckus *et al.*; for an account of this work and analogous pyrido[*c*]carbazole syntheses, including an alternative method for the preparation of the ethylenic photosubstrates and a discussion of the mechanistic aspects of the photocyclisations, see refs. 8 and 10.

† The geometry of the double bond in this condensation product is not known; it appeared to be a single compound. The isomer shown is that which is necessary for cyclisation. Presumably if the compound actually has the opposite geometry, prior *cis–trans* isomerisation must take place under the conditions of the photocyclisation.

[7] S. Meyerson, I. Puskas, and E. K. Fields, *J. Amer. Chem. Soc.*, 1966, **88**, 4974.
[8] S. O. De Silva and V. Snieckus, *Canad. J. Chem.*, in the press.
[9] S. O. De Silva and V. Snieckus, *Synthesis*, 1971, **5**, 254; H-P. Husson, C. Thal, P. Potier, and E. Wenkert, *J. Org. Chem.*, 1970, **35**, 442.
[10] J. A. Eenkhoorn, S. O. De Silva, and V. Snieckus, *Canad. J. Chem.*, 1973, **51**, 792.
[11] D. Jerchel and H. E. Heck, *Annalen*, 1958, **613**, 171.
[12] J. Schmutz, F. Hunziker, and R. Hirt, *Helv. Chim. Acta*, 1957, **40**, 1189; G. Buchi and E. W. Warnhoff, *J. Amer. Chem. Soc.*, 1959, **81**, 4433.
[13] J. A. Joule and C. Djerassi, *J. Chem. Soc.*, 1964, 2777.

olefinic signals of the starting material (τ 4·76 and 5·05), and a new broad one-proton singlet at τ 6·82 (see below) had appeared.

The formation [14] of 2-bromo-1,1-diphenylethylene from 1,1-diphenylethylene and bromine at room temperature exactly parallels what must occur in the present case. Initial attack is followed by loss of a proton rather than addition of bromide, to generate the bromo-substituted conjugated system. Models suggest that the preferred conformation for this elimination would have the C-13 bromo-substituent *cis* to C-5 and predict the formation of (7b) and not its geometrical isomer. This prediction is borne out by the signal at τ 6·82 in the n.m.r. spectrum of the bromo-product, which can be ascribed to the C-5 proton influenced by a through-space interaction with the halogen.

Cleavage of the C(1)–N(2) bond and ring C aromatisation was effected by the reaction of 13-bromouleine hydrobromide with acetyl chloride–potassium carbonate. A single non-basic carbazolic product (10c) was obtained, which however proved to be too unstable for full spectral characterisation. No molecular ion could be found in its mass spectrum, though fragment ions with and without bromine, were visible, corresponding to the patterns established [13] for the fragmentation of molecules of this general type. At *m/e* values below 264, the spectrum was extremely similar to that of the pyridocarbazole (3) (see later), indicating that a cyclisation to (3) involving loss of acetyl bromide might be taking place in the mass spectrometer.

Because of the amide's instability it was hydrolysed without further purification in methanolic aqueous sodium hydroxide. The resulting methoxy-amine (10d) was obtained in 28% yield (from 13-bromouleine), and although it could not be crystallised its structure is established. It shows a carbazole u.v. absorption, the correct molecular composition (mass spectrometry), mass spectral fragmentation [13] involving favoured successive losses of CH:NMe [⟶ *m/e* 153 (95%)], methanol [⟶ *m/e* 221 (100%)], and methyl radical [⟶ *m/e* 206 (56%)], and appropriate n.m.r. signals (see Experimental section).

Cyclisation proved surprisingly difficult: treatment with hydrobromic acid, for example, led either to no reaction or, under more vigorous conditions, to extensive decomposition. Finally a moderate yield of the pyridocarbazole (3) was obtained by heating the methoxy-amine (10d) in acetic acid. The cyclised material proved very susceptible to aerial oxidation, and traces of the dehydro-derivative (5) (see later) were always present in the products from cyclisations. They could be removed and the yield improved by treatment of the total product with sodium borohydride before purification. The cyclic material was identical with that obtained from the fully aromatic tetracycle (2a) by quaternisation with methyl iodide followed by reduction with sodium borohydride.

Modification of the tetracycles (2a) and (3) has given the products (4)—(6) which should provide the means for introducing, at any of the three positions of ring D of the basic skeleton, the further necessary portion of the subincanine structure.

Oxidation of the amine (3) with mercury(II) acetate in aqueous acetic acid gave the iminium system (5) as a crystalline chloride. That oxidation had occurred at the benzylic C-1 and not on the alternative side of the nitrogen atom was shown by the change in u.v. absorption on addition of alkali—a simple carbazole spectrum resulted from hydroxide addition to C-1. Further, the n.m.r. spectrum of (5) showed a one-proton low-field singlet for the C-1 proton. The alternative iminium salt (6) (see later) had its carbazole absorption changed to that of the enamine (4) on addition of alkali.

The enamine (4), prepared by partial reduction [15] of the methiodide of (2a) with lithium aluminium hydride, tended to disproportionate to a mixture of the metho-salt of (2a) and (3). A solid salt (6) could be obtained, however, by treatment with concentrated hydrochloric acid.

EXPERIMENTAL

For general comments see ref. 16.

Isoquinoline-5-carbonitrile.—A mixture of copper(I) cyanide (100 g) and 5-bromoisoquinoline (20 g) in dry dimethyl sulphoxide (500 ml) was heated at reflux with stirring under nitrogen for 2 h, cooled, and poured with agitation into ammonia (*d* 0·88; 500 ml) and water (1 l). The resulting mixture was shaken with ether and filtered, the layers were separated, and the aqueous phase was saturated with sodium chloride and then further extracted with ether (5 l in all). The combined extracts were washed with water, dried, and evaporated to give the nitrile (10·9 g), m.p. 137—139° (from toluene) (lit.,[17] 135°).

5-Ethyl-8-nitroisoquinoline (8a) *and 5-Ethyl-1-methyl-8-nitroisoquinoline* (8b).—Isoquinoline-5-carbonitrile (10 g) in dry benzene (830 ml) was added dropwise to a solution of methylmagnesium iodide [from magnesium (2·4 g) and methyl iodide (15 g)] in ether. The ether was boiled off and the resulting mixture refluxed for 4 h. 2N-Hydrochloric acid (500 ml) was added and the two-phase mixture was refluxed for a further 2 h. The mixture was made basic, the layers were separated, and the aqueous layer was further extracted with ether. The dried organic extracts were evaporated to give an oily mixture (7·7 g) of 5-acetylisoquinoline and 5-acetyl-1-methylisoquinoline [also containing some starting material (g.l.c.)] in a ratio of *ca.* 6 : 1 (g.l.c.); $\nu_{max.}$ (film) 1680 cm^{-1}; *m/e* 171 (M^+, 77%), 156 (100), and 128 (55); 185 (M^+, 40%), 170 (70), and 142 (25).

The crude mixture of ketones (7·7 g) was treated with hydrazine hydrate (12 ml) in diethylene glycol (200 ml) and the mixture was refluxed for 2 h. After cooling, powdered potassium hydroxide (31 g) was added and the mixture was heated at 120—150° until nitrogen evolution ceased (2 h). After cooling and dilution with water the product was

[14] D. Y. Curtin and E. W. Flynn, *J. Amer. Chem. Soc.*, 1959, **81**, 4714.
[15] M. Sainsbury, S. F. Dyke, and A. R. Marshall, *Tetrahedron*, 1966, **22**, 2445.
[16] A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc.* (*C*), 1969, 2738.
[17] N. Jeiteles, *Monatsh.*, 1894, **18**, 810.

extracted into ether to give, after drying and evaporation, an oily mixture (6·7 g) of 5-ethylisoquinoline and 5-ethyl-1-methylisoquinoline in a ratio of *ca.* 2·5 : 1 (g.l.c.); *m/e* 157 (M^+, 100%) and 142 (90); 171 (M^+, 55%) and 156 (75).

The major component was characterised as its methiodide, obtained by treating the mixture with methyl iodide in refluxing methanol to give *5-ethyl-2-methylisoquinolinium iodide*, m.p. 176—178° (from ethanol); $\lambda_{max.}$ (EtOH) 280 and 343 nm (log ε 3·31 and 3·62); $\lambda_{max.}$ (EtOH–0·1N-NaOH) 313 nm (log ε 3·76); τ (D_2O) −0·05 (1H, s, 1-H), 1·2—1·8 (5H, m, ArH), 5·1 (3H, s, N^+CH_3), 6·5 (2H, q, *J* 7 Hz, CH_2Me), and 8·3 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$) (Found: C, 47·8; H, 4·8; N, 4·8. $C_{12}H_{14}IN$ requires C, 48·3; H, 4·7; N, 4·7%).

To the crude mixture of ethylisoquinolines (3·4 g) in concentrated sulphuric acid (32 ml) was added potassium nitrate (2·7 g) in concentrated sulphuric acid (27 ml) during 5 min with the temperature maintained at 20—25°. After 1 h at room temperature the mixture was poured on ice and basified with ammonia (*d* 0·88), and the precipitate (1·91 g) was filtered off. Chromatography [dry column of alumina; with toluene–petroleum (b.p. 40—60°) as eluant] then gave first *5-ethyl-8-nitroisoquinoline* (8a) (0·78 g), m.p. 89—91°; $\lambda_{max.}$ (EtOH) 237, 295infl, and 335 nm (log ε 3·95, 3·56, and 3·66); $\lambda_{max.}$ (EtOH–0·1N-HCl) 234, 304, and 340 nm (log ε 4·20, 3·94, and 3·77); τ −0·05 (1H, s, 1-H), 1·25 (1H, d, *J* 5 Hz, 3-H), 1·74 (1H, d, *J* 7 Hz, 7-H), 2·05 (1H, d, *J* 5 Hz, 4-H), 2·35 (1H, d, *J* 7 Hz, 6-H), 6·8 (2H, q, *J* 7 Hz, CH_2Me), and 8·5 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 202 (M^+, 100%), 172 (63), 154 (30), and 144 (65) (Found: M^+, 202·07439. $C_{11}H_{10}N_2O_2$ requires *M*, 202·07423); and later *5-ethyl-1-methyl-8-nitro-isoquinoline* (8b) (0·33 g), m.p. 96—98°; $\lambda_{max.}$ (EtOH) 220, 283, 292, 310infl, 325, and 347infl nm (log ε 4·53, 3·69, 3·68, 3·46, 3·51, and 3·35); $\lambda_{max.}$ (EtOH–0·1N-HCl) 233, 282, 295, and 337 nm (log ε 4·21, 3·48, 3·50, and 3·89); τ 1·4 (1H, d, *J* 5 Hz, 3-H), 2·2 (1H, d, *J* 5 Hz, 4-H), 2·28 (1H, d, *J* 7 Hz, 7-H), 2·48 (1H, d, *J* 7 Hz, 6-H), 6·8 (2H, q, *J* 7 Hz, CH_2Me), 7·2 (3H, s, 2-CH_3), and 8·5 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 216 (M^+, 35%), 199 (100), 184 (20), 171 (17), and 154 (17) (Found: M^+, 216·09044. $C_{12}H_{12}N_2O_2$ requires *M*, 216·08988).

8-Amino-5-ethylisoquinoline.—5-Ethyl-8-nitroisoquinoline (2·2 g) was reduced with hydrogen at room temperature and pressure over 5% palladium–charcoal (1·1 g). Removal of the catalyst and evaporation gave *8-amino-5-ethylisoquinoline* (1·7 g), m.p. 110—112°; $\lambda_{max.}$ (EtOH) 243infl, 335, and 357 nm (log ε 4·26, 3·68, and 3·70); $\lambda_{max.}$ (EtOH–0·1N-HCl) 239, 262, 345, and 454 nm (log ε 4·14, 4·14, 3·60, and 3·71); τ 0·6 (1H, s, 1-H), 1·47 (1H, d, *J* 5 Hz, 3-H), 2·27 (1H, d, *J* 5 Hz, 4-H), 2·65 (1H, d, *J* 5 Hz, 6-H), 3·25 (1H, d, *J* 5 Hz, 7-H), 5·4br (2H, s, NH_2), 7·08 (2H, q, *J* 7 Hz, CH_2Me), and 8·72 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 172 (M^+, 75%), and 157 (100) (Found: M^+, 172·09904. $C_{11}H_{12}N_2$ requires *M*, 172·10005).

5-Ethyl-8-hydrazinoisoquinoline (8c).—To a solution of 8-amino-5-ethylisoquinoline (1·7 g) in concentrated hydrochloric acid (170 ml) was added sodium nitrite (0·85 g) in portions at 0° and the mixture was then stirred for a further 1 h at that temperature. Tin(II) chloride (6·8 g) was added and the mixture stirred for a further 2 h at 0°. The yellow precipitate was filtered off to give *5-ethyl-8-hydrazinoisoquinoline dihydrochloride* (1·3 g), m.p. 168—170° (from ethanol); $\lambda_{max.}$ (EtOH) 245, 335, and 448 nm (log ε 3·59, 3·02, and 2·79), $\lambda_{max.}$ (EtOH–0·1N-NaOH) 250infl, 319, and 353 nm (log ε 2·35, 2·98, and 2·96); *m/e* 187 (M^+, 35%), 157 (100), and 142 (100) (Found: C, 47·7; H, 5·7; Cl, 25·6; N, 14·6%; M^+, 187·11059. $C_{11}H_{15}Cl_2N_3,H_2O$ requires C, 47·5; H, 6·1; Cl, 25·6; N, 15·1; *M*, 187·11077). The filtrate was evaporated and the residue dissolved in water. The solution was saturated with hydrogen sulphide, the sulphide precipitate was filtered off, and the filtrate was basified with dilute sodium hydroxide and extracted with ether. The dried extract was evaporated to give more of the hydrazine (0·18 g).

5-Ethyl-7,8,9,10-tetrahydro-11H-pyrido[3,4-a]*carbazole* (2b).—The hydrazine (8c) dihydrochloride (130 mg) was treated with cyclohexanone (260 mg) in ethanol (50 ml) at reflux for 1·5 h. The solvents were evaporated off and the residue crystallised from ethanol to give the *pyridocarbazole* (2b) *hydrochloride* (120 mg), m.p. 207—210° (from ethanol); as a free base (2b) had $\lambda_{max.}$ 250infl, 319, and 353 nm (log ε 2·35, 2·98, and 2·96); τ [$(CD_3)_2SO$] 0·4 (1H, s, 1-H), 1·65 (1H, d, *J* 5 Hz, 3-H), 2·25 (1H, d, *J* 5 Hz, 4-H), 2·5 (1H, s, 6-H), 6·8—7·4 (6H, m, 7-H_2, 10-H_2, and CH_2Me), 8·2br (4H, s, 8-H_2 and 9-H_2), and 8·8 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 250 (M^+, 100%), 235 (48), 222 (28), and 207 (29) (Found: M^+, 250·14727. $C_{17}H_{18}N_2$ requires *M*, 250·14700).

1-(1-Acetylindol-3-yl)-2-(4-pyridyl)but-1-ene (9b).—A mixture of 3-formylindole (6 g) and 4-propylpyridine (20 g) in acetic anhydride (200 ml) was refluxed for 15 h. Approximately two-thirds of the solvent was evaporated off and the residue was treated with 3N-hydrochloric acid (80 ml). The precipitate was filtered off and partitioned between aqueous potassium carbonate and methylene chloride, and the dried organic phase was evaporated to give the *product* (9b) (3·1 g), which crystallised from ethanol to give material of m.p. 154—156°; $\nu_{max.}$ (Nujol) 1706s cm^{-1}; $\lambda_{max.}$ (EtOH) 230, 266, and 319 nm (log ε 4·26, 4·17, and 4·21); $\lambda_{max.}$ (EtOH–0·1N-HCl) 233, 271, and 361 nm (log ε 3·87, 3·65, and 3·81); τ 1·2—1·6 (2H, m, pyridine α-H), 2·2—2·8 (7H, ArH, pyridine β-H, C:CH), 3·02 (1H, s, indole 2-H), 7·13 (2H, q, *J* 7 Hz, CH_2Me), 7·3 (3H, s, Ac), and 8·8 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 290 (M^+, 70%), 248 (100), 233 (83), 130 (30), and 117 (24) (Found: C, 78·8; H, 6·3; N, 9·9. $C_{19}H_{18}N_2O$ requires C, 78·6; H, 6·25; N, 9·5%).

1-(Indol-3-yl)-2-(4-pyridyl)but-1-ene (9a).—The *N*-acetyl compound (9b) (320 mg) in ethanol was treated with an excess of dilute aqueous sodium hydroxide at room temperature. After 15 min the solution was concentrated, diluted with water, and extracted with dichloromethane. The dried extract was evaporated and the residue crystallised from ethanol to give the *product* (9a) (230 mg), m.p. 216—219°; $\lambda_{max.}$ 229, 275infl, and 343 nm (log ε 4·44, 3·80, and 4·27; τ [$(CD_3)_2SO$] −1·4 (1H, s, NH), 1·5 (2H, d, *J* 5 Hz, pyridine α-H), 2·15—3·05 (8H, pyridine β-H, C:CH, indole 2-H, ArH), 7·15 (2H, q, *J* 7 Hz, CH_2Me), and 8·85 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 248 (M^+, 100%), 233 (76), 130 (24), and 117 (14) (Found: C, 82·5; H, 6·6; N, 10·4. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·5; N, 11·3%).

5-Ethyl-11H-pyrido[3,4-a]*carbazole* (2a).—(*a*) The Fischer product (2b) (60 mg) was dehydrogenated with palladium–charcoal (10%) (120 mg) in decalin (25 ml) by refluxing for 3 h. The solution was treated with dilute hydrochloric acid and filtered, and the aqueous phase was basified and extracted (ethyl acetate). The extract was dried and evaporated to give the *pyridocarbazole* (2a) (17 mg), m.p. 245—248° (from ethyl acetate); $\lambda_{max.}$ (EtOH) 239, 288, 308infl, and 365 nm (log ε 4·51, 4·46, 4·15, and 3·75), $\lambda_{max.}$ (EtOH–0·1N-HCl) 223, 246, 307, and 435 nm (log ε 4·72,

4·77, 4·67, and 3·87); τ [$(CD_3)_2SO$] −3·0 (1H, s, NH), −0·4 (1H, s, 1-H), 0·9 (1H, d, *J* 6 Hz, 3-H), 1·18 (1H, s, 6-H), 1·52 (1H, d, *J* 6 Hz, 3-H), 1·8—2·3 (3H, m, 10-, 9-, and 8-H), 6·3 (2H, q, *J* 7 Hz, CH_2Me), and 8·1 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 246 (M^+, 75%) and 231 (100) (Found: C, 82·6; H, 5·7; N, 11·4%; M^+, 246·11495. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·75; N, 11·35%; *M*, 246·11600).

(*b*) The olefin (9a) (92 mg) in 95% ethanol (92 ml) containing iodine (23 mg) was irradiated (100 W Hanovia medium-pressure lamp; Pyrex filter) for 3 h, during which time air was blown through the solution in a fine stream. The solution was basified with aqueous potassium carbonate, treated with aqueous sodium thiosulphate, and concentrated under reduced pressure. The product was extracted with dichloromethane and the dried extract was evaporated to give the pyridocarbazole (2a) (16 mg).

(*c*) The *N*-acetyl compound (9b) (567 mg) was irradiated as in (*b*) (500 W lamp) in 95% ethanol (600 ml) containing iodine (156 mg) for 8 h. The solution was basified, treated with an excess of sodium thiosulphate, diluted with water (2 l), and extracted with ethyl acetate. The dried organic layer was evaporated to give a gum (479 mg) from which the pyridocarbazole (2a) (99 mg) could be crystallised with acetone. The mother liquors were chromatographed on neutral alumina to give more product (207 mg).

5-Ethyl-2-methyl-11H-pyrido[3,4-a]*carbazolium Iodide* [(2a) *Methiodide*].—The pyridocarbazole (2a) was quaternised with methyl iodide in methanol at reflux. The solvent was removed and the residual *methiodide* crystallised from methanol; m.p. 228—230°; $\lambda_{max.}$ 222, 245, 308, and 426 nm (log ε 4·09, 4·03, 3·94, and 3·29); $\lambda_{max.}$ (EtOH–0·1N-NaOH) 265, 330, and 530 nm (log ε 4·00, 3·68, and 3·38); τ [$(CD_3)_2SO$] −0·92 (1H, s, NH), −0·6 (1H, s, 1-H), 1·2—2·8 (7H, ArH), 3·5 (3H, s, N^+CH_3), 6·85 (2H, q, *J* 7 Hz, $MeCH_2$), and 8·61 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$) (Found: C, 54·0; H, 4·1; I, 34·2; N, 6·0. $C_{18}H_{17}IN_2$ requires C, 55·6; H, 4·3; I, 34·2; N, 7·2%).

13-Bromouleine (*6-Bromomethylene-12-ethyl-2,3,4,5,6,7-hexahydro-2-methyl-1,5-methano-1H-azocino*[4,3-b]*indole*) (7b).—Uleine (101 mg) in methylene chloride (15 ml) was treated dropwise with shaking with bromine (61 mg) in carbon tetrachloride (10 ml) at 0°. Evaporation left a yellow glass which could be crystallised from methanol to give *13-bromouleine* (7b) *hydrobromide* (160 mg), m.p. 234—236°; $\lambda_{max.}$ (EtOH) 245, 311, and 321 nm (log ε 3·97, 4·28, and 4·27); τ [$(CD_3)_2SO$] −2·1 (1H, s, NH), 2·18 (1H, d, *J* 7 Hz, 11-H), 2·42 (1H, s, C:CHBr), 2·5 (1H, d, *J* 8 Hz, 8-H), 2·6—3·0 (2H, m, ArH), 4·91br (1H, s, 1-H), 7·32 (3H, s, N^+CH_3), 8·96 (2H, q, *J* 7 Hz, CH_2Me), and 9·17 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$); *m/e* 346/344 (M^+, 18%), 303/301 (5), 288/286 (13), 265 (100), 235 (90), 222 (40), 221 (60), 208 (62), 206 (75), and 193 (100) (Found: C, 47·0; H, 4·9; Br, 36·2; N, 6·1. $C_{18}H_{22}Br_2N_2$,MeOH requires C, 47·2; H, 4·9; Br, 35·0; N, 6·1%).

The free base (7b) was obtained by partitioning the hydrobromide between aqueous potassium carbonate and ethyl acetate. The dried evaporated organic extract gave 13-bromouleine as a glass, τ 1·4 (1H, s, NH), 2·5—3·0 (4H, m, ArH), 3·44 (1H, s, C:CHBr), 5·93 (1H, d, *J* 2·5 Hz, 1-H), 6·82br (1H, s, 5-H), 7·72 (3H, s, NCH_3), 8·83 (2H, q, *J* 7 Hz, CH_2Me), and 9·18 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$).

3-Ethyl-1-methoxymethyl-2-(2-methylaminoethyl)carbazole (10d).—13-Bromouleine (7b) hydrobromide (20 mg) was stirred in suspension in dry benzene (10 ml) with anhydrous potassium carbonate (0·5 g) at room temperature for 15 min. Acetyl chloride (20 mg) in dry benzene (10 ml) was then added during 1 h. Water was added and the two layers were separated. The aqueous layer was re-extracted with ether and the combined organic solutions were washed with 0·1N-hydrochloric acid, dried, and evaporated to give the amide (10c) (11 mg), *m/e* (no molecular ion) 315/313 (8%), 307 (5), 302/300 (20), 301/299 (38), 264 (43), 262 (28), 235 (28), 221 (100), and 206 (50).

The amide (10c) (339 mg) in methanol (20 ml) was treated with aqueous sodium hydroxide (30%; 10 ml) at reflux for 2 days. The mixture was poured into water and extracted with chloroform. The dried extract was evaporated to give a glass which was purified by preparative t.l.c. on silica gel (elution with methanol) to give (at R_F 0·15) the *methoxy-amine* (10d) (115 mg) as a glass, $\lambda_{max.}$ 240, 250infl, 263, 290infl, 300, 300, and 342 nm; τ 1·18 (1H, s, NH), 2·0 (1H, s, 4-H), 2·02 (1H, d, *J* 8 Hz, 5-H), 2·6—3·0 (3H, m, ArH), 5·06 (2H, s, $ArCH_2{\cdot}OMe$), 6·56 (3H, s, OCH_3), 7·52 (3H, s, NCH_3), 8·24 (1H, s, NH), 6·8—7·4 (6H, m, $ArCH_2{\cdot}CH_2{\cdot}N$ and CH_2Me), and 8·68 (3H, t, *J* 7·5 Hz, $CH_2{\cdot}CH_2$); *m/e* 296 (M^+, 67%), 253 (95), 222 (50), 221 (100), and 206 (30) (Found: M^+, 296·19010. $C_{19}H_{24}N_2O$ requires *M*, 296·18886).

5-Ethyl-1,2,3,4-tetrahydro-2-methyl-11H-pyrido[3,4-a]*carbazole* (3).—(*a*) The methiodide of (2a) was reduced with an excess of sodium borohydride in ethanol at room temperature. The *tetrahydro-derivative* (3) was obtained as a gum, $\lambda_{max.}$ 250infl, 261, 287infl, 294, 323, and 338 nm; τ 2·02 (1H, d, *J* 8 Hz, 7-H), 2·14 (1H, s, NH), 2·3 (1H, s, 6-H), 2·6—3·0 (3H, m, ArH), 6·26 (2H, s, $ArCH_2{\cdot}N$), 6·9—7·4 (6H, m, $ArCH_2{\cdot}CH_2{\cdot}N$ and CH_2Me), 7·49 (3H, s, NCH_3), and 8·72 (3H, t, $CH_2{\cdot}CH_3$); *m/e* 264 (M^+, 80%) 263 (50), 221 (100), and 206 (56), *m** 231·8 (261 ⟶ 246) and 216·9 (246 ⟶ 231) (Found: M^+, 264·16307. $C_{18}H_{20}N_2$ requires *M*, 264·16265).

(*b*) The methoxy-amine (10d) (28 mg) was heated in glacial acetic acid (4 ml) at 140° under nitrogen for 8 h. The solution was diluted with water, basified, and extracted with chloroform. The dried organic layer gave a crude material which was treated with an excess of sodium borohydride in ethanol at room temperature for 15 min. The mixture was evaporated and the residue partitioned between water and chloroform. The dried organic extract was evaporated and the crude product purified by preparative t.l.c. on silica gel (elution with methanol) to give the product (3) (8 mg) as a gum, R_F 0·4.

5-Ethyl-3,4-dihydro-2-methyl-11H-pyrido[3,4-a]*carbazolium Chloride* (5).—The tetrahydropyridocarbazole (3) (45 mg) in aqueous 5% acetic acid (4 ml) was oxidised with mercury(II) acetate (215 mg) at reflux for 3·5 h. The mercury(I) acetate was filtered off and the filtrate saturated with hydrogen sulphide and acidified with concentrated hydrochloric acid. The precipitate was removed by centrifugation and the solution evaporated. The residual orange glass crystallised on trituration with ethanol to give the *chloride* (5) (30 mg), m.p. 207—209°; $\lambda_{max.}$ 232, 272, 283infl, 297, 305, and 438 nm (log ε 4·59, 4·01, 3·98, 4·08, 4·17, and 3·88); τ [$(CD_3)_2SO$] 0·4 (1H, s, 1-H), 1·3—2·7 (5H, ArH), 6·0 (2H, t, *J* 7 Hz, 3-H_2), 6·3 (3H, s, N^+CH_3), 6·8 (2H, t, *J* 7 Hz, CH_2Me), and 8·8 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$) (Found: C, 60·9; H, 5·7; N, 7·5. $C_{18}H_{19}ClN_2$,-$3H_2O$ requires C, 61·3; H, 7·1; N, 7·9%).

5-Ethyl-1,2-dihydro-2-methyl-11H-pyrido[3,4-a]*carbazole* (4) *and 5-Ethyl-1,4-dihydro-2-methyl-11H-pyrido*[3,4-a]*carb-*

azolium Chloride (6).—The methiodide of (2a) (74 mg) was reduced with an excess of lithium aluminium hydride under nitrogen in suspension in ether (100 ml) at room temperature for 30 min. The mixture was treated with an excess of aqueous potassium sodium tartrate, the layers were separated, and the aqueous layer was re-extracted with ether to give an ethereal solution of the enamine (4), $\lambda_{max.}$ 234, 260infl, 295infl, and 356 nm; *m/e* 262 (M^+, 78%) and 261 (100). The organic solution was extracted with a small volume of concentrated hydrochloric acid and the aqueous layer evaporated to give the *chloride* (6) (55 mg) as an amorphous powder, $\lambda_{max.}$ 230, 250infl, 262, and 287infl nm (Found: C, 64·9; H, 5·9; N, 8·0. $C_{18}H_{19}ClN,2H_2O$ requires C, 64·6; H, 6·9; N, 8·4%).

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