A Synthetic Approach to the Indole Alkaloid Apparicine. Synthesis of the Ring Skeleton

By **David I. C. Scopes, Malcolm S. Allen, Geoffrey J. Hignett, Nigel D. V. Wilson, Martin Harris, and John A. Joule** * Chemistry Department, Manchester University, Manchester M13 9PL

1,4,5,7-Tetrahydro-2,5-ethano-2*H*-azocino[4,3-*b*]indol-6(3*H*)-one (2), a compound having the ring skeleton of apparicine (1), has been synthesised *via* a Mannich type cyclisation of an indol-2-yl piperidin-4-yl ketone acetal. Attempts to extrapolate the approach for the synthesis of the alkaloid itself were frustrated by competing cyclisations leading to 3-(indol-2-yl)-3a,6-methanoperhydrofuro[3,4-*c*]pyridine and 1,2,3,4,4a,5,7,12,13,13a-decahydropyrido[4',3' : 6,7]oxocino[4,3-*b*]indole systems, as in (30) and (29). A route to α-pyridoylindoles, involving α-acylation of 4,5,6,7-tetrahydro- or 4,7-dihydro-indole and then dehydrogenation, is described.

THE alkaloid apparicine (1) [1] is one of a small group of indole bases which lack the otherwise ubiquitous C_2 side chain of biosynthetic precursor [2] tryptophan/tryptamine, though in this alkaloid the C-6 methylene group has been shown [3] to be derived from one of these two tryptamine side chain atoms. The carbon skeleton has been found [4] in only two other alkaloids, vallesamine and its acetate. No synthesis of the ring system has been published.

The synthetic approach described here centres on using an intermediate of general type (3) with insertion of the C-6 methylene to close the eight-membered ring (ring C). In order to provide a means for producing the exocyclic methylene and ethylidene groups of the alkaloid, R^1 and R^2 in the intermediate (3) would be functionalities designed to allow later elaboration of these features. Obvious candidates for R^1 and R^2 would be carbonyl † and hydroxyethyl groups.

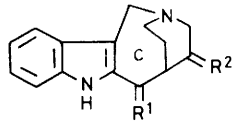
It was the aim to introduce the bridging C_1 unit by some sort of electrophilic substitution at the indole β-position. Since it was anticipated that a 2-acylindole (3; R^1 = O) would have considerably reduced susceptibility to electrophilic attack it was the plan to use a protected ketone. Thus, to test the feasibility of constructing the ring system in this way, the initial synthetic goal was the piperidine acetal (4),[6b] which would give rise to the model system (5) if a means could be found to introduce a carbon atom and close the fourth ring.

Indirect methods have to be employed to prepare α-acylindoles; several routes,[6] some published since this work was undertaken, have been utilised for this

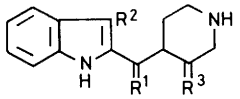
† A 2-acylindole was used as a precursor for a 2-vinylindole in recent syntheses [5] of uleine.

[1] J. A. Joule, H. Monteiro, L. J. Durham, B. Gilbert, and C. Djerassi, *J. Chem. Soc.*, 1965, 4773.
[2] G. A. Cordell, *Lloydia*, 1974, **37**, 219.
[3] J. P. Kutney, V. R. Nelson, and D. C. Wigfield, *J. Amer. Chem. Soc.*, 1969, **92**, 4278.
[4] A. Walser and C. Djerassi, *Helv. Chim. Acta*, 1964, **47**, 2072.
[5] (*a*) A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc.* (*C*), 1969, 2738; (*b*) L. J. Dolby and H. Biere, *J. Org. Chem.*, 1970, **35**, 3843.
[6] (*a*) R. R. Phillips, *Org. Reactions*, 1959, **10**, 143; R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604; R. J. Sundberg, Long-Su Lin, and D. E. Blackburn, *J. Heterocyclic Chem.*, 1969, **6**, 441; R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, 1973, **38**, 3324; (*b*) R. J. Sundberg, H. F. Russell, W. V. Ligon, and Long-Su Lin, *J. Org. Chem.*, 1972, **37**, 719.

purpose. None of these is entirely satisfactory from the points of view of ease of working or high yields, desirable features for the early steps of a synthesis. Accordingly



R^1	R^2
(1) CH_2	CHMe
(2) O	H_2
(5) OCH_2CH_2O	H_2



	R^1	R^2	R^3
(3)		H	
(4)	OCH_2CH_2O	H	H_2
(10)	H,OH	H	H_2
(11)	O	H	H_2
(13)	OCH_2CH_2O	CH_2OH	H_2
(14)	OCH_2CH_2O	$CH_2NC_5H_{10}$	H_2
(15)	OCH_2CH_2O	CH_2OEt	H_2
(16)	H_2	CHO	H_2
(17)	H_2	Me	H_2
(18)	H_2	H	H_2
(19)	OCH_2CH_2O	H	CH(OH)Me

we sought to develop a more useful method for the construction of such compounds and have evolved a route which, at least, compares favourably with others for the synthesis of the α-pyridoylindoles examined in this study.

Direct electrophilic acylation of indoles gives exclusive β-substitution. On the other hand pyrroles, or their *N*-halogenomagnesio-derivatives, react with electrophiles principally at an α-position. This difference lies at the heart of our method.

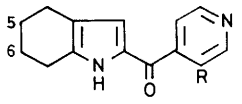
4,5,6,7-Tetrahydroindole,* which in reactivity is simply a dialkylpyrrole, could be acylated *via* its *N*-bromomagnesio-derivative with methyl isonicotinate at the pyrrole α-position † to give the ketone (6). Dehydrogenation to the desired indol-2-yl pyrid-4-yl ketone (7) [5a,6b] could be effected, in good yield, at least on up to a 1 g scale, by the use of *o*-chloranil. Catalytic methods led mainly to the formation of indol-2-ylpyrid-4-ylmethane (8).

The ratio of tetrahydroindolyl magnesium bromide to pyridine ester was found to be critical for high yields ‡ and was optimum when the indole component was present in 2 molar excess over the pyridine. This requirement can be rationalised as a combination of two effects. First, deactivation of 1 mol of tetrahydroindolylmagnesium bromide may occur by displacement (in a dimeric structure [9]) of ethers of solvation by more powerfully donating 4-methoxycarbonylpyridines of solvation. Secondly, the initial product (9) would be expected, very readily, to lose a proton to unchanged tetrahydroindolylmagnesium bromide, thus using up a second mole of this reactant.

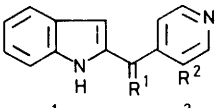
Catalytic reduction of the hydrochloride of the ketone (7) to the piperidine alcohol (10) and re-oxidation to the ketone (11) [6b] with manganese dioxide afforded an opportunity to test the prediction that this deactivated indole would be of no value for introduction of the methylene bridge. It was in fact unchanged by treatment with formaldehyde–acetic acid, a mixture which might have effected either direct hydroxymethylation of the indole ring or an intramolecular Mannich condensation (see below).

Attention was then turned to the preparation of the piperidine acetal (4); this was achieved by two routes. Acetalisation,§ to give (12),[6b] using ethylene glycol and toluene-*p*-sulphonic acid and then controlled hydrogenation of the acetate salt gave the same product (4), in the same overall yield, as the three step procedure of quaternisation with benzyl bromide, reduction with sodium borohydride, and catalytic hydrogenation–hydrogenolysis.

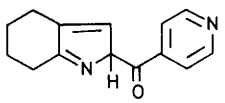
It was known [10] that indol-3-ylmethanol reacts easily



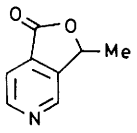
R
(6) H
(21) CH(OH)Me
(22) CH(OH)Me; 5,6-didehydro-



R^1	R^2
(7) O	H
(8) H_2	H
(12) OCH_2CH_2O	H
(23) O	CH(OH)Me



(9)



(20)

with piperidine in alkaline solution to give indol-3-yl-piperidin-1-ylmethane by the overall displacement of oxygen by nitrogen. A comparable intramolecular reaction on a derivative (13) of the piperidine acetal would lead to the target skeleton. The necessary alcohol was easily prepared from (4) by Vilsmeier formylation and reduction with sodium borohydride. In a trial reaction the alcohol (13) did indeed react easily with piperidine in ethanolic sodium ethoxide to yield the base (14), in complete analogy with the simpler

* Tetrahydroindole was best prepared by catalytic hydrogenation of the 4,7-dihydro- and 4,5,6,7-tetrahydro-indole mixture resulting from Birch reduction of indole;[7] an improved amination–decarboxylation of 4,5,6,7-tetrahydro-4-oxo-benz[*b*]-furan-3-carboxylic acid [8] followed by reduction of the resulting 1,5,6,7-tetrahydroindol-4-one with lithium aluminium hydride was utilised in our earlier work and is described in the Experimental section.

† From large-scale reactions, the β-substituted isomer, corresponding to 3% of total ketonic product, could be isolated.

‡ Yields (based on the pyridine component), ratios of tetrahydroindolylmagnesium bromide to pyridine ester: 9%, 1 : 2; 14%, 1 : 1; 55%, 2 : 1; 89%, 3 : 1.

§ Care was necessary to avoid a reverse ring acylation and the production of indole; boron trifluoride as a catalyst was particularly bad from this point of view.

[7] W. A. Remers, G. J. Gibb, C. Pidacks, and M. J. Weiss, *J. Org. Chem.*, 1971, **36**, 279.
[8] H. Stetter and R. Lauterbach, *Annalen*, 1962, **655**, 20.
[9] E. C. Ashby and M. B. Smith, *J. Amer. Chem. Soc.*, 1964, **86**, 4363.
[10] C. Runti, *Gazzetta*, 1951, **81**, 613.

case. However all attempts to bring about the electronically comparable intramolecular process met with failure. Even at high dilution the alcohol was only converted very largely into the ethyl ether (15).

Another unsuccessful attempt to produce the ring skeleton from an intermediate already carrying the one-carbon prospective methylene bridge on the indole was based on the hope that a cyclic carbinolamine or its dehydration product, potentially present in equilibrium with the indole-β-aldehyde, could be trapped by reduction. Accordingly the formylindolylpiperidylmethane (16) was hydrogenated in acidic solution, but the only product obtained was the skatole (17).

Having in hand three compounds, (4), (10), and (18) [the reduction product of (8)], each possessing both a piperidine *N*-hydrogen atom and a non-deactivated indole, further studies on the possible utility of an intramolecular Mannich approach were undertaken. Neither the alcohol (10) nor the methane (18) gave cyclised products with formaldehyde and acetic acid; however from the acetal (4) after * aqueous acidic removal of the protecting group, a product (2) with the desired apparicine ring skeleton could be obtained. The structure of the ketone (2), the yield of which was considerably improved † by carrying out the cyclisation in dilute solution, was confirmed by its spectral data. Thus in its mass spectrum the molecular ion was the base peak and important ions appeared at $M - 28$ (shown by high resolution measurement to be a doublet representing losses of CO and of C_2H_4) and at *m/e* 130 and 129 (characteristic indolyl-CH_2 fragments). Typical 2-acylindole u.v. absorption and an associated i.r. carbonyl stretching band at 1 635 cm^{-1} together with a two-proton singlet ‡ for the methylene bridge at τ 5.46,§ the *presence* of an indole *N*-hydrogen atom signal, and the *absence* of an indole β-proton signal, secure the structure.

With this success in hand attention was turned to the extrapolation of the route using a pyridine having the means for eventual production of the ethylidene group present in apparicine. To this end it was the aim to prepare and attempt an analogous Mannich cyclisation with a piperidine such as (19).

Following the method described above for the construction of α-acylindoles, tetrahydroindolylmagnesium bromide was condensed with the pyridine lactone (20),¶ and the expected α-substituted product (21) obtained in good yield. However, despite considerable efforts, no wholly successful method was found for the dehydrogenation of this intermediate.

In the hope of circumventing this difficulty and finding a more readily dehydrogenatable intermediate, the mixture of 4,7-di- and 4,5,6,7-tetra-hydroindoles obtained by Birch reduction of indole [7] was separated by spinning-band distillation. The Grignard derivative of dihydroindole was then condensed with the pyridine lactone (20), again using the organometallic component in 2 molar excess, whereby a good yield of the α-substitution product (22) was obtained. This oxo-alcohol *could* now be dehydrogenated, best with dichlorodicyanobenzoquinone, in yields of 75% on a scale up to 3 g, thus producing the fully aromatic oxo-alcohol (23).

No simple ethylene acetal could be obtained from this ketone, presumably because of interference from the alcohol function. It was decided therefore to continue the synthesis using the 1 : 1 stereoisomeric mixture of cyclic acetals (24) obtained cleanly from (23) by reaction with ethanolic hydrogen chloride.

This more hindered pyridine (24) could not be reduced cleanly by the direct method which worked for its simpler analogue. Recourse to the roundabout method of N_b-benzylation, reduction with sodium borohydride, and catalytic hydrogenation–hydrogenolysis did however give the desired piperidine, but even by this method only relatively poor recoveries of material were achieved in the final step. A further difficulty was the sensitivity of the borohydride reduction product (25) which, with the slightest trace of acid, or even when kept at room temperature in neutral solution, underwent loss of alcohol producing the indolylfuran (26). The dihydrofuran could be handled by maintaining it in a basic solution.

The catalytic reduction of (25) produced a mixture separable by preparative t.l.c. into apparently only three components. The first of these, which was produced to a greater extent when aqueous potassium carbonate was used as stabilising base during the reduction, proved to be the result of further hydrogenolysis and to have the structure (27). The remaining two, apparently homogeneous, components were stereoisomers of the desired piperidine acetal (28).

On the assumption that reduction of the double bond occurred in a *cis* manner, four possible isomers could have been obtained by the three-step sequence from the 1 : 1 mixture (24). Of these four possibilities only two would have indole and piperidine rings on the same side of the tetrahydrofuran ring, a necessary condition for a subsequent intramolecular Mannich reaction.

Since it seems that stereoselection is exhibited in the reduction step (only two straightforward products) one may tentatively make the further reasonable assumption

* Attempts to isolate cyclised acetal (5) were unsuccessful.

† Yields % (concentrations in mg ml^{-1}): 0.7 (17); 6.5 (2); 35 (0.2).

‡ The corresponding protons in apparicine resonate as an AB quartet at τ 5.44 and 5.81. The most likely explanation of this difference is that in both the model ketone (2) and apparicine (1) ring C is rapidly flipping, thus averaging the environment of the two protons in the symmetrical (2) but not in (1).

§ Since no compound with a totally comparable cyclic α-ketogramine-type methylene group is available as an n.m.r. model, further confirmation that this signal is due to NCH_2 was sought. Recording the n.m.r. spectrum in CD_3CO_2D resulted in a downfield shift in the chemical shift of this signal of 0.51 p.p.m., consistent with the effect to be expected from adjacent N_b-protonation; [11] the chemical shifts of the AB signal for the corresponding protons in apparicine were comparably altered by 0.45 and 0.31 p.p.m. respectively in CD_3CO_2D.

¶ The lactone (20) was prepared by side chain bromination of methyl 3-ethylpyridine-4-carboxylate [5a] with *N*-bromosuccinimide and subsequent acidic hydrolysis.

[11] J. C. N. Ma and E. W. Warnhoff, *Canad. J. Chem.*, 1965, **43**, 1849.

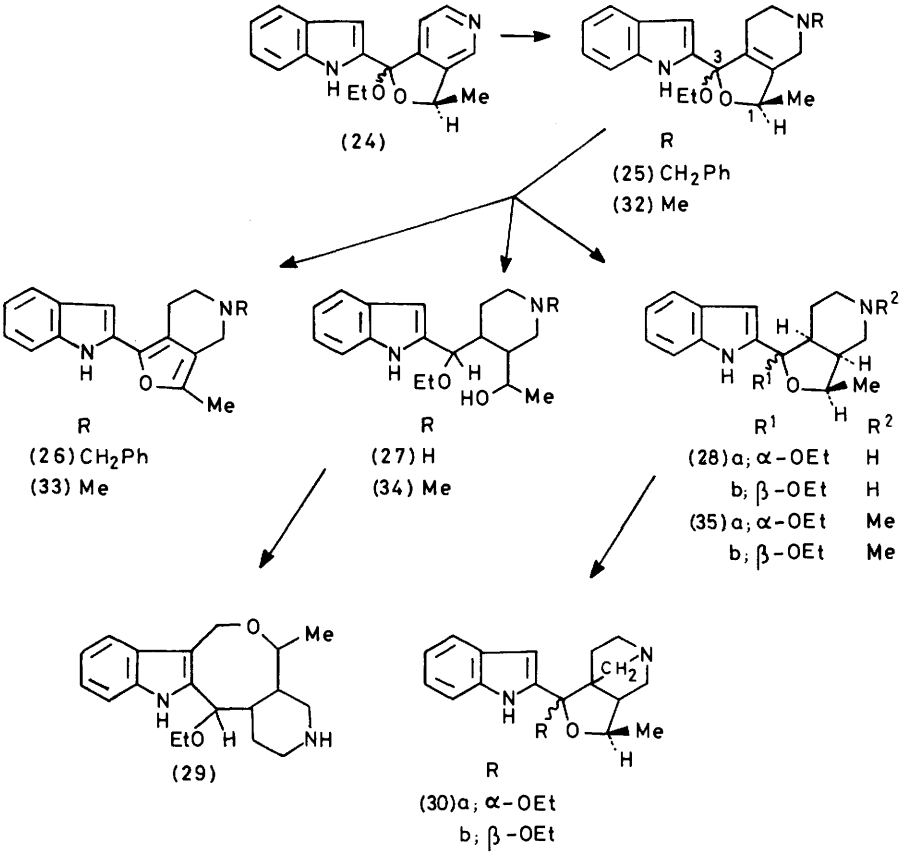
that reduction occurs from that side of the dihydrofuran ring which carries one and not two substituents; this would lead to the production of isomers (28a and b), of which the former would be able to undergo an intramolecular Mannich cyclisation. It is further worth noting that under acidic conditions it would not be unreasonable to expect equilibration at the benzylic acetal carbon, thus allowing the geometry required for cyclisation to be adopted by any of the theoretically possible stereoisomers.

Notwithstanding the validity of these arguments, each of the three reduction products was now subjected to high dilution Mannich conditions. The conditions employed had to be milder than those used in the model series, as the latter conditions were shown to lead to rapid degradation of the protecting acetal function. Further, the less acidic conditions which were accordingly applied to (27) and (28) did *not* effect cyclisation of (4). Nevertheless, in each of the present cases, the uptake of a methylene group at the expense of two hydrogen atoms was indeed observed; however in no case did the resulting product have the desired ring skeleton.

The alcohol (27) gave a product to which we tentatively assign structure (29), resulting from attack at the indole β-position but involving the alcoholic oxygen and not the desired piperidine nitrogen atom. Principal in this structural assignment is the absence of an indole β-proton signal in the n.m.r. spectrum, the presence of a singlet at τ 5.36 for the methylene protons between the indole and the ether oxygen,* and the failure to observe a coupled [12] C*H*OH in Me_2SO solution.

The two piperidine acetals (28) gave a pair of compounds of unexpected structure. Each isomer gave one product, and these were different but closely analogous to each other in their spectral properties. Each retained indole *N*-hydrogen and β-hydrogen n.m.r. signals; each had easily hydrolysed acetal groups (u.v. and n.m.r.) but had lost the aliphatic *N*-hydrogen atom and gained a methylene group at the expense of two hydrogen atoms; however in these cases, in contrast to (29), the introduced methylene absorbed in the n.m.r. above τ 6.5. We propose for these products stereoisomeric structures (30a and b) [assuming (28a and b) to represent the precursors] and envisage their formation as involving an equilibrium concentration of ring-opened enol (31).

In view of the sensitivity of the cyclic acetals (28) to acid, attempts were made to generate the necessary iminium function at N_b by other non-acidic methods.[13-15]



* Similar protons in the ether (15) resonate at τ 5.24 and those in a 3-methoxymethylindolic degradation product [1] of apparicine at τ 5.39.

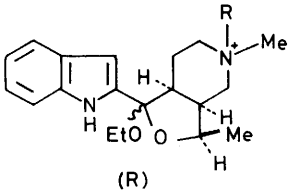
[12] O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, 1964, **86**, 1256.

[13] J. Schneifer, H. Maag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem. Internat. Edn.*, 1971, **10**, 330.

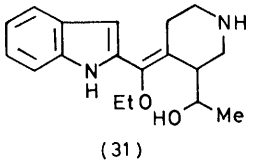
[14] J. P. Ferris, R. D. Gerwe, and G. R. Gapski, *J. Org. Chem.*, 1968, **33**, 3493.

[15] *E.g.* A. Ahond, A. Cave, C. Kan-Fan, H.-P. Husson, J. de Rostolan, and P. Potier, *J. Amer. Chem. Soc.*, 1968, **90**, 5622.

However, in no case was the result of an intramolecular cyclic Mannich reaction obtained. The mixture of acetals (24) was quaternised with methyl iodide and the resulting salt reduced with sodium borohydride. The



(R)



(31)

(36) CH_2I,I^-

(37) O^-

N-methyldihydrofuran (32) proved just as labile as (25), losing ethanol easily to give the furan (33). As before, though, it could be handled in basic solution and catalytically reduced to give a comparable mixture of hydrogenation–hydrogenolysis product (34) and two stereoisomeric reduction products (35a and b). The stereoisomeric mixture was utilised as such for the preparation of the *N*-oxide (36) and the iodomethyl iodide (37). Unfortunately neither heating [13] the iodomethyl iodide nor treatment of the *N*-oxide with iron(II) sulphate [14] or trifluoroacetic anhydride [15] led to isolable products.

EXPERIMENTAL

For general comments see ref. 5*a*.

4,5,6,7-*Tetrahydroindole*.—(*a*) A solution of 4,5,6,7-tetrahydro-4-oxobenzo[*b*]furan-3-carboxylic acid [8] (49.7 g) and ammonium acetate (100.3 g) in water (400 ml) was heated on a steam-bath for 18 h, filtered hot, cooled, basified, and extracted with chloroform to give 6,7-dihydrobenzo[*b*]furan-4(5*H*)-one (30.5 g, 85%), identical with material prepared by the literature method.[8] A slurry of the ketone (67.3 g) in dry ether (900 ml) was stirred and cooled in an ice-bath while lithium aluminium hydride (30 g) was added under nitrogen over several minutes. A vigorous reaction requiring efficient cooling ensued after a few minutes. After 1 h the mixture was refluxed for a further 12 h, then cooled, and the excess of reagent was decomposed by addition of water with cooling. When the precipitate was granular, addition of water was stopped and the ethereal solution decanted. This together with washings of the precipitate was dried and evaporated to give an oil, which was distilled (b.p. 80—88° at 1.5—2 mmHg) to give 4,5,6,7-tetrahydroindole as a liquid (36.6 g, 61%) which crystallised; m.p. 54—55.5° (lit.,[16] 55°).

(*b*) The mixture [7] of 4,7-di- and 4,5,6,7-tetra-hydroindole resulting from Birch reduction of indole (23.4 g) was hydrogenated in portions (6.2 g) over 10% Pd–C (0.5 g) in ethyl acetate (60 ml) at room temperature and at 45 lb in^{-2} for 9 h. The catalyst was filtered off, the solvent removed, and the residue distilled to give 4,5,6,7-tetrahydroindole (5.2 g, 70%), identical with a sample prepared as above.

4,7-*Dihydroindole*.—The mixture (19.3 g) of di- and tetra-hydroindole from Birch reduction of indole [7] was separated using a spinning-band distillation column at 0.1 mmHg. Fraction 1 (60 °C) contained mainly tetrahydroindole. The final fraction, b.p. *ca.* 65 °C, contained dihydroindole (5.47 g) together with 3% of indole.

4,5,6,7-*Tetrahydroindol-2-yl Pyridin-4-yl Ketone* (6).—To ethylmagnesium bromide [from ethyl bromide (0.5 g) and magnesium (0.134 g) in ether (10 ml)] under nitrogen was added dropwise a solution of tetrahydroindole (0.56 g; freshly distilled) in ether (10 ml). After refluxing for 0.5 h, the cooled mixture was treated with methyl isonicotinate (0.207 g) in benzene (20 ml) dropwise with vigorous stirring. An orange precipitate formed immediately. The ether was removed by distillation and the mixture refluxed for 18 h with stirring. The cooled mixture was stirred vigorously and treated with ammonium chloride (3 g) in water (15 ml). The mixture was filtered and separated, the benzene layer then being washed with aqueous potassium carbonate and then extracted with hydrochloric acid (0.2N). The aqueous layer was basified and extracted with ethyl acetate to give a partially crystalline residue which, after trituration with ether, gave the *ketone* (6) (0.30 g, 89%). The non-basic fraction yielded tetrahydroindole (0.33 g, 59% recovery). 4,5,6,7-Tetrahydroindol-2-yl pyridin-4-yl ketone had m.p. 187—191° (from methanol); $\lambda_{max.}$ 253 and 341 nm (log ε 3.79 and 4.18), $\lambda_{max.}$ (EtOH–0.1N-HCl) 275 and 376 nm (log ε 4.10 and 3.90); $\nu_{max.}$ (Nujol) 3 435s, 3 260m, and 1 612s cm^{-1}; τ −0.76br (1 H, NH), 1.21 and 2.34 (4 H, 2 dd, *J* 4.5 and 1.5 Hz, pyridine H), 3.39 (1 H, d, *J* 2 Hz, H_β of indole), 7.3—7.5 (4 H, m, H_2C-pyrrole), and 8.2 (4 H, m, H_2C); *m/e* 226 (M^+, 96%), 198 (100), 148 (28), 120 (15), 106 (11), 91 (13), and 78 (21), *m** 173.5 (226 → 198), 97.1 (226 → 148 or 148 → 120), 63.8 (226 → 120), and 57.4 (106 → 78) (Found: C, 74.4; H, 6.2; N, 12.5. $C_{14}H_{14}N_2O$ requires C, 74.3; H, 6.2; N, 12.4%).

Indol-2-yl Pyridin-4-yl Ketone (7).—The tetrahydroindole (6) (3.0 g) in decalin (500 ml) was stirred and heated to reflux, while tetrachloro-1,2-benzoquinone (19.5 g, powdered) was added during 10 min. After a further reflux (10 min) the colour of the quinone had been discharged and the solution was cooled and thoroughly extracted in portions with glacial acetic acid (800 ml). The extracts were treated with conc. hydrochloric acid (20 ml), concentrated to 200 ml, and diluted with water (1 l) while stirring vigorously. With the aid of Hyflo Supercel the resulting precipitate was removed and the filtrate together with washings (20 ml AcOH) of the precipitate was washed with ether, basified, and extracted with ethyl acetate to give the ketone (7) (1.89 g), identical with authentic material.[5a]

Indol-2-ylpyridin-4-ylmethane (8).—The tetrahydroindole (6) (0.5 g) and palladium–charcoal (0.1 g, 10%) were heated together in refluxing decalin (25 ml) for 60 h with stirring. The catalyst was filtered off and the filtrate extracted with hydrochloric acid (0.5N). After washing with ether the aqueous layer was basified and extracted with ethyl acetate. The extract was evaporated and the residue (0.35 g) was purified by dry column chromatography (silica; ethyl acetate) to give first the ketone (7) (81 mg) and then the *methane* (8) (242 mg, 53%), m.p. 137—142° (from benzene); $\lambda_{max.}$ 219, 264, 280, and 289 nm (log ε 4.61, 3.96, 3.94, and 3.87); $\nu_{max.}$ ($CHCl_3$) 3 460s cm^{-1}; τ 1.25br (1 H, s, HN), 1.56 (2 H, d, *J* 4.5 Hz, H_α of pyridine), 2.42—3.0 (6 H, m, HAr and H_β of pyridine), 3.67br (1 H, s, H_β of indole), and 5.94 (2 H, s, H_2C); *m/e* 208 (M^+, 100%), 207 (31), 130 (95), 103 (11), 78 (28), and 51 (11), *m** 81.3 (130 → 103) and 57.5 (103 → 77) (Found: C, 80.4; H, 5.8; N, 12.8. $C_{14}H_{12}N_2$ requires C, 80.7; H, 5.8; N, 13.4%).

[16] J. M. Patterson and S. Soedigdo, *J. Org. Chem.*, 1967, **32**, 2969.

Indol-2-ylpiperidin-4-ylmethanol (10).—The ketone (7) (250 mg) in ethanol (20 ml) was treated with hydrochloric acid (concentrated) until the solution was just acidic, and the solvent was then evaporated off. The resulting hydrochloride was hydrogenated in ethanol over Adams catalyst (65 mg) at 60 lb in^{-2} for 15 h. The catalyst was filtered off and the solution evaporated, and the residue was partitioned between ethyl acetate and aqueous potassium carbonate to give, from the organic phase, a gum (278 mg), from which the *alcohol* (10) could be crystallised from ethyl acetate, with ethyl acetate of solvation; m.p. 172—176°; $\lambda_{max.}$ 221, 274, 282, and 290 nm (log ε 4.48, 3.81, 3.81, and 3.75); $\nu_{max.}$ (Nujol) 3 230s, 2 730m, 2 670m, and 1 730s (ethyl acetate) cm^{-1}; τ [2 : 1 $CDCl_3$–$(CD_3)_2SO$] −0.32br (1 H, s, HN of indole), 2.4—3.3 (4 H, m, HAr), 3.78 (1 H, s, H_β of indole), 5.53 (1 H, d, *J* 6 Hz, *H*COH), 5.92 (1 H, q, *J* 7 Hz, ethyl acetate), and 8.00 (1.5 H, s, ethyl acetate); *m/e* 230 (M^+, 100%), 212 (14), 146 (52), 118 (97), 117 (32), 85 (97), 84 (79), 82 (94), 56 (52), and 55 (43), *m** 195.3 (230 ⟶ 212) and 95.3 (146 ⟶ 118) (Found: C, 70.5; H, 7.7; N, 11.2. $C_{14}H_{18}N_2O$, ½EtOAc requires C, 70.3; H, 7.7; N, 10.2%).

Indol-2-yl Piperidin-4-yl Ketone (11).—The alcohol (10) (75 mg) was oxidised with manganese dioxide (450 mg) by stirring in methylene chloride (30 ml) solution at room temperature for 2 h. After filtration, evaporation gave a brown gum (57 mg) which was purified by dry column chromatography (silica; Et_3N–MeOH, 1 : 9) to give the *ketone* (11) (47 mg, 63%), m.p. 156—160° (from C_6H_6) (lit.,[6b] 163—164°); $\lambda_{max.}$ 225 and 310 nm (log ε 4.20 and 4.37); $\nu_{max.}$ ($CHCl_3$) 3 450s, 3 320m, 2 820m, 2 740m, and 1 655s cm^{-1}; τ 2.1—3.1 (5 H, m, HAr and H_β of indole) and 4.0br (2 H, HN); *m/e* 228 (M^+, 67%), 185 (14), 173 (37), 172 (50), 144 (19), 89 (29), 84 (13), 82 (19), 78 (14), 57 (39), and 56 (100), *m** 150.1 (228 ⟶ 185), 119.8 (173 ⟶ 144), 54.9 (144 ⟶ 89) (Found: M^+, 228.126 262. $C_{14}H_{16}N_2O$ requires *M*, 228.126 080).

Indol-2-yl Pyridin-4-yl Ketone Ethylene Acetal (12).—A mixture of the ketone (7) (600 mg), ethylene glycol (15 ml), benzene (50 ml), and toluene-*p*-sulphonic acid (641 mg) was refluxed, with water removal by molecular sieves in a Soxhlet apparatus, for 12 h. The cooled solution was washed with aqueous potassium carbonate, dried, and evaporated to give a gum from which the *acetal* (12) (385 mg) could be crystallised using benzene; a further quantity (112 mg) (76% in all) could be obtained by treating the residue with sodium borohydride and dry column chromatography of the resulting mixture of acetal and alcohol (alumina; ethyl acetate). The *acetal* had m.p. 164—165° (from MeOH–EtOAc); $\lambda_{max.}$ 227, 266, 283, and 289sh nm (log ε 4.3, 3.99, 3.97, and 3.88); $\nu_{max.}$ ($CHCl_3$) 3 460s cm^{-1}; τ 1.2—1.6br (3 H, s, HN and H_α of pyridine), 2.4—3.1 (6 H, m, HAr and H_β of pyridine), 3.64 (1 H, s, H_β of indole), and 5.5—6.3 (4 H, m, OCH_2CH_2O); *m/e* 266 (M^+, 48%), 188 (100), 144 (55), and 166 (11), *m** 132.9 (266 ⟶ 188), 110.3 (188 ⟶ 144), and 93.5 (144 ⟶ 116) (Found: C, 71.6; H, 5.3; N, 10.5. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%).

Indol-2-yl Piperidin-4-yl Ketone Ethylene Acetal (4).—(*a*) A solution of the acetal (12) (230 mg) in ethyl acetate (15 ml) was quaternised with benzyl bromide (0.13 ml) at reflux for 5 h. The salt separated as an orange solid on the walls of the flask and the solvent and excess of reagent were decanted. The dried residue was reduced with sodium borohydride (in excess) in methanol solution at 10 °C. The solution was evaporated and the residue partitioned between ethyl acetate and aqueous potassium carbonate. *1-Benzyl-1,2,5,6-tetrahydropyridin-4-yl indol-2-yl ketone ethylene acetal* (301 mg) was obtained from the organic phase and could be purified by preparative t.l.c. (silica; C_6H_6–EtOAc, 2 : 3 + 1% Et_3N) and crystallisation from methanol; m.p. 150—152°; $\lambda_{max.}$ 220, 274, 283, and 291 nm (log ε 4.72, 3.94, 3.92, and 3.78); $\nu_{max.}$ ($CHCl_3$) 3 460s cm^{-1}; τ 1.66br (1 H, s, HN), 2.4—3.0 (9 H, m, HAr), 3.51 (1 H, d, *J* 2 Hz, H_β of indole), 4.20 (1 H, t, *J* 3 Hz, HC:C), 6.04 (4 H, m, OCH_2CH_2O), and 6.48 (2 H, s, NCH_2Ph); *m/e* 360 (M^+, 33%), 243 (51), 188 (100), 172 (75), 144 (25), and 91 (89) (Found: M^+, 360.182 863. $C_{23}H_{24}N_2O_2$ requires *M*, 360.183 776). Catalytic reduction and hydrogenolysis was effected by treatment of this product (223 mg) with hydrogen (15 lb in^{-2}) in methanol (110 ml) over Pd–C (223 mg; 10%) at room temperature for 16 h. Filtration and evaporation gave a gum which was purified by dry column chromatography (alumina; methanol) to give the *piperidine acetal* (4) (70 mg), m.p. 184—222° (from EtOAc–MeOH); $\lambda_{max.}$ 220, 272, 281, and 289 nm (log ε 4.50, 3.90, 3.89, and 3.78); $\nu_{max.}$ ($CHCl_3$) 3 460s cm^{-1}; τ 1.5br (1 H, s, HN of indole), 2.35—3.1 (4 H, m, HAr), 3.58 (1 H, s, H_β of indole), and 5.9—6.4 (4 H, m, OCH_2CH_2O); *m/e* 272 (M^+, 48%), 188 (100), 154 (34), 144 (72), 116 (14), and 89 (72) (Found: M^+, 272.151 429. $C_{16}H_{20}N_2O_2$ requires *M*, 272.152 476).

(*b*) The pyridine acetal (12) (200 mg) was hydrogenated in methanol (60 ml) over Pd–C (400 mg; 10%) at 75 lb in^{-2} for 1 day at room temperature. Removal of the catalyst, evaporation of solvent, and purification as above gave the piperidine acetal (4) (81 mg, 40%), together with *indol-2-yl 1-methylpiperidin-4-yl ketone ethylene acetal* (15 mg), m.p. 190—192°; $\lambda_{max.}$ 272, 281, and 289 nm (log ε 3.98, 4.01, and 3.96), 1.66br (1 H, s, HN), 2.4—3.10 (4 H, m, HAr), 3.59 (1 H, d, *J* 2 Hz, H_β of indole), 6.08 (4 H, m, OCH_2CH_2O), and 7.18 (3 H, s, CH_3N); *m/e* 286 (M^+, 60%), 190 (30), 188 (80), 144 (50), and 96 (100) (Found: M^+, 286.168 49; *m/e*, 188.070 53. $C_{17}H_{22}N_2O_2$ requires *M*, 286.168 12; $C_{11}H_{10}NO_2$ requires *m/e* 188.071 15).

3-Formylindoly-2-yl Piperidin-4-yl Ketone Ethylene Acetal.—The acetal (4) (102 mg) in dimethylformamide (1 ml) was added to a mixture of phosphoryl chloride (0.1 ml) and dimethylformamide (0.5 ml) and the resulting solution kept at 40 °C for 1.5 h. After pouring onto aqueous sodium hydroxide (10%; 30 ml) and leaving for 30 min, extraction with ethyl acetate gave the *formyl derivative* (91 mg, 85%), m.p. 124—126°; $\lambda_{max.}$ 246, 262, and 303 nm (log ε 4.10, 4.01, and 4.00), τ −1.05 (1 H, s, CHO), 0.6br (1 H, s, HN), 6.11 (4 H, m, OCH_2CH_2O), and 7.21br (1 H, s, HN); *m/e* 300 (M^+, 14%), 228 (30), 218 (100), 216 (100), 172 (80), 154 (30), 144 (25), 129 (70), 82 (50) (Found: M^+, 300.146 74; *m/e*, 172.039 07. $C_{17}H_{20}N_2O_3$ requires *M*, 300.147 38; $C_{10}H_6NO_2$ requires *m/e* 172.039 850).

3-Hydroxymethylindol-2-yl Piperidin-4-yl Ketone Ethylene Acetal (13).—The aldehyde (70 mg) was reduced with an excess of sodium borohydride in ethanol at room temperature for 12 h. The solution was evaporated and the residue partitioned between ethyl acetate and water; the dried organic extract gave the *alcohol* (13) (59 mg, 89%), m.p. 171—173° (from ether); $\lambda_{max.}$ 274, 282, and 290 nm (log ε 3.98, 4.01, and 3.96); τ 1.52br (1 H, s, HN), 2.32—2.94 (4 H, m, HAr), 5.08 (2 H, s, $HOCH_2$), and 6.04 (4 H, m, OCH_2CH_2O); *m/e* 302 (M^+, 5%), 284 (10), 257 (15), 218 (100), 200 (20), 156 (100), 128 (25), and 82 (36); *m*

183.5 (218 → 200), and 111.5 (218 → 156) (Found: M^+, 302.163 15; *m/e* 200.071 16 and 156.044 99. $C_{17}H_{22}N_2O_3$ requires *M*, 302.163 03; $C_{12}H_{10}NO_2$ requires *m/e*, 200.071 15; $C_{10}H_6NO$ requires *m/e*, 156.044 94).

3-(*Piperidin-4-ylmethyl*)*indol-2-yl Piperidin-4-yl Ketone Ethylene Acetal* (14).—The alcohol (13) (20 mg) was treated with piperidine (0.2 ml) in ethanolic sodium ethoxide (0.28 g Na in 15 ml) at reflux for 18 h. The solvent was evaporated off and the residue partitioned between water and ethyl acetate to give a gum, which was purified by preparative t.l.c. (silica; MeOH + 2% Et_2NH) to give the *gramine* (14) (15 mg, 65%), m.p. 230—232°; $\lambda_{max.}$ 275, 283, and 291 nm (log ε 3.98, 4.01, and 3.96); τ 1.66br (1 H, s, HN), 1.1—3.0 (4 H, m, HAr), 5.93—6.24 (4 H, m, OCH_2CH_2O), 6.34 (2 H, s, NCH_2-indole), and 6.8—8.84 (19 H, piperidine); *m/e* 369 (M^+, 10%), 324 (10), 285 (12), 284 (15), 241 (12), 240 (10), 239 (15), 213 (100), 202 (100), 156 (20), 130 (15), 129 (15), and 84 (75), *m** 218.9 (369 → 284), and 123.0 (369 → 213) (Found: M^+, 369.241 61; *m/e*, 202.086 64. $C_{22}H_{31}N_3O_2$ requires *M*, 369.241 61; $C_{12}H_{12}NO_2$ requires *m/e*, 202.086 66).

3-*Ethoxymethylindol-2-yl Piperidin-4-yl Ketone Ethylene Acetal* (15).—The alcohol (13) (22 mg) was treated with sodium ethoxide in ethanol at reflux for 6 h. Evaporation, and isolation with chloroform gave a gum, from which the *ether* (15) was obtained as a gum by preparative t.l.c. (silica; MeOH + 2% Et_2NH); $\lambda_{max.}$ 274, 282, and 290 nm; τ 1.70br (1 H, s, HN), 1.24—3.0 (4 H, m, HAr), 5.24 (2 H, s, $EtOCH_2$), 5.9—6.2 (4 H, m, OCH_2CH_2O), 6.46 (2 H, q, *J* 7 Hz, CH_2Me), 6.86—8.65 (9 H, m, piperidine), and 8.79 (3 H, t, *J* 7 Hz, CH_3CH_2); *m/e* 330 (M^+, 10%), 285 (18), 246 (100), 202 (40), 200 (35), 174 (15), 156 (100), 130 (40), 129 (35), 128 (35), and 82 (50); *m** 166.0 (246 → 202), and 162.5 (246 → 200) (Found: M^+, 330.194 33; *m/e*, 202.086 66 and 200.071 71. $C_{19}H_{26}N_2O_3$ requires *M*, 330.194 33; $C_{12}H_{12}NO_2$ requires *m/e*, 202.086 79; $C_{12}H_{10}NO_2$ requires *m/e*, 200.071 15).

Indolyl-2-ylpiperid-4-ylmethane (18).—The pyridine methane (8) (400 g) was treated with conc. hydrochloric acid (1.1 equiv.) in methanol and the solvents and excess of acid were removed. The residual hydrochloride was reduced over Adams catalyst (100 mg) in ethanol at 60 lb in^{-2} and room temperature for 1 day. Filtration and evaporation followed by partitioning between ethyl acetate and aqueous potassium carbonate gave, from the organic phase, a gum which crystallised from ethyl acetate to give the *piperidine methane* (18) (268 mg), m.p. 169—175°; $\lambda_{max.}$ 220, 274, 282, and 290 nm (log ε 4.55, 3.87, 3.87, and 3.79); $\nu_{max.}$ ($CHCl_3$) 3 470s, 2 820w, and 2 740m cm^{-1}; τ 1.75br (1 H, s, HN of indole), 2.4—3.1 (4 H, m, HAr), and 3.80 (1 H, s, H_β of indole); *m/e* 214 (M^+, 100%), 131 (22), 130 (54), 118 (15), 108 (66), 84 (19), 83 (14), 82 (56), 69 (24), 56 (21), and 55 (18), *m** 54.6 (214 → 108) (Found: C, 78.1; H, 8.7; N, 12.4. $C_{14}H_{18}N_2$ requires C, 78.5; H, 8.4; N, 13.1%).

3-*Formylindol-2-yl*(*piperidin-4-yl*)*methane* (16).—The piperidine (18) (118 mg) was treated with phosphoryl chloride (freshly distilled; 0.02 ml) in dimethylformamide (2 ml) and the mixture maintained at 40 °C for 2 h. After pouring onto aqueous sodium hydroxide (10%; 30 ml) and leaving for 30 min, the product was isolated by extraction with chloroform to give the *formyl derivative* (16) (70 mg, 52%), m.p. 211—213° (from MeOH–Et_2O); $\lambda_{max.}$ 246, 263, and 304 nm (log ε 4.10, 4.08, and 4.11); *m/e* 242 (M^+, 5%), 224 (20), 181 (10), 161 (20), 158 (20), 130 (20), and 82 (100); *m** 207.0 (242 → 224), 146.2 (224 → 181), and 106.9 (158 → 130) (Found: M^+, 242.141 98. $C_{15}H_{18}N_2O$ requires *M*, 242.141 91).

3-*Methylindol-2-yl*(*piperidin-4-yl*)*methane* (17).—The aldehyde (17 mg) in glacial acetic acid (10 ml) was hydrogenated over Adams catalyst (10 mg) at atmospheric pressure for 1 day. The mixture was filtered and evaporated and the residue partitioned between aqueous potassium carbonate and ethyl acetate whence the *skatole* (17) (6 mg, 37%) was obtained as a gum after preparative t.l.c. (silica; MeOH + 2% Et_2NH); $\lambda_{max.}$ 276, 284, and 291 nm; τ 2.05br (1 H, s, HN), 2.52—3.03 (4 H, m, HAr), 7.43 (4 H, m, piperidine), 7.1 (2 H, m, CH_2-indole), 7.81 (3 H, s, CH_3-indole), and 8.26—8.94 (5 H, m, piperidine); *m/e* 228 (M^+, 100%), 144 (100), and 82 (95) (Found: M^+, 228.162 87. $C_{15}H_{20}N_2$ requires *M*, 228.162 64).

1,4,5,7-*Tetrahydro*-2,5-*ethano*-2H-*azocino*[4,3-b]*indol*-6(3H)-*one* (2).—The piperidine acetal (4) (200 mg) was stirred in glacial acetic acid (300 ml) with formalin (6 ml) at room temperature for 4.5 h; hydrochloric acid (1M; 25 ml) was added and the mixture stirred for 1 day. The solvents were then removed under reduced pressure and the residue partitioned between aqueous potassium carbonate and ethyl acetate to yield a gum which was purified by preparative t.l.c. (silica; MeOH) to give the *cyclic ketone* (2) (62 mg, 35%), m.p. 210—214° (from MeOH); $\lambda_{max.}$ 239 and 310 nm (log ε 4.23 and 4.39); $\nu_{max.}$ ($CHCl_3$) 3 440m and 1 634s cm^{-1}; τ 0.82br (1 H, s, HN), 2.4—3.02 (4 H, m, HAr), 5.46 (2 H, s, NCH_2-indole), and 6.42—8.08 (9 H, m, piperidine); *m/e* 240 (M^+, 100%), 212 (15), 198 (12), 184 (10), 170 (30), 156 (12), 143 (11), 130 (40), and 129 (49), *m** 187.5 (240 → 212), 163.4 (240 → 198), and 136.3 (212 → 170) (Found: M^+, 240.125 616; *m/e* 212.131 646 and 212.094 869. $C_{15}H_{16}N_2O$ requires *M*, 240.126 256; $C_{14}H_{16}N_2$ requires *m/e*, 212.131 342; $C_{13}H_{12}N_2O$ requires *m/e*, 212.094 958).

3-(1-*Hydroxyethyl*)*pyridine-4-carboxylic Acid Lactone* (20).—*N*-Bromosuccinimide (22.5 g) was suspended in a solution of methyl 3-ethylpyridine-4-carboxylate [5a] (10 g) in carbon tetrachloride (500 ml). After addition of dibenzoyl peroxide (0.6 g) the mixture was refluxed with vigorous stirring for 0.75 h. After cooling and filtration the solution was evaporated and the resulting yellow oil dissolved in hydrobromic acid (100 ml; 5N) and refluxed for 3 h. The product was obtained by basifying the cooled solution with potassium hydrogen carbonate, extraction with ether, removal of solvent, and distillation to give the *lactone* (20) (4 g, 44%), b.p. 90—95° at 0.3 mmHg, which solidified; m.p. 37—39°; $\lambda_{max.}$ 276 and 283infl nm (log ε 3.57 and 3.47); $\nu_{max.}$ (film) 1 765s cm^{-1}; τ 1.09 (1 H, s, H_α of pyridine), 1.16 (1 H, d, *J* 5 Hz, H_α of pyridine), 2.25 (1 H, dd, *J* 5 and 1 Hz, H_β of pyridine), 4.28 (1 H, q, *J* 7 Hz, *H*CMe), and 8.28 (3 H, d, *J* 7 Hz, $H_3C{\cdot}CH$); *m/e* 149 (M^+, 53%), 134 (100), 121 (53), 106 (84), 79 (44), and 78 (64) {Found [for hydrobromide salt, m.p. 165—168° (from acetone)]: C, 41.5; H, 3.5; N, 6.3. $C_8H_8BrNO_2$ requires C, 41.8; H, 3.5; N, 6.1%}.

4,5,6,7-*Tetrahydroindol-2-yl* 3-(1-*Hydroxyethyl*)*pyridin-4-yl Ketone* (21).—Tetrahydroindolylmagnesium bromide [from 4,5,6,7-tetrahydroindole (0.36 g)] was prepared as above; to it was added a solution of the lactone (20) (0.15 g) in benzene (15 ml). A yellow-orange precipitate appeared immediately. The ether was boiled off and the mixture refluxed for 14 h. The ice-cold mixture was treated with ammonium chloride (2 g) in water (10 ml) with stirring for

1 h, and the product isolated by filtration, extraction of the organic phase with dilute hydrochloric acid, rebasification, and extraction into ethyl acetate to give, on evaporation, a gum which crystallised on trituration with ether affording the *ketone* (265 mg, 95%), m.p. 173—176° (from C_6H_6); $\lambda_{max.}$ 260 and 330 nm (log ε 3.82 and 4.24); $\nu_{max.}$ ($CHCl_3$) 3 600w, 3 550—3 200w, 3 440w, and 1 600s cm^{-1}; τ −0.23br (1 H, s, HN of pyrrole), 1.14 (1 H, s, H_α of pyridine), 1.40 (1 H, d, *J* 4.5 Hz, H_α of pyridine), 2.66 (1 H, d, *J* 4.5 Hz, H_β of pyridine), 3.63 (1 H, s, *J* 2 Hz, H_β of pyrrole), 4.99 [1 H, q, *J* 7 Hz, *H*C(OH)Me], 6.01br (1 H, s, HO), 7.32—7.53 (4 H, m, H_2CAr), 8.21 (4 H, m, H_2C), and 8.45 (3 H, d, *J* 7 Hz, $H_3C{\cdot}CHOH$); *m/e* 270 (M^+, 32%), 252 (93), 237 (39), 224 (78), 209 (39), 122 (100), 106 (54), 93 (23), 91 (20), 78 (25), and 77 (22) (Found: C, 70.9; H, 6.4; N, 10.3. $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4%).

4,7-*Dihydroindol-2-yl* 3-(1-*Hydroxyethyl*)*pyridin-4-yl Ketone* (22).—By the procedure given above, dihydroindole (10.2 g) and the lactone (4.26 g), gave, after crystallisation from ethyl acetate, the *ketone* (22) (6 g, 78%), m.p. 164—168°; $\lambda_{max.}$ 258 and 326 nm (log ε 3.84 and 4.25); $\nu_{max.}$ ($CHCl_3$) 3 600w, 3 550—3 200w, 3 440m, and 1 605s cm^{-1}; τ [$(CD_3)_2SO$] −1.86br (1 H, s, HN), 1.14 (1 H, s, H_α of pyridine), 1.47 (1 H, d, *J* 5 Hz, H_α of pyridine), 2.73 (1 H, d, *J* 5 Hz, H_β of pyridine), 3.75 (1 H, d, *J* 2 Hz, H_β of pyrrole), 4.17 (2 H, s, *H*C:CH), 4.69 (1 H, d, *J* 4 Hz, HO), 5.08 (1 H, m, *H*COHMe), 6.73—6.89 (4 H, m, H_2CAr), and 8.67 (3 H, d, *J* 6.5 Hz, H_3CCHOH); *m/e* 268 (M^+, 29%), 250 (100), 235 (50), 207 (47), 120 (92), and 106 (61) (Found: C, 71.4; H, 5.9; N, 10.1. $C_{16}H_{16}N_2O_2$ requires C, 71.6; H, 6.0; N, 10.4%).

3-(1-*Hydroxyethyl*)*pyridin-4-yl Indol-2-yl Ketone* (23).—A solution of 2,3-dichloro-4,5-dicyano-1,4-benzoquinone (2 g) in benzene (40 ml) was added dropwise to a solution of the ketone (22) (2 g) in ethyl acetate (80 ml) and benzene (300 ml) at room temperature during 1 h. The mixture was extracted with aqueous 3N-hydrochloric acid and the product isolated by basification, extraction with ethyl acetate, and column chromatography (alumina; ether) of the material (2.1 g) from the organic extract. The *indole ketone* (23) (1.59 g, 80%) had m.p. 143—145° (from ether); $\lambda_{max.}$ 240infl, 265, and 321 nm (log ε 4.08, 3.67, and 4.35); $\nu_{max.}$ ($CHCl_3$) 3 605w, 3 650—3 200w, 3 450s, and 1 635 cm^{-1}; τ [$(CD_3)_2SO$] −2.07br (1 H, s, HN), 1.10 (1 H, s, H_α of pyridine), 1.39 (1 H, d, *J* 5 Hz, H_α of pyridine), 2.25—3.05 (5 H, m, HAr and H_β of pyridine), 3.18 (1 H, d, *J* 2 Hz, H_β of indole), 4.62 (1 H, d, *J* 4 Hz, HO), 5.05 (1 H, m, *H*CHOHMe), and 8.82 (3 H, d, *J* 6.5 Hz, H_3CCHOH); *m/e* 266 (M^+, 45%), 251 (45), 248 (32), 233 (71), 219 (21), 205 (25), 118 (100), 106 (40), 89 (38), and 78 (16); *m** 236.9 (266 ⟶ 251), 180.4 (233 ⟶ 205), and 52.4 (266 ⟶ 118) (Found: C, 72.2; H, 5.0; N, 10.2. $C_{16}H_{14}N_2O_2$ requires C, 72.2; H, 5.3; N, 10.5%).

3-*Ethoxy*-1,3-*dihydro*-3-(*indol*-2-*yl*)-1-*methylfuro*[3,4-c]-*pyridine* (24).—The oxo-alcohol (23) (1.6 g) in absolute alcohol (400 ml) was treated with ethanolic hydrogen chloride till no further change in u.v. absorption was noted. The mixture was basified with vigorous stirring with saturated aqueous potassium carbonate, and the ethanolic solution was decanted and partitioned between water and ethyl acetate. The organic phase was dried and treated with charcoal and on evaporation gave a yellow foam. A trace of starting ketone was removed by treatment with sodium borohydride in ethanol. Work-up on partitioning between water and ethyl acetate gave the stereoisomeric mixture of *acetals* (24) (1.55 g, 88%) as an off-white foam after column chromatography (silica; ether); $\nu_{max.}$ ($CHCl_3$) 3 460s and 1 605 cm^{-1}; τ 0.88br and 1.00br (1 H, 2 × s, HN), 1.45br (2 H, s, H_α of pyridine), 2.34—3.05 (5 H, m, HAr and H_β of pyridine), 3.45 and 3.57 (1 H, 2 × d, *J* 2 Hz, H_β of indole), 4.41 and 4.53 (1 H, 2 × q, *J* 6.5 Hz, OC*H*Me), 6.47 (2 H, m, OH_2CMe), 8.35 (3 H, d, *J* 6.5 Hz, H_3CCHO), and 8.79 and 8.81 (3 H, 2 × t, *J* 7 Hz, H_3CCH_2O); *m/e* 294 (M^+, 30%), 249 (76), 248 (76), 234 (39), and 233 (100), *m** 220.0 (249 ⟶ 234), 219.0 (248 ⟶ 233), and 209.2 (294 ⟶ 248) (Found: M^+, 294.137 067; *m/e*, 249.099 512; *m/e*, 234.076 386. $C_{18}H_{18}N_2O_2$ requires *M*, 294.236 826; $C_{16}H_{13}N_2O$ requires *m/e*, 249.102 782; $C_{15}H_{10}N_2O$ requires *m/e*, 234.079 308).

6-*Benzyl*-3-*ethoxy*-1,3,4,5,6,7-*hexahydro*-3-(*indol*-2-*yl*)-1-*methylfuro*[3,4-c]*pyridine* (25).—The acetals (24) (443 mg) were quaternised with benzyl bromide (288 mg) in ethanol (10 ml) at room temperature for 64 h. The solvent was removed and the amorphous orange solid triturated with ether to give the salt (702 mg, 100%), which was utilised without further purification for reaction with an excess of sodium borohydride in ethanol (15 ml) at 0—5 °C for 10 min and then at room temperature for 0.5 h. The solvent was evaporated off and the residue was partitioned between water and ethyl acetate. The organic extract was evaporated and the residue was dissolved in $CDCl_3$ containing a trace of [$^2H_5$]pyridine for spectral measurement; τ 0.44br and 0.65br (1 H, 2 × s, HN), 2.34—3.10 (9 H, m, HAr), 3.57br (1 H, s, H_β of indole), 5.15 (1 H, m, OHCMe), 6.40 (2 H, s, $NH_2CPhNCH_2Ph$), 6.46 (2 H, q, *J* 7 Hz, OCH_2Me), 7.02br (2 H, s, $:C{\cdot}CH_2N$), 7.45 (2 H, m, CH_2CH_2N), 7.89 (2 H, m, CH_2CH_2N), 8.68 (3 H, d, *J* 7 Hz, $H_3C{\cdot}CHO$), and 8.78 and 8.79 (3 H, 2 × t, *J* 7 Hz, H_3CCH_2O).

6-*Benzyl*-4,5,6,7-*tetrahydro*-3-(*indol*-2-*yl*)-1-*methylfuro*-[3,4-c]*pyridine* (26).—The piperideine (25) was induced to lose ethanol by passing down an alumina column in benzene. A quantitative conversion took place into the *indolylfuran* (26), m.p. 141—143° [from petroleum (b.p. 60—80 °C)]; $\lambda_{max.}$ 255, 322, 327sh, and 339 nm (log ε 4.09, 4.53, 4.48, and 4.44); $\nu_{max.}$ ($CHCl_3$) 3 470s cm^{-1}; τ 1.60br (1 H, s, HN), 2.38—3.06 (9 H, m, HAr), 3.58 (1 H, d, *J* 2 Hz, H_β of indole), 6.32 (2 H, s, NCH_2Ph), 6.61 (2 H, s, $:C{\cdot}CH_2N$), 7.25 (4 H, m, $:C{\cdot}CH_2CH_2N$), and 7.82 (3 H, s, H_3C); *m/e* 342 (M^+, 9%), 251 (8), 250 (9), 223 (100), and 180 (49), *m** 145.3 (223 ⟶ 180) (Found: M^+, 342.173 238; *m/e*, 223.099 046; *m/e*, 180.080 852. $C_{23}H_{22}N_2O$ requires *M*, 342.173 212; $C_{15}H_{13}NO$ requires *m/e*, 223.099 708; $C_{13}H_{10}N$ requires *m/e*, 180.081 32).

3-*Ethoxy*-3-(*indol*-2-*yl*)-1-*methylperhydrofuro*[3,4-c]*pyridines* (28) *and* 4-[*Ethoxy*(*indol*-2-*yl*)*methyl*]-3-(1-*hydroxyethyl*)*piperidine* (27).—Hydrogenation of the acetals (25) was conducted over Pd–C (10%) at 90 lb in^{-2} at room temperature for 2 days. The use of a trace of triethylamine, as stabilising base, in ethanol as solvent, led to a mixture of all three reduction products. The use of potassium carbonate in a mixture of ethanol and water (9 : 1) led mainly to the alcohol (27). One of the components (28) was separable from the other two. Cyclisation attempts with the other isomer of (28) and the alcohol (27) were conducted on mixtures of these two, richer in one or the other as indicated below.

Separation of the total reduction mixture isolated after filtration and evaporation was effected by partitioning between aqueous potassium carbonate and ethyl acetate. Dry column chromatography (silica) of the material

obtained from the organic phase allowed removal of less polar components [MeOH–EtOAc (1 : 1) and then MeOH] leaving the desired components to be eluted with MeOH–Et_2NH (20 : 1); 20% yield based on starting pyridine acetals (24). Further separation was achieved by preparative layer chromatography (silica; MeOH–Et_2NH, 99 : 1). The isomer (28) with lowest R_F (obtained as a gum) had $\lambda_{max.}$ 273, 282, and 289 nm; $\nu_{max.}$ ($CHCl_3$) 3 470s cm^{-1}; τ 1.65br (1 H, s, HN), 2.38—3.00 (4 H, m, HAr), 3.58br (1 H, s, H_β of indole), 5.54 [1 H, m, OC*H*(CH)Me], 8.69 (3 H, d, *J* 6.5 Hz, $H_3C{\cdot}CHO$), and 8.82 (3 H, t, *J* 7 Hz, $H_3C{\cdot}CH_2O$); *m/e* 300 (M^+, 19%), 255 (30), 254 (70), 198 (78), 144 (35), 143 (22), 130 (24), and 110 (100), *m** 215.0 (300 ⟶ 254), 154.4 (254 ⟶ 198), and 47.6 (254 ⟶ 110); the isomer (28) with highest R_F value (obtained as a gum) had [contaminated with *ca.* 25% (27); an asterisk denotes signals attributed to this alcohol] $\lambda_{max.}$ 273, 282, and 289 nm; $\nu_{max.}$ ($CHCl_3$) 3 470s cm^{-1}; τ 1.44br * and 1.62br (1 H, s, HN of indole), 2.38—3.10 (4 H, m HAr), 3.53br and 3.72br * (1 H, s, H_β of indole), 4.83 * [*ca.* ¼ H, d, *J* 7 Hz, α-indolyl-C*H*(OEt)·CH], and 8.83 (*ca.* 3 H, t, *J* 7 Hz, $H_3C{\cdot}CH_2O$); *m/e* 300 (M^+, 20%), 256 (44), 255 (36), 212 (90), 199 (24), 198 (100), 144 (33), 130 (33), 118 (25), 110 (40), and 97 (30), *m** 215.0 (300 ⟶ 254) {Found [for a mixture of both isomers (28) and (27)]: M^+, 300.183 848; *m/e*, 254.141 004; *m/e*, 198.090 453. $C_{18}H_{24}N_2O_2$ requires *M*, 300.183 776; $C_{16}H_{18}N_2O$ requires *m/e*, 254.141 905; $C_{13}H_{12}NO$ requires *m/e*, 198.091 88}.

13-*Ethoxy*-1,1,3,4,4a,5,7,12,13,13a-*decahydro*-5-*methylpyrido*[4′,3′:6,7]*oxocino*[4,3-b]*indole* (29).—The benzylpyridinium salt (250 mg) of (24) was reduced with sodium borohydride (see above) and the product hydrogenated in ethanol–aqueous potassium carbonate. After chromatographic purification the alcohol (27) together with traces of the isomers of (28) was obtained, and this mixture was treated with formalin (0.1 ml) in ethanol (60 ml) and glacial acetic acid (90 mg) at reflux under nitrogen for 5 h. Evaporation and partition between ethyl acetate and aqueous potassium carbonate gave an organic fraction (20 mg), which was purified by preparative t.l.c. (silica; MeOH–1.5% Et_2NH) to give the *cyclic ether* (29) (10 mg) as a gum; $\lambda_{max.}$ 274, 282, and 290 nm; $\nu_{max.}$ 3 470s cm^{-1}; τ 1.40br (1 H, s, HN of indole), 2.3—3.0 (4 H, HAr), 4.73 [1 H, d, *J* 6.5 Hz, indolyl-CH(OEt)·CH], 5.36 (2 H, s, indolyl-CH_2O), 5.74 (dq, *J* 7 and 6.5 Hz, OC*H*Me), 6.49 (2 H, q, *J* 7 Hz, OCH_2Me), and 8.80 (3 H, t, *J* 7 Hz, H_3CCH_2O); *m/e* 314 (M^+, 41%), 269 (15), 175 (19), 174 (100), 140 (41), and 130 (22); *m/e* (D_2O) 316 (18), 315 (15), 271 (8), 270 (8), 269 (10), 175 (100), 174 (45), 141 (28), 140 (15), 140 (15), 131 (27), and 130 (22) (Found: M^+, 314.199 293; *m/e*, 174.091 944; *m/e*, 140.105 386. $C_{19}H_{26}N_2O$ requires *M*, 314.199 417; $C_{11}H_{12}NO$ requires *m/e*, 174.091 884; $C_8H_{14}NO$ requires *m/e*, 140.107 533).

3-*Ethoxy*-3-(*indol*-2-*yl*)-3a,6-*methanoperhydrofuro*[3,4-c]-*pyridines* (30a *and* b).—The piperidine (28a or b) (25 mg) was treated with formalin (0.12 ml) and glacial acetic acid (90 mg) in absolute ethanol (60 ml) at reflux for 5 h. In each case work-up was effected by addition of a little aqueous potassium carbonate, evaporation, and partitioning of the residue between ethyl acetate and aqueous potassium carbonate. The crude product (25 mg) was purified by preparative t.l.c. (silica; MeOH–1—2% Et_2NH) and gave finally the cyclised isomers (30a and b) (8 mg) as gums. Each isomer had $\lambda_{max.}$ 270, 273, 281, and 289 nm; $\nu_{max.}$ 3 470s cm^{-1}; the higher R_F isomer had τ 1.60br (1 H, s, HN of indole), 2.43—3.0 (4 H, HAr), 3.54 (1 H, s, H_β of indole), 5.54 (1 H, m, OC*H*Me), 8.69 (3 H, d, *J* 6.5 Hz, $H_3C{\cdot}CHO$), and 8.85 (3 H, t, *J* 7 Hz, H_3CCH_2O); *m/e* 312 (M^+, 21%), 268 (19), 267 (81), 266 (100), 251 (21), 238 (31), 224 (34), 223 (24), 144 (26), and 130 (78); *m/e* (D_2O) 313 (30), 312 (11), 269 (19), 268 (61), 267 (41), 266 (94), 251 (22), 239 (14), 238 (33), 225 (17), 224 (25), 223 (22), 145 (25), 144 (19), 131 (100), and 130 (41) (Found: M^+, 312.183 227; *m/e*, 267.148 610; *m/e*, 267.148 610; *m/e*, 266.143 610; *m/e*, 130.065 423. $C_{19}H_{24}N_2O_2$ requires *M*, 312.183 768; $C_{17}H_{19}N_2O$ requires *m/e*, 267.149 730; $C_{17}H_{18}N_2O$ requires *m/e*, 266.141 905; C_9H_8N requires *m/e*, 130.065 671); the lower R_F isomer had τ 1.55br (1 H, s, HN of indole), 2.43—3.05 (4 H, m, HAr), 3.35 (1 H, d, *J* 2 Hz, H_β of indole), 8.61 (3 H, d, *J* 6 Hz, H_3CCHO), and 8.85 (3 H, t, *J* 7 Hz, H_3CCH_2O); *m/e* 312 (M^+, 75%), 268 (34), 267 (100), 266 (100), 251 (28), 238 (46), 224 (46), 223 (29), 144 (25), and 130 (91), *m** 226.8 (312 ⟶ 266); *m/e* (D_2O) 313 (23), 312 (9), 269 (18), 268 (59), 267 (50), 266 (100), 251 (18), 238 (35), 225 (18), 224 (27), 223 (23), 145 (23), 144 (18), 131 (77), and 130 (41) (Found: M^+, 312.182 606; *m/e*, 267.149 401; *m/e*, 266.143 610; *m/e*, 130.065 553. $C_{19}H_{24}N_2O_2$ requires *M*, 312.183 765; $C_{17}H_{19}N_2O$ requires *m/e*, 267.149 730; $C_{17}H_{18}N_2O$ requires *m/e*, 266.141 905; C_9H_8N requires *m/e*, 130.065 671).

3-*Ethoxy*-3-(*indol*-2-*yl*)-1,6-*dimethylperhydrofuro*[3,4-c]-*pyridine* (35).—The acetals (24) (330 mg) were quaternised with methyl iodide (3.5 ml) in benzene (15 ml) at room temperature for 3 days. The precipitate was filtered off and crystallised to give the *methiodide* of (24), m.p. 180—182° (from MeOH–Et_2O) (Found: C, 52.2; H, 4.7; I, 27.7; N, 6.3. $C_{19}H_{21}IN_2O_2$ requires C, 52.3; H, 4.8; I, 29.1; N, 6.4%). The salt (650 mg) was reduced with an excess of sodium borohydride in ethanol at room temperature for 20 min. The solvent was evaporated off and the residue partitioned between water and ethyl acetate. The dried organic phase was evaporated almost to dryness and ethanol added and then triethylamine, until the pH of the solution was 9. This solution was hydrogenated over Pd–C (10%; 800 mg) at 90 lb in^{-2} for 46 h, and the product gum (464 mg), obtained by filtration and evaporation, was purified by chromatography (silica; MeOH + 2% Et_2NH) to give the piperidine acetals (35) (327 mg, 70%), $\lambda_{max.}$ 273, 282, and 290 nm; τ 1.4—1.7br (1 H, s, HN), 1.35—3.0 (4 H, m, HAr), 3.55br (1 H, 2 × s, H_α of indole), 5.5 and 5.8 (1 H, 2 × m, OC*H*Me), 6.25—6.8 (2 H, 2 × q, OCH_2Me), 7.58 and 7.68 (3 H, 2 × s, CH_3N), and 8.5—8.9 (6 H, m, OCH_2CH_3 and $OCHCH_3$), *m/e* 314 (M^+, 15%), 285 (9), 270 (30), 269 (15), 268 (50), 198 (100), 124 (80), and 96 (30), *m** 228.3 (314 ⟶ 268) (Found: M^+, 314.199 53; *m/e*, 268.157 58. $C_{19}H_{26}N_2O_2$ requires *M*, 314.199 42; $C_{17}H_{20}N_2O$ requires *m/e*, 268.157 56).

4,5,6,7-*Tetrahydro*-3-(*indol*-2-*yl*)-1,6-*dimethylfuro*[3,4-c]-*pyridine* (33).—The piperideine (32) (50 mg) was passed down a silica column in ethyl acetate. Evaporation of the eluate gave the *furan* (33) (41 mg), m.p. 158—160° (from Et_2O), $\lambda_{max.}$ 321, 328sh, and 337 nm (log ε 4.53, 4.48, and 4.45); τ 1.45br (1 H, s, HN), 2.3—3.0 (4 H, HAr), 3.54 (1 H, d, *J* 3 Hz, H_β of indole), 6.65—7.35 (6 H, m, piperidine), 7.55 (3 H, s, CH_3N), and 7.8 (3 H, s, CH_3-furan); *m/e* 266 (M^+, 60%), 223 (100), 180 (45), and 58 (100) (Found: M^+, 266.141 88. $C_{17}H_{18}N_2O$ requires *M*, 266.141 91).

3-*Ethoxy*-3-(*indol*-2-*yl*)-1,6-*dimethylperhydrofuro*[3,4-c]-*pyridine* N-*oxide* (37).—The *N*-methylpiperidine (35) (115 mg) in methanol (25 ml) was treated with hydrogen peroxide

(0.7 ml; 50%). After 4 days at room temperature manganese dioxide was added, the mixture filtered and evaporated, and the residue purified by column chromatography (silica; MeOH–EtOAc, 1 : 1) to give a pale yellow gum (83 mg, 69%), $\lambda_{max.}$ 272, 281, and 289 nm; τ 1.2br (1 H, s, HN), 2.3—3.1 (4 H, HAr), 3.58 (1 H, d, J 2 Hz, H_β of indole), 6.78 and 6.80 (3 H, 2 × s, CH_3N^+), and 8.5—8.9 (6 H, m, CH_3CH_2O and CH_3CHO); *m/e* 330 (M^+, 3%), 314 (12), 270 (30), 269 (25), 268 (65), 198 (75), 124 (100), 123 (60), and 122 (45) (Found: M^+, 330.1943; *m/e*, 314.1993. $C_{19}H_{26}N_2O_3$ requires M, 330.1943; $C_{19}H_{26}N_2O_2$ requires *m/e*, 314.1994).

3-*Ethoxy*-3-(*indol*-2-*yl*)-6-*iodomethyl*-1,6-*dimethylperhydrofuro*[3,4-c]*pyridinium Iodide* (36).—The *N*-methylpiperidine (35) (163 mg) was treated with di-iodomethane (1.5 ml) in ethanol (absolute; 10 ml) and sufficient ether to make a homogeneous solution. After leaving at room temperature in the dark for 7 days, the solvents were evaporated off and the resulting product triturated with ether to give the *iodide* (37) (272 mg, 95%), m.p. 128—130°; $\lambda_{max.}$ 271, 281, and 288 nm (log ε 3.96, 4.01, and 3.94); τ [$(CD_3)_2SO$] —1.5br (1 H, s, HN), 2.5—3.2 (4 H, HAr), 3.6br (1 H, s, H_β of indole), 4.70br (2 H, s, ICH_2N^+), 6.82 (3 H, s, CH_3N^+), and 8.6—9.0 (6 H, m, CH_3CH_2O and CH_3CHO) (Found: C, 41.4; H, 4.8; N, 4.7. $C_{20}H_{28}I_2N_2O_2$ requires C, 41.3; H, 4.8; N, 4.8%).

D. I. C. S., M. S. A., G. J. H., N. D. V. W., and M. H. were all supported by S.R.C. studentships, for which they here record their thanks.

[7/764 *Received*, 5*th May*, 1977]