New Synthesis of Olivacine *via* Heteroarylation[1]

Takeaki Naito, Naoko Iida, and Ichiya Ninomiya*
Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan

Heteroarylation under acylating conditions, between indole and 4-substituted pyridines (**1a**—**c**), followed by acidic cyclisation, provides a useful route to indole alkaloids, as exemplified by a new synthesis of olivacine (**12**).

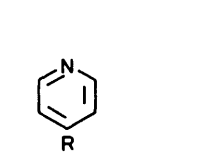
The discovery[2-7] that under acylating conditions enamides of the *N*-pyridinecarbonyl enamine-type undergo thermal cyclisation has been explained in terms of an intramolecular nucleophilic attack by the enamine function on the *N*-acylpyridinium moiety. This has prompted us to investigate the intermolecular reaction between *N*-acylpyridinium salts and enamines. The reaction, which leads to the facile introduction of aromatic heterocyclic residues into organic species, is known as heteroarylation.[8] The few examples of this reaction which are known have been between indole and 4-substituted pyridines. Therefore we first investigated the condensation in the presence of an acylating agent of indole with pyridines bearing an electron-attracting 4-substituent. In this way, we discovered a simple preparation of the synthetically useful 3-(2-piperidyl)-indoles, compounds which have a skeleton common in a large number of indole alkaloids. This reaction provided a novel synthetic route to the anti-tumour alkaloid olivacine.[9]

Heteroarylation in the Presence of an Acylating Agent between Indole and 4-Substituted Pyridines.—As summarised by Kost *et al.*,[8] it has already been established that the heteroarylations between indole and either unsubstituted or 3-substituted pyridines afford condensation products which would be formed by nucleophilic attack of the 3-position of indole at the electrophilic 4-position of *N*-acylpyridinium salts. Although similar reactions between indole and pyridine *N*-oxide in the presence of an acylating agent have been reported,[10,11] low yields and the formation of products structurally unfavourable for further conversion into alkaloids have limited the scope of their general synthetic application.

In order to establish an effective and general reaction between indole and 4-substituted pyridines to give 3-(2-piperidyl) indoles,[12] we investigated the reaction of indole with pyridines substituted at the 4-position with an electron-attracting group such as acetyl, methoxycarbonyl, or nitrile.

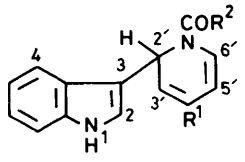
To a mixture of 4-cyanopyridine (**1a**) (3 mmol) and benzoyl chloride (3 mmol) in dichloromethane (10 ml), indole (2 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 24 h. Purification by preparative thin layer or column chromatography gave the condensation product (**2a**) (73%), the structure of which was established on the basis of spectral evidence and the chemical conversion of the compound into the known compound[10] (**3b**). Since (**2a**) showed a molecular ion at *m/z* 325, this suggested that it was a condensation product between indole and *N*-benzoyl-4-cyanopyridinium salt. I.r. absorption was observed at 3 475 (NH), 2 225 (CN), and 1 655 cm^{-1} (NCO). The ^1H n.m.r. spectrum showed signals for 3 indole protons at δ_H 8.69 (br, NH), 7.93 (m, 4-H), and 7.13 (d, *J* 3 Hz, 2-H) and 4 dihydropyridine protons at δ_H 6.72 (d, *J* 6 Hz, 2′-H), 6.53 (d, *J* 8 Hz, 6′-H), 6.52 (dd, *J* 6 and 1.6 Hz, 3′-H), and 5.45 (dd, *J* 8 and 1.6 Hz, 5′-H). This evidence firmly established the condensation product (**2a**) as having the 1,2-dihydropyridine structure.

Treatment of the product (**2a**) with 1% methanolic potassium hydroxide at 50 °C for 5 min resulted in removal of the *N*-benzoyl group by hydrolysis followed by dehydrogenation of the resulting unstable dihydropyridine. Among the products, we could isolate only a stable pyridine derivative (**3a**) (11%) which was converted into the known ester (**3b**)[10] by methanolysis. The latter was identical (m.p.s. and spectra) with the known, key intermediate[10] in the synthesis of de-ethyldasycarpidone.



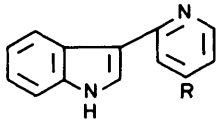
(1)

a; R = CN
b; R = CO_2Me
c; R = Ac



(2)

	R^1	R^2
a;	CN	Ph
b;	CN	OEt
c;	CN	OCH_2Ph
d;	CO_2Me	Ph
e;	CO_2Me	OEt
f;	CO_2Me	OCH_2Ph
g;	Ac	Ph
h;	Ac	Me



(3)

a; R = CN
b; R = CO_2Me

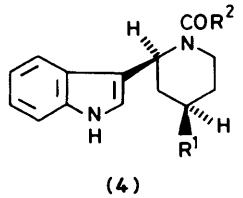
Similar heteroarylations between indole and other 4-substituted pyridines (**1b**) and (**1c**) in the presence of acetyl chloride, ethyl chloroformate, or benzyl chloroformate proceeded smoothly at 0—20 °C to give the corresponding condensation products (**2b**—**h**). These products were insufficiently stable to be recrystallised from organic solvents, but details of their mass, i.r., and n.m.r. spectra are given in Table 2. Among the 4-substituted pyridines used as a substrate, 4-cyanopyridine (**1a**) gave the best result followed by 4-acetyl-(**1c**) and 4-methoxycarbonyl-pyridine (**1b**). Thus, we have established a simple and general synthetic route to 3-(2-piperidyl)indoles.

Catalytic Hydrogenation of the Condensation Products (**1a**—**h**).—For the conversion of the condensation products (**1a**—**h**) into indole alkaloids, we next investigated their catalytic hydrogenation. Catalytic hydrogenation of (**2d**) over platinum dioxide under hydrogen atmosphere at room temperature afforded the *cis*-piperidine (**4a**) (44%) which because of its instability was quantitatively isomerised into the *trans*-isomer (**5**) on being left in deuteriochloroform at room temperature. The stereochemistries of the two isomers (**4a**) and (**5**) are discussed later. Catalytic hydrogenation of (**2d**) over 10% palladium on charcoal afforded a mixture of the tetrahydropyridines (**6**) and (**7**) which were separated in 15 and 45% yields,

Table 1. Condensation products (**2a**—**h**)

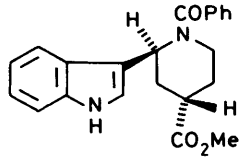
Compd.	React. Temp. (°C)	React. Time (h)	Yield (%)	Formula	Analysis (%) or Accurate Mass (M^+) (m/z) (Required) C	H	N
(**2a**)[a]	20	24	73	$C_{21}H_{15}N_3O$ 0.2MeOH	77.2 (76.70	5.15 4.80	12.35 12.65)
(**2b**)[d]	20	3.5	44	$C_{17}H_{15}N_3O_2$		293.1159 (293.1163)	
(**2c**)[b]	20	3.5	68	$C_{22}H_{17}N_3O_2$	74.55 (74.35	4.85 4.8	11.55 11.85)
(**2d**)[d]	0	2	32	$C_{22}H_{18}N_2O_3$		358.1320 (358.1322)	
(**2e**)[c]	20	21	38	$C_{18}H_{18}N_2O_4$	66.05 (66.25	5.4 5.55	8.65 8.6)
(**2f**)[d]	20	24	39	$C_{23}H_{20}N_2O_4$		388.1455 (388.1422)	
(**2g**)[d]	0	1	39	$C_{22}H_{18}N_2O_2$		342.1368 (342.1368)	
(**2h**)[d]	0	1	35	$C_{17}H_{16}N_2O_2$		280.1216 (280.1211)	

[a] M.p. 115.5—116 °C (from MeOH). [b] M.p. 58—60 °C. [c] M.p. 138—140 °C. [d] These compounds, colourless or pale yellow glasses, were too unstable to be recrystallised for elemental analysis.

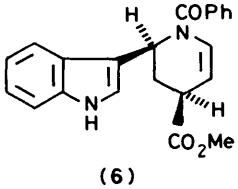


(**4**)

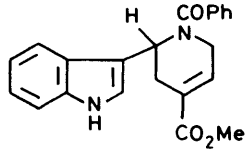
	R^1	R^2
a;	CO_2Me	Ph
b;	Ac	Ph
c;	Ac	Me



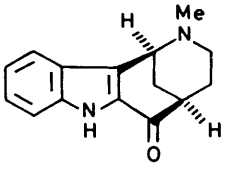
(**5**)



(**6**)



(**7**)

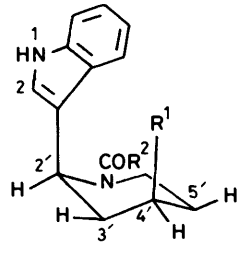


(**8**)

respectively and characterised from their spectral data as follows. The tetrahydropyridine structures for (**6**) and (**7**) were established on the basis of their mass spectra both of which showed a peak at m/z 360 (M^+). The i.r. spectra of the compounds showed ester absorption at 1 725 cm^{-1}, for (**6**), and 1 720 cm^{-1}, for (**7**); this suggested the existence of an isolated ester group in (**6**) and of an α,β-unsaturated ester group in (**7**). Both compounds had complex n.m.r. spectra at room temperature but in [$^2H_7$]dimethylformamide at 100 °C showed clearly distinguishable signals. Thus for (**6**) there were signals for 2′-, 3′-, 4′-, and 5′-H of the dihydropyridine moiety and for (**7**) signals for 2′-, 3′-, 5′-, and 6′-H. These spectral data suggest that (**6**) has a 1,2,3,4-tetrahydropyridine structure while (**7**) has a 1,2,3,6-tetrahydro structure. The temperature dependent n.m.r. spectra of (**6**) and (**7**) indicated that there would be considerable hindrance to rotation around the N–CO bond of the *N*-benzoyl group at low temperature but that this would be less at 100 °C.

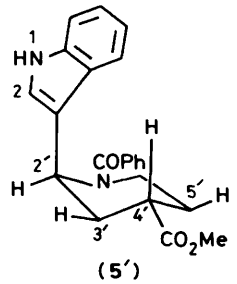
Upon catalytic hydrogenation over platinum dioxide, the tetrahydropyridine (**6**) was smoothly converted into the *cis*-piperidine (**4a**) while (**7**) afforded a mixture of the *cis*- and *trans*-piperidines (**4a**) and (**5**) in roughly equal amounts. Similarly, upon catalytic hydrogenation over platinum dioxide, two condensation products (**2g**) and (**2h**), prepared from 4-acetylpyridine, afforded the corresponding *cis*-piperidines (**4b**) and (**4c**) in good yields. The stability of these was such that, unlike (**4a**), they failed to isomerise to the corresponding *trans*-isomers when kept in deuteriochloroform solution at room temperature for several days.

Stereochemistry of cis- *and* trans-*Piperidines.*—The stereochemistry of the *cis*- and *trans*-piperidines (**4a**—**c**) and (**5**) was deduced by comparison of their spectral data. Thus, in the n.m.r.



(**4**)

	R^1	R^2
a′;	CO_2Me	Ph
b′;	Ac	Ph
c′;	Ac	Me



(**5′**)

Table 2. Spectral data for condensation products (**2a**—**h**)

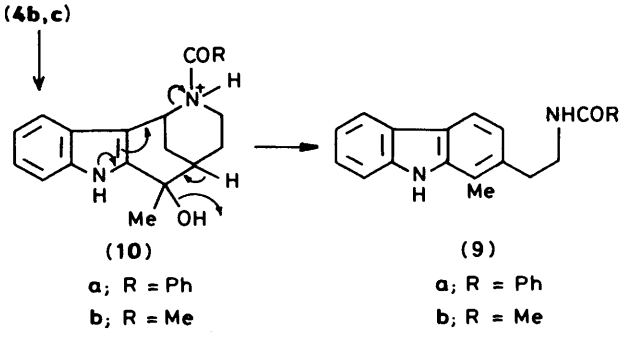
Compd.	$\nu_{max.}$/cm^{-1} ($CHCl_3$)	(MHz) δ (*inter alia*) ($CDCl_3$)
(**2a**)	3 475 (NH) 2 225 (CN) 1 655 (NCO)	(200) 8.69 (1 H, br, NH), 7.93 (1 H, m, 4-H), 7.13 (1 H, d, *J* 3 Hz, 2-H), 6.72 (1H, d, *J* 6 Hz, 2′-H), 6.53 (1 H, d, *J* 8 Hz, 6′-H), 6.52 (1 H, dd, *J* 6 and 1.6 Hz, 3′-H), 5.45 (1 H, dd, *J* 8 and 1.6 Hz, 5′-H)
(**2b**)	3 480 (NH) 2 225 (CN) 1 710 (NCO_2Et)	(200) 8.47 (1 H, br, NH), 7.90 (1 H, m, 4-H), 7.00 (1 H, d, *J* 8 Hz, 6′-H), 6.47 (2 H, s, 2′- and 3′-H), 5.60 (1 H, d, *J* 8 Hz, 5′-H), 4.37 (2 H, q, *J* 7 Hz, OCH_2CH_3), 1.30 (3 H, t, *J* 7 Hz, OCH_2CH_3)
(**2c**)	3 480 (NH) 2 230 (CN) 1 710 (NCO_2CH_2Ph)	(60) 8.40 (1 H, br, NH), 7.83 (1 H, m, 4-H), 7.00 (1 H, d, *J* 8 Hz, 6′-H), 6.40 (2 H, s, 2′- and 3′-H), 5.57 (1 H, d, *J* 8 Hz, 5′-H), 5.33 (2 H, s, OCH_2Ph)
(**2d**)	3 480 (NH) 1 719 (CO_2Me) 1 638 (NCO)	(60) 8.50 (1 H, br, NH), 8.07 (1 H, m, 4-H), 6.93 (1 H, dd, *J* 6 and 1.6 Hz, 3′-H), 6.80 (1 H, d, *J* 6 Hz, 2′-H), 6.57 (1 H, d, *J* 8 Hz, 6′-H), 5.93 (1 H, dd, *J* 8 and 1.6 Hz, 5′-H), 3.93 (3 H, s, OMe)
(**2e**)	3 500 (NH) 1 720—1 705 (CO_2Me and NCO_2Et)	(60) 8.20 (1 H, br, NH), 6.77 (1 H, br d, *J* 8 Hz, 6′-H), 6.73 (1 H, br, d, *J* 6 Hz, 2′- or 3′-H), 6.35 (1 H, br d, *J* 6 Hz, 2′- or 3′-H), 5.90 (1 H, dd, *J* 8 and 1.6 Hz, 5′-H), 4.17 (2 H, q, *J* 7 Hz, OCH_2CH_3), 3.77 (3 H, s, OMe), 1.23 (3 H, t, *J* 7 Hz, OCH_2CH_3)
(**2f**)	3 500 (NH) 1 720—1 710 (CO_2Me and NCO_2CH_2Ph)	(60) 8.00 (1 H, br, NH), 6.57 (3 H, m, 2′-, 3′-, and 6′-H), 5.90 (1 H, dd, *J* 8 and 1.6 Hz, 5′-H), 5.17 (2 H, s, OCH_2Ph), 3.77 (3 H, s, OMe)
(**2g**)	3 495 (NH) 1 675 (Ac) 1 660 (NCO)	(60) 8.67 (1 H, br, NH), 8.03 (1 H, m, 4-H), 6.67 (2 H, s, 2′- and 3′-H), 6.47 (1 H, d, *J* 8 Hz, 6′-H), 5.97 (1 H, d, *J* 8 Hz, 5′-H), 2.33 (3 H, s, Ac)
(**2h**)	3 470 (NH) 1 670 (Ac) 1 640 (NCO)	(60) 8.33 (1 H, br, NH), 7.87 (1 H, m, 4-H), 6.70 (3 H, m, 2′-, 3′-, and 6′-H), 6.10 (1 H, d, *J* 8 Hz, 5′-H), 2.33 (3 H, s, 4′-Ac), 2.13 (3 H, s, 1′-Ac)

spectrum of the *cis*-piperidine (**4a**), there were signals for 2′-H at δ_H 5.68 (br t, *J* 5 Hz) and, at highfield, for a methoxy group at δ_H 2.90 (s); there were also two W-shaped long-range couplings between 3′-$H_{eq.}$ and 5′-$H_{eq.}$ and 2′-$H_{eq.}$ and 4′-$H_{eq.}$. The latter suggested a conformation involving a 1,3-diaxial relationship between the indole function and the methoxycarbonyl substituent in the chair conformer of the piperidine ring (see diagram). In the *N*-acylpiperidine system, it is known that a 2-substituent preferentially adopts an axial orientation owing to steric congestion between the substituent and the *N*-acyl group.[13,14]

The *trans*-isomer (**5**) showed a molecular ion at *m/z* 362 in its mass spectrum and i.r. absorption at 1 720 cm^{-1} (ester); in its n.m.r. spectrum there were signals at δ_H 6.10 (br s, $W_{\frac{1}{2}}$ 13 Hz, 2′-H), 3.69 (s, OMe), and 2.96 (tt, *J* 13 and 4 Hz, 4′-H). From these results together with the observation of W-shaped long-range coupling between 3′-$H_{eq.}$ and 5′-$H_{eq.}$ and the absence of similar coupling between 2′-$H_{eq.}$ and 4′-$H_{ax.}$ we draw the conclusion that the *trans*-isomer (**5**) has conformation (**5′**) with an axially orientated 2-indole ring and an equatorially orientated 4-methoxycarbonyl group. Similarly, the stereochemistries of the *cis*-4-acetylpiperidines (**4b**) and (**4c**) were deduced from their spectral data; the n.m.r. signals for 2′-H, 4′-H, and the acetyl group were particularly useful although direct comparison of the spectral data for the *cis*- and *trans*-isomers was not possible.

The *cis*-4-acetyl-*N*-benzoylpiperidine (**4b**) showed i.r. absorption at 1 705 cm^{-1} (acetyl) and n.m.r. signals at δ_H 5.75 (br t, *J* 5 Hz, 2′-H), 2.68 (quint., *J* 5 Hz, 4′-H), and 1.80 (s, Ac); the acetyl highfield chemical shift together with the observed W-shaped long-range coupling between 3′-$H_{eq.}$ and 5′-$H_{eq.}$ suggested that (**4b**) has conformation (**4b′**), the indole function and the acetyl group being in a 1,3-diaxial orientation as in the case of (**4a**). It is also suggested, on the basis of spectral data, that the *cis*-1,4-diacetylpiperidine (**4c**) has a conformation similar to those of (**4a**) and (**4b**).

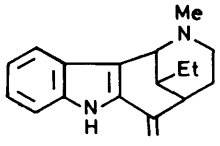
Acidic Cyclisation of 3-(2-*Piperidyl*)*indoles*.—The synthetic utility of the condensation products (**1a**—**h**) was demonstrated by the synthesis of the anti-tumour alkaloid olivacine, described below;[9] earlier other examples of the synthesis of uleine type alkaloids, such as *N*-nordasycarpidone, dasycarpidone, and epiuleine from 3-(2-piperidyl)indoles have been reported.[13,15–17] Since attempted cyclisation of either the *N*-benzoyl-4-methoxycarbonylpiperidines (**4a**) and (**5**) or the corresponding carboxylic acid to the de-ethyldasycarpidone skeleton (**8**) was unsuccessful, we investigated acidic cyclisation of the 4-acetylpiperidines (**4b**) and (**4c**).



Scheme.

Treatment of the 4-acetyl-*N*-benzoylpiperidine (**4b**) with toluene-*p*-sulphonic acid or boron trifluoride–ether in chloroform afforded the carbazole (**9a**) (62 and 60% yields, respectively) the spectral results for which were as expected (see Experimental section). Similarly, upon treatment with toluene-*p*-sulphonic acid, 1,4-diacetylpiperidine (**4c**) afforded the known[18] carbazole (**9b**) (56%) which was also prepared from the *N*-benzoate (**9a**) upon acidic hydrolysis followed by reacylation with acetyl chloride. Thus, this cyclisation is established as a general and useful reaction for the synthesis of indole alkaloids; it is suggested that the cyclisation proceeds *via* the intermediates[17] (**10a**) and (**10b**), followed by spontaneous

ring opening (see Scheme). In addition to the previously reported cyclisation[15,16] of the *N*-alkyl derivatives of the piperidines (**4b**) and (**4c**) into other indole alkaloids, such as uleine (**11**), the work described here suggests that both carbazole and uleine alkaloids may be synthesized by the reaction sequence described, the reaction course simply depending on the piperidine nitrogen substituent. The carbazole (**9b**) is a potential key intermediate for the synthesis of olivacine (**12**).[18] The subsequent steps to olivacine (**12**), that is, cyclisation



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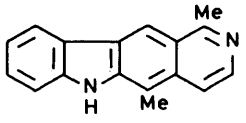

(12)

with phosphorus trichloride oxide and dehydrogenation with palladium on charcoal, proceeded smoothly according to the known procedure[18] to yield the pyridocarbazole (**12**) which was identical with authentic olivacine.[9]

Experimental

^{1}H N.m.r. spectra were measured with JEOL PMX-60 and Varian XL-200 instruments for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane as internal reference), mass spectra with JEOL JMS-01SG and Hitachi M-80 machines, and i.r. spectra for solutions in chloroform with a Hitachi 215 spectrophotometer. M.p.s. were determined with a Kofler-type hot-stage apparatus. Extracts from the reaction mixture were dried over anhydrous sodium sulphate. Ether refers to diethyl ether.

General Procedure for Heteroarylations between Indole and 4-Substituted Pyridines (**1a—c**) *in the Presence of an Acylating Agent.*—To a stirred solution of the 4-substituted pyridine (**1a—c**) (3 mmol) in anhydrous dichloromethane (**10—20** ml) an acylating agent (3 mmol) was added dropwise with stirring under a nitrogen stream at the temperature indicated in Table 1. The mixture was stirred for 5—10 min, after which indole (2 mmol) was added and stirring was continued under the same conditions for the reaction time indicated in Table 1. The supernatant liquid was decanted from the precipitated solid, concentrated to half volume, and then chromatographed on silica gel (ether–hexane as eluant) to give the condensation products (**2a—h**) in yields shown in Table 1.

2-*Indol*-3-*ylpyridine*-4-*carbonitrile* (**3a**).—A solution of the condensation product (**1a**) (500 mg) in 1% methanolic potassium hydroxide (30 ml) was heated at 50 °C for 5 min and then evaporated at room temperature. A solution of the resulting residue in chloroform was washed, dried, and evaporated to give a solid which was recrystallised from ether to afford the *pyridine* (**3a**) (36 mg, 11%) as yellow crystals, m.p. 202—203 °C, $\nu_{max.}$ 3 220 (NH) and 2 230 cm^{-1} (CN); δ_H (*inter alia*) (CD_3OD; 200 MHz) 8.80 (1 H, dd, *J* 5 and 1 Hz, 6′-H), 8.33 (1 H, m, 4-H), 8.00 (1 H, t, *J* 1 Hz, 3′-H), 7.93 (1 H, s, 2-H), and 7.36 (1 H, dd, *J* 5 and 1 Hz, 5′-H); *m/z* 219 (M^+) (Found: C, 76.55; H, 3.9; N, 18.95. $C_{14}H_9N_3$ requires C, 76.7; H, 4.1; N, 19.15%).

Methyl 2-*Indol*-3-*ylpyridine*-4-*carboxylate* (**3b**).—Anhydrous hydrogen chloride was bubbled into a cold solution of the nitrile (**3a**) (22 mg) in anhydrous methanol (30 ml) until it was saturated. After being refluxed for 5.5 h, the reaction mixture was concentrated, made alkaline by the addition of potassium carbonate with cooling, and extracted with chloroform. The extract was washed, dried, and evaporated to give a residue. Purification of the crude product by p.l.c. on silica gel [ether as eluant] afforded the ester (**3b**) (22 mg, 89%) as pale brown crystals, m.p. 161—162 °C (from ether) (lit.,[10] 163 °C): $\nu_{max.}$ 3 480 (NH) and 1 725 cm^{-1} (CO_2Me); δ_H (*inter alia*) (60 MHz) 8.76 (1 H, d, *J* 5.6 Hz, 6′-H), 8.73 (1 H, br, NH), 8.39 (1 H, m, 4-H), 8.19 (1 H, d-like, *J* 2 Hz, 3′-H), 7.72 (1 H, d, *J* 3 Hz, 2-H), 7.56 (1 H, dd, *J* 5.6 and 2 Hz, 5′-H), and 3.97 (3 H, s, OMe) (Found: M^+, 252.0894. Calc. for $C_{15}H_{12}N_2O_2$: *M*, 252.0897).

Methyl cis-1-*Benzoyl*-2-*indol*-3-*ylpiperidine*-4-*carboxylate* (**4a**) *and the* trans-*Isomer* (**5**).—A solution of the condensation product (**2d**) (430 mg) in tetrahydrofuran (50 ml) was hydrogenated over platinum dioxide (100 mg) under hydrogen (1 atm) at room temperature for 3.5 h. The catalyst was filtered off and the filtrate was evaporated to give an oil which was purified by p.l.c. on silica gel (ether as eluant) to afford a solid (190 mg, 44%). Although the solid was found to be almost pure *cis*-piperidine (**4a**) (n.m.r.), further chromatography (p.l.c.) on alumina (chloroform as eluant) separated two *piperidines* (**4a**) (92 mg) and (**5**) (90 mg); the former was quantitatively isomerised into the latter on being kept in deuteriochloroform at room temperature for *ca.* 1 day: (**4a**), m.p. 200.5—201 °C (from ether); $\nu_{max.}$ 1 720 (CO_2Me) and 1 615 cm^{-1} (NCO); δ_H (*inter alia*) (200 MHz) 8.52 (1 H, br, NH), 7.58 (1 H, br d, *J* 8 Hz, 4-H), 7.01 (1 H, q, *J* 1.5 Hz, 2-H), 5.68 (1 H, br t, *J* 5 Hz, 2′-H), 4.33 (1 H, br, 6′-$H_{eq.}$), 3.67 (1 H, td, *J* 13 and 5 Hz, 6′-$H_{ax.}$), 2.90 (3 H, s, OMe), 2.86 (1 H, dt, *J* 13 and 5 Hz, 3′-$H_{eq.}$), 2.72 (1 H, br quint., *J* 5 Hz, 4′-H), 2.34 (1 H, dt, *J* 13 and 5 Hz, 3′-$H_{ax.}$), 2.13 (1 H, br d, *J* 13 Hz, 5′-$H_{eq.}$), and 1.85 (1 H, tt, *J* 13 and 5 Hz, 5′-$H_{ax.}$). Two W-shaped long-range couplings between 2′-$H_{eq.}$ and 4′-$H_{eq.}$ and 3′-$H_{eq.}$ and 5′-$H_{eq.}$ were observed by decoupling experiments; *m/z* 362 (M^+) (Found: C, 72.75; H, 6.25; N, 7.65. $C_{22}H_{22}N_2O_3$ requires C, 72.9; H, 6.1; N, 7.75%); (**5**), m.p. 243—245 °C (from ether); $\nu_{max.}$ 1 720 (CO_2Me) and 1 615 cm^{-1} (NCO); δ_H (*inter alia*) [$(CD_3)_2CDO$, at 100 °C, 200 MHz] 7.64 (1 H, d, *J* 8 Hz, 2-H), 7.15 and 7.04 (each 1 H, td, *J* 8 and 1 Hz, 5- and 6-H), 6.10 (1 H, br s, $W_{\frac{1}{2}}$ 13 Hz, 2′-H), 4.01 (1 H, br d, *J* 13 Hz, and 6′-$H_{eq.}$), 3.69 (3 H, s, OMe), 3.14 (1 H, td, *J* 13 and 3 Hz, 6′-$H_{ax.}$), 2.96 (1 H, tt, *J* 13 and 4 Hz, 4′-H), 2.66 (1 H, br d, *J* 13 Hz, 3′-$H_{eq.}$), 2.09 (1 H, td, *J* 13 and 5.5 Hz, 3′-$H_{ax.}$), 1.91 (1 H, br d, *J* 13 Hz, 5′-$H_{eq.}$), and 1.65 (1 H, qd, *J* 13 and 4.5 Hz, 5′-$H_{ax.}$). A W-shaped long-range coupling between 3′-$H_{eq.}$ and 5′-$H_{eq.}$ was observed by decoupling experiments; *m/z* 362 (M^+) (Found: C, 73.0; H, 6.15; N, 7.6. $C_{22}H_{22}N_2O_3$ requires C, 72.9; H, 6.1; N, 7.75%).

Catalytic Hydrogenation of the Condensation Product (**2d**) *in the Presence of* 10% *Palladium Carbon.*—By the procedure described for the preparation of (**4a**) and (**5**), catalytic hydrogenation of (**2d**) (1 g) in tetrahydrofuran (100 ml) over 10% palladium carbon (250 mg) for 3 h, and purification of the crude product by p.l.c. on alumina (chloroform as eluant) gave the following two products. *Methyl* 1-*benzoyl*-1,2,3,4-*tetrahydro*-2-*indol*-3-*ylpyridine*-4-*carboxylate* (**6**) (153 mg, 15%), m.p. 249.5—250 °C (from methanol); $\nu_{max.}$ 3 480 (NH), 1 725 (CO_2Me), and 1 630 cm^{-1} (NCO); δ_H (*inter alia*) [$(CD_3)_2CDO$, at 100 °C, 200 MHz] 7.06 (4 H, m, 6′-and Ar-H), 5.88 (1 H, dd, *J* 4.5 and 2.5 Hz, 2′-H), 5.19 (1 H, ddd, *J* 8.5, 5, and 1.5 Hz, 5′-H), 3.16 (1 H, dd, *J* 7 and 5 Hz, 4′-H), 3.04 (1 H, ddd, *J* 14, 2.5, and 1.5 Hz, 3′-$H_{eq.}$), 2.84 (3 H, s, OMe), and 2.38 (1 H, ddd, *J* 14, 7, and 4.5 Hz, 3′-$H_{ax.}$) (Found: M^+, 360.1465. $C_{22}H_{20}N_2O_3$ requires *M*, 360.1472); and *methyl* 1-*benzoyl*-1,2,3,6-*tetrahydro*-2-*indol*-3-*ylpyridine*-4-*carboxylate* (**7**) (457 mg, 45%), m.p. 252.5—253 °C (from methanol); $\nu_{max.}$ 3 500 (NH), 1 720

(CO_2Me), and 1 625 cm^{-1} (NCO); δ_H (*inter alia*) [$(CD_3)_2CDO$, at 100 °C, 200 MHz] 6.82 (1 H, br s, 5′-H), 6.16 (1 H, br d, *J* 5 Hz, 2′-H), 4.41 (1 H, br d, *J* 20 Hz, 6′-$H_{eq.}$), 3.77 (3 H, s, OMe), 3.61 (1 H, dtd, *J* 20, 3.5, and 3 Hz, 6′-$H_{ax.}$), 3.10 (1H, br d, *J* 18 Hz, 3′-H_{eq}), and 2.93 (1H, br d, *J* 18 Hz, 3′-H_{ax}); *m/z* 360 (M^+) (Found: C, 73.2; H, 5.6; N, 7.55. $C_{22}H_{20}N_2O_3$ requires C, 73.3; H, 5.6; N, 7.75%).

Catalytic Hydrogenation of the Tetrahydropyridines (**6**) *and* (**7**).—Catalytic hydrogenation of either (**6**) or (**7**) over platinum dioxide in tetrahydrofuran under hydrogen (1 atm) proceeded smoothly, and (**6**) gave exclusively the *cis*-piperidine (**4a**) while (**7**) gave a mixture (*ca.* 1:1) of the *cis*-(**4a**) and *trans*- (**5**) piperidines. These piperidines were identical (t.l.c. and i.r. spectra) with the piperidines prepared by the catalytic hydrogenation of the condensation product (**3d**).

cis-4-*Acetyl*-1-*benzoyl*-2-*indol*-3-*ylpiperidine* (**4b**).—According to the procedure given for the preparation of the *cis*-piperidine (**4a**), catalytic hydrogenation of the condensation product (**2g**) over platinum dioxide gave the *cis*-piperidine (**4b**) (52%) as crystals, m.p. 161.5—162 °C (from ether); $\nu_{max.}$ 3 480 (NH), 1 705 (Ac), and 1 620 cm^{-1} (NCO); δ_H (*inter alia*) (200 MHz) 8.32 (1 H, br, NH), 7.59 (1 H, br d, *J* 8 Hz, 4-H), 7.05 (1 H, q, *J* 1.5 Hz, 2-H), 5.75 (1 H, br t, *J* 5 Hz, 2′-H), 4.20 (1 H, br, 6′-$H_{eq.}$), 3.59 (1 H, ddd, *J* 13, 11, and 5 Hz, 6′-$H_{ax.}$), 2.68 (1 H, quint., *J* 5 Hz, 4′-H), 2.50 (2 H, m, 3′-H_2), 2.10 (1 H, m, 5′-$H_{eq.}$), 1.86 (1 H, ddt, *J* 13, 11, and 5 Hz, 5′-$H_{ax.}$), and 1.80 (3 H, s, Ac). A W-shaped long-range coupling between 3′-$H_{eq.}$ and 5′-$H_{eq.}$ was observed by decoupling experiments; *m/z* 346 (M^+) (Found: C, 75.45; H, 6.45; N, 8.05. $C_{22}H_{22}N_2O_2$1·6H_2O requires C, 75.6; H, 6.45; N, 8.0%).

cis-1,4-*Diacetyl*-2-*indol*-3-*ylpiperidine* (**4c**).—According to the procedure given for the preparation of the *cis*-piperidine (**4a**), catalytic hydrogenation of the condensation product (**2h**) over platinum dioxide gave the *cis*-piperidine (**4c**) (55%) as pale yellow glass; $\nu_{max.}$ 3 490 (NH), 1 705 (Ac), and 1 625 cm^{-1} (NCO); δ_H (*inter alia*) (60 MHz) 8.40 (1 H, br, NH), 6.90 (1 H, d, *J* 3 Hz, 2-H), 5.53 (1 H, t, *J* 6 Hz, 2′-H), 2.07 (3 H, s, 1-Ac), and 1.83 (3 H, s, 4-Ac) (Found: M^+, 284.1510. $C_{17}H_{20}N_2O_2$ requires *M*, 284.1525).

N-*Benzoyl*-2-(1-*methyl*-9H-*carbazol*-2-*yl*)*ethylamine* (**9a**).—(*a*) *By toluene*-p-*sulphonic acid.* A solution of the piperidine (**4b**) (70 mg) and toluene-*p*-sulphonic acid (*ca.* 10 mg) in chloroform (2 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with chloroform, washed successively with aqueous sodium hydrogen carbonate and water, and dried. Evaporation of the solvent gave a residue which was purified by p.l.c. on alumina (chloroform as eluant) to give the *carbazole* (**9a**) (42 mg, 62%) as pale yellow crystals, m.p. 200—201 °C (from benzene); $\nu_{max.}$ 3 480 (br, NH × 2) and 1 650 and 1 515 cm^{-1} (NHCO); δ_H (*inter alia*) (200 MHz) 8.08 (1 H, dd, *J* 8 and 2 Hz, 5-H), 8.06 (1 H, br s, NH), 7.93 (1 H, d, *J* 8 Hz, 4-H), 7.74 (2 H, dt, *J* 8 and 2 Hz), 7.58—7.38 (5 H, m), and 7.26 (1 H, dt, *J* 8 and 2 Hz) (COPh and 6-, 7-, and 8-H), 7.14 (1 H, d, *J* 8 Hz, 3-H), 6.25 (1 H, br, NH), 3.77 (2 H, q, *J* 6 Hz, CH_2NH), 3.18 (2 H, t, *J* 6 Hz, CH_2CH_2NH), and 2.58 (3 H, s, 1-Me); *m/z* 328 (M^+) (Found: C, 81.25; H, 6.1; N, 8.15. $C_{22}H_{20}N_2O$·0.2C_6H_6 requires C, 81.00; H, 6.2; N, 8.15%).

(*b*) *By boron trifluoride–ether.* To an ice-cooled solution of the piperidine (**4b**) (27 mg) in dichloromethane (10 ml) was added boron trifluoride–ether (0.25 ml) dropwise with stirring. After being stirred at room temperature for 18 h, the reaction mixture was diluted with dichloromethane, washed successively with 5% aqueous ammonium hydroxide and water, and dried. Evaporation of the solvent gave a residue which was purified by p.l.c. on alumina (chloroform as eluant) to afford the carbazole (**9a**) (16 mg, 60%), identical (t.l.c. and i.r. spectra) with the carbazole (**9a**) prepared as in (*a*).

N-*Acetyl*-2-(1-*methyl*-9H-*carbazol*-2-*yl*)*ethylamine* (**9b**).—(*a*) *From the piperidine* (**4c**). According to the procedure given for the preparation of the carbazole (**9a**), treatment of the piperidine (**4c**) with toluene-*p*-sulphonic acid in chloroform gave the *carbazole* (**9b**) (56%) as pale yellow crystals, m.p. 163—164 °C (from ether) (lit.,[18] 161—163 °C), $\nu_{max.}$ 3 490 (NH × 2) and 1 665 cm^{-1} (NCO); δ_H (*inter alia*) (200 MHz) 8.10 (1 H, br s, NH), 8.07 (1 H, dd, *J* 8 and 2 Hz, 5-H), 7.90 (1 H, d, *J* 8 Hz, 4-H), 7.55—7.36 (2 H, m) and 7.25 (1 H, td, *J* 8 and 2 Hz) (6-, 7-, and 8-H), 7.06 (1 H, d, *J* 8 Hz, 3-H), 5.54 (1 H, br, NH), 3.54 (2 H, q, *J* 6 Hz, CH_2NH), 3.03 (2 H, t, *J* 6 Hz, CH_2CH_2N), 2.54 (3 H, s, 1-Me), and 1.96 (3 H, s, Ac) (Found: M^+, 266.1397. Calc. for $C_{17}H_{18}N_2O$: *M*, 266.1417).

(*b*) *From the carbazole* (**9a**). A solution of the carbazole (**9a**) (8 mg) in a mixture of 35% hydrochloric acid (4 ml) and acetic acid (2 ml) was refluxed for 9 h. The reaction mixture was concentrated under reduced pressure, made alkaline with aqueous potassium carbonate, and then extracted with chloroform. The extract was washed, dried, and evaporated to give an amine (7 mg) which was, without purification, acylated in chloroform (2 ml) with acetyl chloride (10 mg) in the presence of triethylamine (20 mg) to afford the *acetate* (**9b**) (4 mg, 42%), identical (t.l.c. and i.r. spectra) with the acetate (**9b**) prepared as in (*a*).

1,5-*Dimethyl*-6H-*pyrido*[4,3-b]*carbazole* (*Olivacine*) (**12**).—According to the procedure given in the literature,[18] Bischler-Napieralski cyclisation of the acetate (**9b**) with phosphorus trichloride oxide followed by dehydrogenation with 10% palladium charcoal afforded the *pyridocarbazole* (**12**) (40%) as yellow brown crystals, m.p. > 300 °C (lit.,[18] 318—326 °C) (decomp.), which was found to be identical with the authentic olivacine[9] upon comparison of their i.r. spectra and R_F-values; $\nu_{max.}$ 3 450 (NH), 1 610, and 1 600 cm^{-1} (C=C); δ_H (*inter alia*) [$(CD_3)_2SO$, 200 MHz] 8.94 (1 H, s, 11-H), 8.39 (1 H, d, *J* 7.5 Hz, 10-H), 8.28 (1 H, d, *J* 6 Hz, 3-H), 7.82 (1 H, d, *J* 6 Hz, 4-H), 7.54 (2 H, m), 7.26 (1 H, ddd, *J* 7.5, 6, and 2 Hz) (7-, 8-, and 9-H), 3.05 (3 H, s, Me), and 2.93 (3 H, s, Me) (Found: M^+, 246.1144. Calc. for $C_{17}H_{14}N_2$: *M*, 246.1155).

Acknowledgements

The authors thank the Ministry of Education, Science, and Culture (Japan) for a research grant and Professor O. Yonemitsu of Hokkaido University, Japan, for a sample of olivacine.

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Received 7th May 1985; *Paper* 5/741