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THE SYNTHESIS OF FUSED RING NITROGEN HETEROCYCLES VIA REGIOSPECIFIC INTRAMOLECULAR HECK REACTIONS[1]

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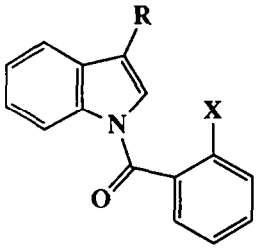
Abstract A series of palladium (and in some cases rhodium) catalysed regiospecific 5-exo-, 6-endo- and 6-exo-trig cyclisations of aryl iodides and vinyl bromides onto proximate alkenes or heteroaromatic rings (indole, pyrrole) lead to a wide variety of fused ring systems. In appropriate cases the methodology provides a facile approach to the creation of tetrasubstituted carbon centres. Double bond isomerisation in the product is only observed in a few cases.

The Heck reaction,[2] the palladium-catalysed arylation of olefins, is a widely used process for the regiospecific and stereoselective formation of substituted aromatic compounds. It continues to attract a high level of research interest in both simple coupling processes[3] and cyclisation reactions.[4] Interest in the latter area, which was pioneered by Heck, Ban and Hegedus,[5] has undergone a sustained revival following extension of the methodology to the synthesis of bridged-, and spiro-cyclic compounds and to the creation of tetrasubstituted carbon-centres by Heck-type cyclisations.[1,6,7] In this paper we discuss our studies of metal catalysed 5-exo-, 6-endo-, and 6-exo-trig cyclisations together with processes creating tetrasubstituted carbon-centres[1]

5-Exo-Trig Cyclisations. Our previous work on the cyclisation selectivity (exo-versus endo-trig) of intermediate vinyl-palladium (II) and -rhodium (III) species onto proximate alkenes established that exo-trig cyclisation is usually preferred over endo-trig cyclisation in reactions generating 5- and 6-membered rings, and that 5-membered ring formation is kinetically favoured over 6-membered ring formation.[6,8,9]

It has been reported[10] that 1-aroylindoles(1a) undergo dehydrogenation to (2a) in hot acetic acid in the presence of palladium acetate (0.5 mol). Yields do not exceed 50% suggesting the process is stoichiometric in palladium. It was of interest to explore a catalytic version of this process. Thus the 1-aroylindoles (1b) and (1c) were cyclised in boiling acetonitrile to (2a) and (2b) in 80 and 63% yield respectively using a catalyst system comprising 10 mol % palladium acetate, 20 mol % triphenylphosphine, tetraethylammonium chloride (1 mol) and potassium carbonate (2 mol).[11] The pyrrole (3a) undergoes an analogous cyclisation to (4) (80%) whilst the pyrazole (3b) failed to cyclise probably due to formation of a stable intermediate (5). The cyclisation of (6a) to (7) in hot acetic acid in 31% yield using palladium acetate (0.5 mol) has been reported.[12] However, (6b) failed to undergo catalytic cyclisation using our standard catalyst system.[11]



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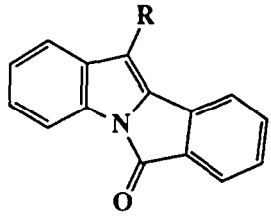
b. X = I, R = H
c. X = I, R = Me



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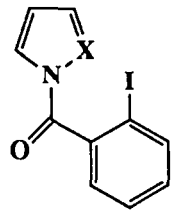

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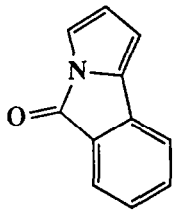

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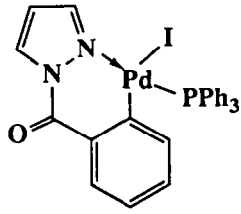

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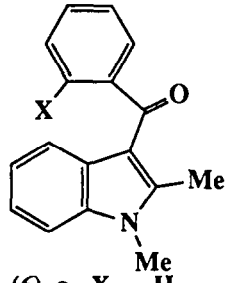

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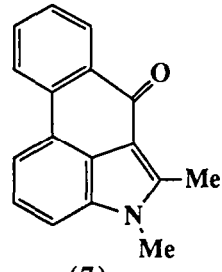

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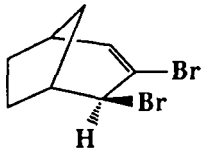

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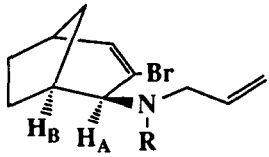
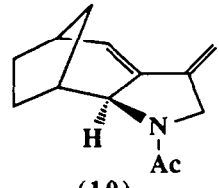


(9) a. R = H
b. R = Ac



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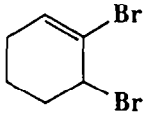

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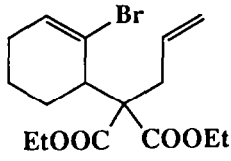

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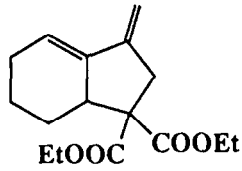

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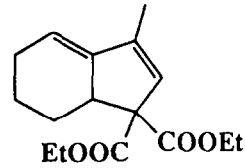

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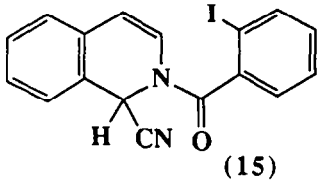

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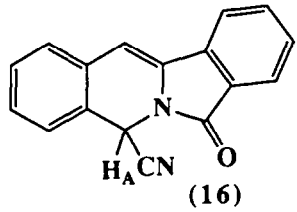

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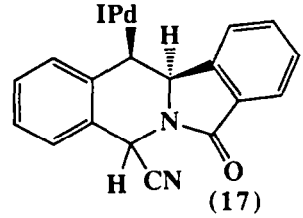
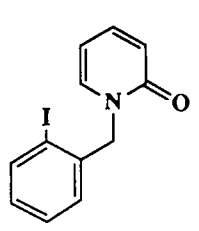


(17)

The vinyl bromide (8) was prepared from norbornene via the standard dibromocarbene addition-rearrangement route.[13] Reaction of (8) with allylamine occured via S_N2' displacement to give the exo-amine (9a) (J_{AB} 2.5Hz) which was acetylated to give (9b). Cyclisation of (9b) ocurred with our standard catalyst system to afford (10) (60%). No double bond isomers were detected. Alkylation of diethyl allylmalonate with dibromide (11) afforded (12) which was cyclised by our standard catalyst system to a 1.3:1 mixture of (13) and (14) in 53% yield.

Reissert compounds provide further substrates for intramolecular Heck reactions as shown by the cyclisation of (15) to (16) in 59% yield. In this case the cyclisation was carried out at 100°C in DMF. Lower temperatures (MeCN, 80°C or DMF, 60°C) were insufficient to promote the reaction. The product (16), with the acidic proton H_A offers scope for further synthetic manipulation. The expected initial cyclisation product (17) (cis addition of Pd-Ar)[14] has the wrong stereochemistry for the required cis-elimination of HPdI. A similar unfavourable stereochemistry is present in the analogous intermediates in the cyclisations of (1a), (1b) and (3a). In all cases the PdI moiety is located at a benzylic site and clearly either undergoes a facile stereomutation furnishing the required cis-stereochemistry or undergoes a trans-elimination.



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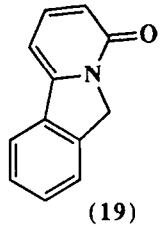

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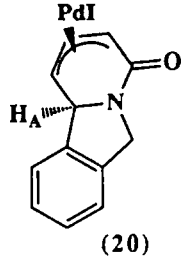

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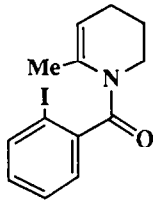

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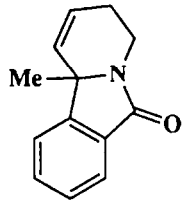

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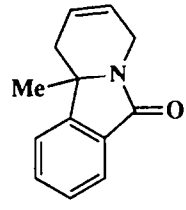

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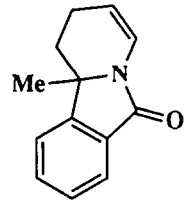

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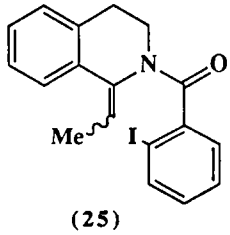

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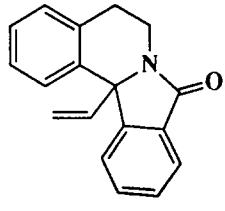

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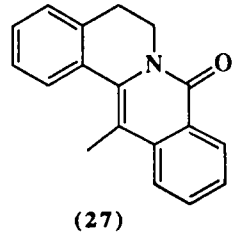


(27)

The dienamide (18) is cyclised (MeCN, 80°C, 12h) by our standard catalyst system to (19) (62%). Heck[15] has reported the intermolecular version of this type of process (aryl iodide addition to a diene) but (18) → (19) appears to be the first recorded intramolecular example. It is interesting that formation of (19) requires either stereomutation of the initial π-allyl-palladium species (20) to establish the necessary cis-relationship between H_A and palladium for the β-hydride elimination step or a trans-elimination.

The catalytic cyclisation of enamide (21) gives a mixture of double bond isomers (22)-(24) whose composition depends on the catalyst system used (Table 1).

Table 1 Cyclisation of (21) with palladium and rhodium catalysts in the presence of anhydrous potassium carbonate.

Entry	Catalyst	Solvent	Temp(°C)	Time(h)	Yield(%)[a]	Ratio[b] (22) : (23) : (24)
1	10 mol % $Pd(OAc)_2$ 20 mol % PPh_3	DMF	100	2	92	1.45 : 1.27 : 1
2	10 mol % $Pd(OAc)_2$ 20 mol % PPh_3 1 mol Et_4NCl	DMF	30	2	72	2.13 : 1 : -
3	10 mol % $RhCl(PPh_3)_3$	DMF	100	48	55	1.14 : 1 : 1.78
4	15 mol % $RhCl(PPh_3)_3$	MeCN	80	48	45	1 : 1 : 1

a. Isolated yields.
b. Estimated from p.m.r. spectra of mixed isomers after chromatography.

Table 2 Catalytic cyclisation of enamide (25) by palladium acetate in the presence of potassium carbonate (2.5 mol).

Catalyst	Solvent	Temp(°C)	Time(h)	Yield(%)[a]	Ratio (26) : (27)[b]
5 mol % $Pd(OAC)_2$ 10 mol % PPh_3	DMF	100	2	84	6.7 : 1
10 mol % $Pd(OAc)_2$ 20 mol % PPh_3	DMF	100	1	80	3.9 : 1
10 mol % $Pd(OAc)_2$ 20 mol % PPh_3 1 mol Et_4NCl	MeCN	80	1	91	10 : 1
12.5 mol % $Pd(OAc)_2$ 25 mol % PPh_3 1 mol Et_4NCl	MeCN	30-50	168	83	13 : 1

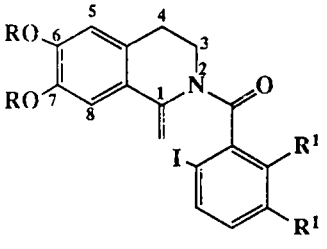
a. Isolated yield.
b. Estimated by integration of the p.m.r. spectrum of the crude products.

Palladium acetate is a more efficient catalyst for the cyclisation of (21) than Wilkinson's catalyst [$RhCl(PPh_3)_3$], and whilst addition of tetraethylammonium chloride to the palladium acetate catalysed reaction resulted in cyclisation occuring at reduced temperature and with less isomerisation, (Table 1, entry 2) addition of tetraethylammonium chloride to the Rh(1) catalysed process had little effect. Double bond isomerisation is always a potential problem in Heck type reactions and addition of either tetraalkylammonium chloride[11] or silver salts (nitrate, carbonate)[16] suppresses this with the latter claimed to be the more efficient.[7,17] Isomerisation arises if the rate of readdition of the hydridopalladium halide, in a π-complexed alkene, to the alkene, is faster than dissociation of the complex.[18]

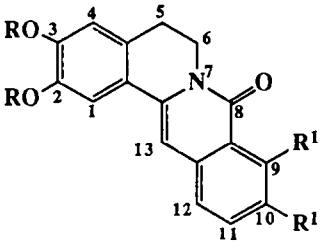
Enamide (25) was prepared by acylation of 1-ethyl-3,4-dihydroisoquinoline with 2-iodobenzoyl chloride. This compound comprises a mixture of four isomers arising from restricted rotation about the CO-N bond and geometrical isomerism associated with the alkene.[19] Cyclisation of this isomeric mixture gave a mixture of 5-exo-trig cyclisation product (26) and 6-endo-trig cyclisation product (27), with the former predominating (Table 2). Addition of tetraethylammonium chloride permitted the reaction to be carried out at lower temperature and resulted in increased selectivity for (26) (Table 2). Reduced amounts of catalyst also increase the selectivity for (26).

The good selectivity for (26) suggests processes of this type will prove valuable in natural product synthesis. An analogous process proceeding through a π-allyl intermediate has recently been reported.[20]

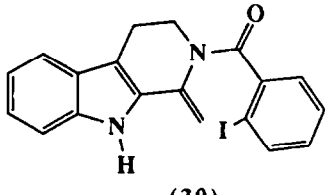
6-Endo-Trig Cyclisations. The formation of small amounts of (27) in the cyclisation of (25) prompted a study of several enamides in which 6-endo-trig cyclisations were the sole cyclisation option.



(28) a. R = Me, R^1 = H
b. R/R = CH_2, R^1 = H
c. R/R = CH_2, R^1 = OMe
d. R = Me, R^1 = OMe



(29) a. R = Me, R^1 = H
b. R/R = CH_2, R^1 = H
c. R/R = CH_2, R^1 = OMe
d. R = Me, R^1 = OMe



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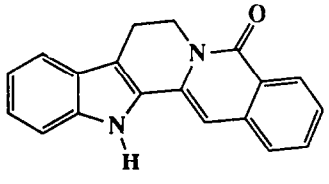
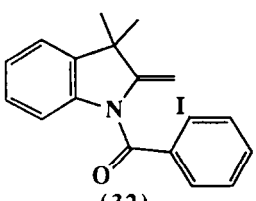


(31)

The enamides (28a-c) were prepared in good yield according to Ninomiya's method.[21] The presence of the two electron-donating OR groups on the isoquinoline moiety renders the enamides somewhat unstable. Reaction of (28a) with 15 mol % $Pd(OAc)_2$/30 mol % PPh_3 in DMF at 100°C for 4 h afforded (29a) in 51% yield. Addition of tetraethylammonium chloride was not advantageous in this case. Enamide (28b) was similarly cyclised (MeCN, 80°C, 14h) to (29b)(43.5%) whilst (28c) afforded (29c) in 55% yield provided (28c) was added slowly to the catalyst system. Thus (28d) gave (29d) in only (38%) under our standard conditions. These low to moderate yields reflect the sensitivity of the starting enamides and the relatively slow rate of the 6-endo-trig cyclisation. Enamide (30) also gave a disappointing yield of (31) (32%) upon cyclisation with our standard catalyst system. However, the more stable enamide (32) is catalytically cyclised to (33) in 62% yield.

6-Exo-Trig Cyclisation. We have briefly explored the combination of the Diels-Alder reaction with a palladium catalysed cyclisation. Thus dienamide (34) was prepared by acylation of the benzylamine imine of crotonaldehyde with 2-iodobenzoyl chloride. The dienamide (34) undergoes a 5-exo-trig cyclisation with our standard catalyst system to give (35) (34%), and reacts with methyl acrylate (benzene, 80°C) to give a mixture of cycloadducts. The major cis-endo-isomer (36) can be isolated from the mixture by fractional crystallisation. Closely related Diels-Alder reactions have been reported by Oppolzer.[22] 6-Exo-trig cyclisation of (36) in acetonitrile at 80°C using our standard catalyst system gives a 1.8: 1 mixture (78%) of (37) and (38).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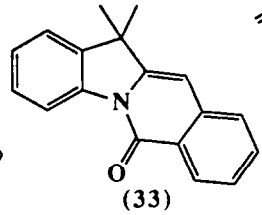
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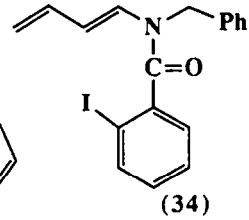
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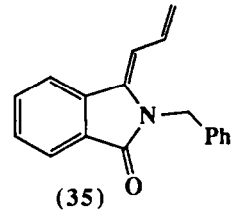
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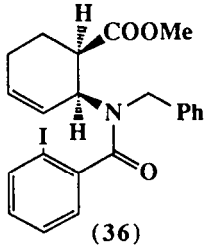
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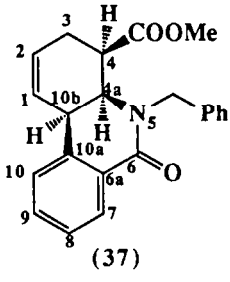
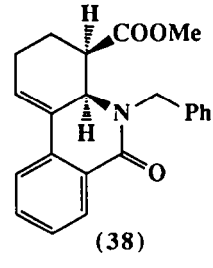
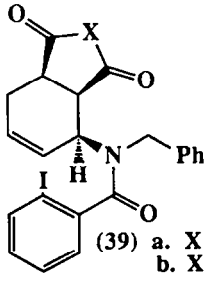
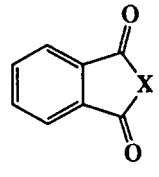
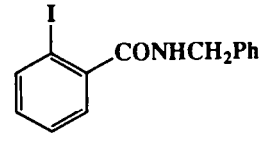

(37)


(38)


(39) a. X = NMe
b. X = O


(40) X = NMe


(41)

The stereochemistry of (37) and (38) was established by n.O.e. difference spectroscopy. Thus irradiation ($CDCl_3$) of 4-H of (37) effected enhancements on 4a-H (5.1%) and on 3-H (3.8%) whilst for (38) irradiation of 4-H effected an 8.4% enhancement in the signal for H-4a. The spectrum of (37) is complicated by the overlap of the 4a-H and 10b-H resonances but the magnitude of their coupling (J~6.5Hz) supported the cis-stereochemistry (eq-ax coupling). When the n.O.e. experiment was conducted in deuterobenzene the resonances for the 4a-H (δ3.60) and 10b-H(δ3.41) were sufficiently separated. Thus irradiation of the 4a-H caused enhancement of the signals for the 10b-H(6.7%) whilst irradiation of the 10b-H effected a 5% enhancement on the 4a-H. Modification of the catalyst system by addition of silver nitrate or silver carbonate in place of tetraethylammonium chloride resulted in a slower reaction but the reaction was now selective for (37). Thus (37) (36%) was formed after 1d in boiling acetonitrile together with substantial amounts of unreacted (36). No (38) was detected in this case. The Diels-Alder cycloadducts (39a) and (39b) were also prepared. Attempts to cyclise these using our standard catalyst system were unsuccessful. After heating at 60°C in acetonitrile for 3 h the only detectable products were (40) and (41). This result presumably reflects the steric effect of the fused 5-membered ring on syn-coordination of palladium.

Experimental General experimental details were as previously noted.[8] Petroleum ether refers to the fraction with b.p. 40-60°C.

Aryl- and Vinyl-halides.

1-(2′-Iodobenzoyl)-indole(1b) Prepared (63%) by adaptation of the method of Itahara et al.[10] The *product* formed colourless plates from methanol-petroleum ether, m.p. 94-95°C (Found: C 51.95; H, 2.95; N, 4.05. $C_{15}H_{10}INO$ requires C, 51.85; H, 2.85; N, 4.05%); δ 8.4-7.0(m, 8H, ArH), 6.8(d, 1H, indole 2-H), and 6.5(d, 1H, indole 3-H); m/z(%) 347(M^+, 51), 231(100), 219(10), 217(44) and 76(27).

1-(2′-Iodobenzoyl)-3-methylindole(1c) Prepared (82%) by adaptation of the method Kikugawa.[23] The *product* crystallised from methanol as colourles needles, m.p. 102-104°C(Found: C, 53.35; H, 3.45; N, 4.0. $C_{16}H_{12}INO$ requires C, 53.2; H, 3.35; N, 3.9%); δ 7.84(dd, 1H, ArH), 7.46-7.12(m, 7H, ArH), 6.61(br s, 1H, indole 2-H), and 2.14(s, 3H, Me); m/z(%) 361(M^+, 57), 234(11), 232(11), 231(100), 203(17), and 76(15); ν_{max} 3047, 2916, 1676, 1607, 1582, 1450, 1389, and 750cm^{-1}.

1-(2′-Iodobenzoyl)-pyrrole(3a) Prepared by adaptation of the method of Itahara et al.[10] The *product* (60%) was a pale yellow oil, b.p. 200°C/0.1mmHg (molecular distillation)(Found: C, 77.8; H, 4.1; N, 8.3. $C_{11}H_7NO$ requires C, 78.1; H, 4.2; N, 8.3%); δ 8.0-7.0 (m, 6H, ArH + pyrrole 2- and 5-H), and 6.25(m, 2H, pyrrole 3- and 4-H); m/z(%) 297(M^+, 16), , 231(100), 203(27), 170(33), and 76(39).

1-(2′-Iodobenzoyl)-pyrazole(3b) Prepared by adaptation of the method of Mingoia.[24] The *product* (87%) crystallised as colourless cubes from ether-petroleum ether, m.p. 56-58°C(Found: C, 40.35; H, 2.3; N, 9.5; I, 42.4. $C_{10}H_7IN_2O$ requires C, 40.3; H, 2.35; N, 9.4; I, 42.55%); δ 8.4(m, 1H), 7.95(d, 1H), 7.8(m, 1H), 7.48(m, 2H), 7.25(m, 1H) and 6.57(br s, 1H); m/z(%) 298(M^+, 10) 231(85), 203(32), 171(100) and 76(38).

3-(2′-Iodobenzoyl)-1,2-dimethylindole(6b) A solution of 1,2-dimethylindole (2.9g, 20 mmol) and 2-iodobenzoyl chloride(5.32g, 20 mmol) in dry THF (75 ml) was boiled under reflux for 5 days. The solvent was then evaporated under reduced pressure and the residue crystallised from ethanol to give the product (2.6g, 35%) as colourless prisms, m.p. 154-156°C(Found: C, 54.55; H, 3.6; N, 3.75; I, 33.75. $C_{17}H_{14}INO$requires C, 54.4; H, 3.75; N, 3.75; I, 33.8%); δ 7.9(d, 1H, ArH), 7.48(t, 1H, ArH), 7.3-7.1(m, 6H, ArH), and 3.78 and 2.63(2 x s, 2 x 3H, Me); m/z(%) 375(M^+, 34), 249(14), 248(50), 247(12) and 172(26).

Exo-4-(aminoprop-2-enyl)-3-bromobicyclo[3.2.1]oct-2-ene(9a). A solution of exo-3,4-dibromobicyclo [3.2.1]oct-2-ene (6.63g, 25 mmol) and allylamine(4.73g, 75 mmol) in benzene(25 ml) was boiled under reflux for 0.5 h. The solvent was then removed under reduced pressure and the residual oil distilled to afford the *product* (6.02g, 76%), b.p. 80-82°C/0.5 mm Hg, as a colourless oil(Found: C 54.2, H 6.4., N 5.55. $C_{11}H_{16}BrN$ requires C 54.55, H, 6.65, N 5.8%); δ 6.26(d, 1H, J 7Hz, CH=CBr), 5.92(m, 1H, C<u>H</u>=CH_2), 5.23 and 5.10(2 x m, 2 x 1H, CH=C<u>H</u>$_2$), 3.41 and 3.29 (2 x dd, 2 x 1H, NCH_2), 2.89(d, 1H, J 2.5Hz, NCH), 2.50(m, 2H), and 1.95-1.19(m 7H); m/z(%) 243, 241(M^+, 18), 202, 200(100), 162(32), 121(21), 120(16), and 105(13); ν_{max}(film)3330, 3070, 2930, 2865, 1640, 1630, 1460, and 1330 cm^{-1}.

Exo-4-(acetylaminoprop-2-enyl)-3-bromobicyclo[3.2.1]oct-2-ene(9b). A solution of acetyl chloride (1.76g, 22 mmol) in methylene chloride (20ml) was added dropwise over 30 min with ice cooling to a stirred solution of exo-4-(aminoprop-2-enyl)-3-bromobicyclo[3.2.1]oct-2-ene (3.63g, 15 mmol) and triethylamine (1.52g, 15 mmol) in methylene chloride (10 ml). The resulting mixture was stirred for a further 1 h at room temperature and then filtered. The filtrate was diluted with methylene chloride (20 ml) and washed with water (2 x 50 ml). The methylene chloride layer was dried (anhy. Na_2SO_4) and evaporated under reduced pressure. The residual oil was distilled to afford the *product* (2.4g, 57%), b.p. 114-116°C/0.1 mmHg, as a thick yellow oil(Found: C, 55.2; H, 5.45; N, 4.9. $C_{13}H_{18}BrNO$ requires C, 54.95; H, 5.65; N, 4.95%); δ 6.55(d, 1H, J 6.7Hz, CH=CBr), 5.87(m, 1H, C<u>H</u>=CH_2), 5.26-4.94(m, 3H, C=C<u>H</u>$_2$ and NCH), 4.04 and 3.88(2 x d, 2 x 1H, J 18.5Hz, NCH_2), 2.61 and 2.47(2 x br s, 2 x 1H), 2.11(s, 3H, Me), and 2.0-1.24(m, 6H); m/z(%) 285, 283 (M^+, 17), 244, 242(100), 204(64), 202,200(53), 105(22) and 77(46); ν_{max} (film) 3080, 2950, 2870, 1650 and 1450 cm^{-1}.

Diethyl allyl-2-bromocyclohex-2-enylmalonate(12). Diethyl allylmalonate(4g, 20 mmol) was slowly added with stirring to a solution of sodium ethoxide [from Na(0.46g)] in dry ethanol (25 ml) and the resulting mixture stirred at room temperature for 15 min. 2,3-Dibromocyclohexene (4.78g, 20 mmol) was then added dropwise over 0.5 h and the mixture was boiled under reflux for 16 h. The reaction mixture was then cooled and partitioned between water (75 ml) and ether (75 ml). The aqueous layer was extracted with ether (50 ml) and the combined ether extracts dried (Na_2SO_4), and evaporated under reduced pressure. The residual oil was distilled to afford the product (3.7g, 52%), b.p. 126-130°C/0.5 mm Hg, as a colourless oil (Found: C, 53.7; H, 6.65. $C_{16}H_{23}BrO_4$ requires C, 53.5; H, 6.45%); δ 6.21(m, 1H, CH=CBr), 5.95(m, 1H, C<u>H</u>=CH_2), 5.09(m, 2H, CH=C<u>H</u>$_2$), 4.20(m, 4H, C<u>H</u>$_2$Me), 3.40(m, 1H, CHC=C), 2.9 and 2.52(2 x dd, 2 x 1H), 2.08-1.49(m, 6H), and 1.32-1.22(2 x t, 2 x 3H, CH_2<u>Me</u>); m/z(%) 360, 358 (M^+, 1), 279(60), 239(33), 205(12), 165(24) and 79(19); ν_{max}(film) 3070,

2980, 1735-1730, 1370, 1445, 1235 and 1205 cm^{-1}.

1-Cyano-2-(2′-iodobenzoyl)-1,2-dihydroisoquinoline(15) A solution of 2-iodobenzoyl chloride (16g, 62 mmol) in methylene chloride (30 ml) was added over 2 h. to a stirred two phase mixture of isoquinoline (4.13g, 32 mmol) in methylene chloride and potassium cyanide (6.25g, 96 mmol) in water (16 ml). After an additional 7 h stirring, the two layers were separated and the aqueous layer extracted with methylene chloride (20 ml). The combined methylene chloride extracts were washed with water (2 x 10 ml), 5% hydrochloric acid (20 ml), water(20 ml), 5% aqueous sodium hydoxide (20 ml) and water (20 ml), and then dried (Mg SO_4). The solvent was then removed under reduced pressure and the residue (7.8g, 62%) crystallised from ethanol to afford the product (4.1g, 32%) as cream rods, m.p. 158-160°C(Found: C, 52.6; H, 2.85; N, 7.05. $C_{17}H_{11}N_20$ requires C, 52.85; H, 2.85; N, 7.25%); δ 7.54, (m, 8H, ArH), 6.79(s, 1H, ArCHN), and 6.25 and 6.01 (2 x d, 2 x 1H, J 7.8 Hz, CH=CH); m/z(%) 386(M^+, 16), 231(100), 203(16), 155(2), 129(17), 77(9) and 76(21); ν_{max} 3030, 2912, 2835, 1665, 1622, 1343, 1278, 777, 765 and 748 cm^{-1}.

1-(2′-Iodobenzyl)-2-(1H)-pyridone(18) A suspension of 2-(1H)-pyridone(5g, 50 mmol) and anhydrous potassium carbonate (15g) in dry dimethoxyethane (70 ml) was stirred and boiled under reflux for 1 h. A solution of 2-iodobenzoyl chloride (15.1g, 60 mmol) in dry dimethoxyethane (20 ml) was then added dropwise over 30 min. and heating continued for a further 10 h. The mixture was filtered hot and the inorganic salts washed with dimethoxyethane (2 x 20 ml). The combined dimethoxyethane extracts were evaporated and the residue crystallised from methanol-petroleum ether to afford the product (10.9g, 70%) as colourless prisms, m.p. 115-116°C(Found: C, 46.3; H, 3.2; N, 4.35. $C_{12}H_{10}INO$ requires C, 46.3; H, 3.2; N, 4.5%); δ 7.83(d, 1H, ArH), 7.39-7.01(m, 5H, ArH), 6.6(d, 1H, ArH), 6.17(t, 1H, ArH), and 5.16(s, 2H, NCH_2); m/z(%) 311(M^+, 2), 217(13), 184(100), 91(7) and 90(27).

1-(2′-Iodobenzoyl)-2-methyl-1,4,5,6-tetrahydorpyridine(21). A solution of 2-methyl-3,4,5,6-tetrahydropyridine (2.0g, 20 mmol), 2-iodobenzoyl chloride (5.3g, 20 mmol) and triethylamine (2g, 20 mmol) in benzene(20 ml) was boiled under reflux for 1h. The solvent was then removed under reduced pressure and the residue partitioned between methylene chloride and water. The organic layer was separated, dried (Mg SO_4), and concentrated, and the residue distilled to give the *product* (5g, 76%) as a colourless viscous oil, b.p. 156-160°C/0.15 mmHg (Found: C, 45.45; H, 4.45; N, 4.15. $C_{13}H_{15}INO$ requires C, 45.6; H, 4.6; N, 4.15%), δ 7.45(m, 4H, ArH), 5.11(br, s 1H, CH=CMe), 3.43 and 3.27[q + br s, 2H, NCH_2(amide isomers)], 2.52 and 2.28[t + br s, 2H, C=CHCH_2(amide isomers)], 2.15(s, 3H, Me), and 1.82 and 1.66(m, 2H, CH_2); m/z(%) 327(M^+, 22), 276(34) and 231(100); ν_{max}(film) 3040, 3020. 2990, 2960, 2920, 2865, 2830, 1630, 1580, 1495, 1145 and 995 cm^{-1}.

1-Ethylidene-2-(2′-iodobenzoyl)-1,2,3,4-tetrahydroisoquinoline(25). Prepared from 1-ethyl-3,4-dihydroisoquinoline in an analogous manner to that described above. The *product* (50%) was obtained as a pale yellow viscous oil, comprising a mixture of four isomers, after purification by column chromatography (silica) eluting with ether (Found: C, 55.25; H, 4.2; N, 3.45. $C_{18}H_{16}INO$ requires C, 55.55; H, 4.15; N, 3.6%); δ 6.4 (m, 8H, ArH), 6.34, 5.73 5.34 and 4.97(4 x q, 1H, MeCH=C, 4 isomers), 3.91 and 3.2(t and m, 2H, NCH_2), 2.89 and 2.77(t and m, 2H, $ArCH_2$), and 1.99, 1.90, 1.50 and 1.43

(4 x d, 3H, MeCH=C, 4 isomers); m/z(%) 389(M^+, 60), 374(33), 262(87), 261(27), 246(35), 234(49), 231(100), 203(36), 156(27), 128(43), 105(39), 77(33) and 76(28).

1-Methylidene-2-(2′-iodobenzoyl)-6,7-dimethoxy-1,2,3,4,-tetrahydroisoquinoline(28a). Prepared from 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline in an analogous manner to that described above. The *product* (56%) was obtained as a pale yellow solid, m.p. 124-127°C(Found: C, 52.75; H, 4.15; N, 3.05. $C_{19}H_{18}INO_3$ requires C, 52.45; H, 4.15; N, 3.2%), δ 7.22(d, 1H, ArH), 6.44(m, 3H, ArH), 6.54 and 5.96(2xs, 2 x 1H, ArH), 4.85 and 4.35(2 x br s, 2 x 1H, $C=CH_2$), 3.82(br s, 2H, NCH_2), 3.05 and 2.99(2 x s, 2 x 3H, OMe), and 2.34(br s, 2H, $ArCH_2$); m/z(%) 435(M^+, 14), 309(22), 308(98), 307(18), 292(17), 281(20), 280(100), 264(18), 231(26) and 203(21); ν_{max} 3050, 3030, 2940, 2910, 2805, 1625, 1613, 1500, 1440, 1400, 1380, 1260, 1247, 1205, 1155, 1065, 903, 873, 845 and 768 cm^{-1}.

1-Methylidene-2-(2′-iodobenzoyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline(28b). Prepared from 1-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline in an analogous manner to that described above. The *product* (75%), was an unstable pale yellow solid, m.p. 116-120°C (Found: C, 52.6; H, 4.4; N, 2.8. $C_{18}H_{14}INO_3$. 0.5 Et_20 requires C, 52.65; H, 4.2; N, 3.05%); δ 7.1(m, 6H, ArH), 5.8(s, 2H, OCH_2O), 5.2 and 4.5(2 x m, $C=CH_2$), 4.0(m, 2H, NCH_2), and 2.9(m, 2H, $ArCH_2$); m/z(%) 419(M^+, 8), 292(89), 264(100), 231(27), 203(25), and 76(24); ν_{max} 3025, 2895, 1633, 1490, 1475, 1387, 1250, 1035, 935, 895, 860, 845, 775, 760 and 735 cm^{-1}.

1-Methylidene-2-(2′,3′-dimethoxy-6′-iodobenzoyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline(28c). Prepared from 1-methyl-6,7-methylenedioxy-3,4-dihydroisoquinoline and 2,3-dimethoxy-6-iodobenzoyl chloride in an analogous manner to that described above. The *product* (75%) was obtained as a pale yellow solid, m.p. 160-165°C (Found: C, 49.75; H, 3.6; N, 2.65. $C_{20}H_{18}INO_5$ requires C, 50.1; H, 3.8; N, 2.9%); δ 7.4 and 6.62 (2 x d, 2 x 1H, ArH), 6.9 and 6.57(2 x s, 2 x 1H, ArH), 5.94(d, 2H, OCH_2O), 5.17 and 4.82(2 x d, 2 x 1H, $C=CH_2$), 4.36 and 3.94(2 x m, 2 x 1H, NCH_2), 3.83 and 3.77(2 x s, 2 x 3H, OMe), and 3.08 and 2.88(2 x m, 2 x 1H, $ArCH_2$); m/z(%) 479(M^+, 11), 448(100), 420(58), 352(86), 324(35), 293(26), and 291(27); ν_{max} 2930, 2900, 1628, 1615, 1490, 1473, 1458, 1413, 1250, 1030, 1000, and 800 cm^{-1}.

1-Methylidene-2-(2′,3′-dimethoxy-6′-iodobenzoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline(28d). Prepared from 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline and 2,3-dimethoxy-6-iodobenzoyl chloride in an analogous manner to that described above. The crude product (70%) was obtained as a viscous pale yellow oil which was used directly for the next stage without further purification. δ 7.45(d, 1H, ArH), 7.0(s, 1H, ArH), 6.8(d, 1H, ArH), 6.5(s, 1H, ArH), 5.2 and 4.8(2 x d, 2 x 1H, $C=CH_2$), 4.4 and 3.8(2 x m, 2 x 1H, NCH_2), 4.0, 3.86, 3.85 and 3.75(4 x s, 4 x 3H, OMe), and 3.2 and 2.85(2 x m, 2 x 1H, $ArCH_2$).

1-Methylidene-2-(2′-iodobenzoyl)-1,2,3,4-tetrahydro-β-carboline(30). Prepared from 1-methyl-3,4-dihydro-β-carboline in a manner analogous to that described above. The *product* (60%) crystallised from ethanol as off white prisms, m.p. 98-100°C(Found: C, 55.35; H, 3.6; N, 7.1. $C_{19}H_{15}IN_2O$ requires C, 55.05; H, 3.6; N, 6.75%); δ 7.2-6.2(m, 8H, ArH), 4.8(br s, 2H, $C=CH_2$), 3.4(br t, 2H, NCH_2), and 2.3(t, 2H, $ArCH_2$); m/z(%) 414(M^+, 13), 288(21), 287(100) and 185(54); ν_{max}. 1685(br), 1655, 1620 and

1420 cm^{-1}.

1-(2′-Iodobenzoyl)-2-methylidene-3,3-dimethylindoline(32) Prepared from 2,3,3-trimethylindolenine in a manner analogous to that described above. The *product* (70%) was obtained as a thick red oil on removal of the reaction solvent (benzene). Attempted purification by chromatography (silica) or by distillation resulted in decomposition. It was therefore used directly for the next stage. δ 7.9-7.0 (m, 8H, ArH), 5.0 and 4.6(2 x s, 2 x 1H, C=CH_2), and 1.5(s, 6H, 2 x Me); m/z(%) 389(M^+, 13), 262(26), 234(12), 231(100) and 78(35); ν_{max} 1660(br), 1420 and 1300 cm^{-1}.

N-Benzyl-N-(but-1′,3′-dienyl)-2-iodobenzamide(34). A solution of 2-iodobenzoyl chloride (13.33 g, 50 mmol) in dry benzene(30 ml) was slowly added to a stirred solution of the benzylamine imine of crotonaldehyde (7.95g, 50 mmol) and N,N-diethylaniline (8.21g, 55 mmol) in dry benzene (100 ml) with ice cooling. The resulting mixture was stirred at room temperature for a further 15 h, filtered, and the filtrate evaporated. The residual oil was purified by flash chromatography (silica) eluting with 1:3 v/v ether-petroleum ether to afford the *product* (11.5g, 59%) as a viscous pale yellow oil (Found: C, 55.8; H, 3.9; N, 3.7. $C_{18}H_{16}INO$ requires C, 55.55; H, 4.15; N, 3.6%); δ 7.88(dd, 1H, ArH), 7.47-7.02(m, 8H, ArH), 6.41(d, 1H, J 13.8Hz, CH=C<u>H</u>N), 5.99(m, 1H, CH_2=C<u>H</u>), 5.73(dd, 1H, J 13.8 and 10.5Hz, C<u>H</u>=CHN), 5.10 and 5.09(2 x s, 2H, NCH_2), 4.98 and 4.87(2 x dd, 2 x 1H, CH=<u>CH_2</u>); m/z(%) 389(M^+, 41), 231(100), 203(16) and 91(43).

N-Benzyl-N-(2′-methoxycarbonylcyclohex-5-enyl)-2-iodobenzamide(36). A solution of N-benzyl-N-(but-1′,3′-dienyl)-2-iodobenzamide (7.78g, 20 mmol) and methyl acrylate (72 ml, 800 mmol) in benzene (100 ml) was boiled under reflux for 3 days. The solvent was then removed under reduced pressure and the residue purified by flash chromatography (silica) eluting with 1:1 v/v ether-petroleum ether to give the *product* (6.4g, 68%) as a colourless solid which comprised a ca. 4:1 mixture of stereoisomers. Crystallisation fromn ethanol afforded the pure cis-endo-isomer (36)(50%) as a colourless prisms, m.p. 105-107°C (Found: C, 55.35; H, 4.7; N, 2.8. $C_{22}H_{22}INO_3$ requires C, 55.6; H, 4.65; N, 2.95%); δ[(DMSO-d_6) 175°C] (p.m.r. at normal probe temperature is broad) 7.79 and 7.36(2 x m, 2 x 1H, ArH), 7.29-7.15(m, 6H, ArH), 7.05(m, 1H, ArH), 5.91 and 5.76 (2 x m, 2 x 1H, CH=CH), 5.0(br s, 1H, NCH), 4.62 and 4.51 (2 x d, 2 x 1H, NCH_2), 3.67(s, 3H, OMe), 3.01(m, 1H, C<u>H</u>CO_2Me), and 2.28-1.79(m, 4H, 2 x CH_2); m/z(%) 475(M^+, 6), 384(15), 336(24), 244(51), 231(100), 105(16) and 91(26).

N-Benzyl-N-(3a′,4′,7′,7a′-tetrahydro-1′,3′-dioxo-2′-methylisoindoline-4′-yl)-2-iodobenzamide(39a). A solution of N-benzyl-N-(but-1′,3′-dienyl)-2-iodobenzamide (2.73g, 7mmol) and N-methylmaleimide(770 mg, 7 mmol) in benzene was boiled under reflux for 1 day. Removal of the solvent, followed by flash chromatography of the residue (silica, 2:1 v/v ether-petroleum ether) afforded the product (3.2g, 91%) as a 10:1 mixture of stereoisomers. Crystallisation from ethanol afforded the major endo isomer as colourless plates, m.p. 143-145°C(Found: C, 55.35; H, 4.25; N, 5.55; I, 25.5. $C_{23}H_{21}IN_2O_3$ requires C, 55.2; H, 4.25; N, 5.6; I, 25.35%); δ(60°C) 7.75(d, 1H, ArH), 7.42(m, 1H, ArH), 7.27(m, 6H, ArH), 6.97(m, 1H, ArH), 6.05 and 5.87 (2 x m, 2 x 1H, CH=CH), 4.69-4.46(m, 3H, NCH_2 and NCH), 3.46 and 3.08(2 x m, 2 x 1H, CHCO), 2.95(s, 3H, NMe), and 2.81 and 2.14(2 x m, 2 x 1H, CH_2C=C); m/z(%) 500(M^+, 3), 336(27), 269(59), 231(100), 105(23) and 91(38); ν_{max}(nujol) 1770, 1690, 1630 cm^{-1}.

N-Benzyl-N-(1′,3′,3a′,4′,7′,7a′-hexahydro-1′,3′-dioxoisobenzofuran-4′-yl)-2-iodobenzamide(39b). Prepared in an analogous manner to that described above using maleic anhydride as the dipolarophile and toluene as the solvent. The reaction was carried out at 85°C for 1 day and on cooling the product crystallised out as colourless rods(2.8g, 82%) which comprised a 10:1 mixture of endo- and exo-isomers. Recrystallisation from toluene afforded the endo- isomer m.p. 192-194°C (Found: C, 53.9; H, 3.55; N, 2.65. $C_{22}H_{18}INO_4$ requires C, 54.25; H, 3.7; N, 2.85%); δ(60°C) 7.78(d, 1H, ArH), 7.37-7.21(m, 7H, ArH), 7.01(m, 1H, ArH), 6.0(s, 2H, CH=CH), 4.68-4.48(m, 3H, NCH_2 and NCH), and 3.76, 3.43, 2.88 and 2.31 (4 x m, 4 x 1H, 2 x CHCO and CH_2CHCO); m/z(%) 487(M^+, 6), 337(32), 336(29), 231(100), 203(19), 158(23), 105(22), 91(46)and 77(23); ν_{max}(nujol) 1840, 1780, 1635,and 1210 cm^{-1}.

General Procedure for Cyclisation Reactions. A mixture of the aryl- or vinyl-halide (0.5 mmol), palladium acetate (0.05 mmol), triphenylphosphine (0.1 mmol), anhydrous potassium carbonate (1 mmol) and tetraethylammonium chloride (0.5 mmol) in dry acetonitrile (80 ml) was boiled under reflux under an atmosphere of dry nitrogen until t.l.c. monitoring showed all the starting material had been consumed. The mixture was then filtered to remove inorganic salts and the filtrate evaporated under reduced pressure. The residue was dissolved in ether and filtered through a short column of silica eluting with ether. Removal of the ether afforded the crude product which was purified by crystallisation or preparative t.l.c. as appropriate.

5-Exo-Trig Cyclisations.

6-Oxo-6H-isoindolo[2,1-a]indole(2a). Work up after 12 h followed by crystallisation from chloroform-petroleum ether afforded the *product*(80%) as yellow needles, m.p. 153-155°C(lit.[10] m.p. 154-155°C) δ 7.89-7.0(m, 8H, ArH) and 6.59(s, 1H, indole 3-H); m/z (%) 219(M^+, 100), 190(29) and 130(17).

11-Methyl-6-oxo-6H-isoindolo[2,1-a]indole(2b). After a reaction time of 4 h. the *product* (63%), m.p. 173-175°C crystallised as yellow needles on cooling the reaction mixture (Found: C, 82.6; H, 4.4; N, 6.15. $C_{16}H_{11}NO$ requires C, 82.4; H, 4.7; N, 6.0%); δ 7.84-7.10(m, 8H, ArH), and 2.38(s, 3H, Me); m/z(%) 233(M^+, 91), 232(75), 204(12) and 203(10); ν_{max} 1707, 1609, 1450, and 746 cm^{-1}.

4-Oxo-4H-isoindolo[2,1-a]pyrrole(4). Work up after 12 h followed by crystallisation from ether-petroleum ether afforded the *product* (80%) as yellow needles, m.p. 70-71°C(Found: C, 77.8; H, 4.1; N, 8.45. $C_{11}H_7NO$ requires C, 78.1; H, 4.15; N, 8.3); δ 7.63-7.0(m, 4H, ArH), 6.9(d, 1H, pyrrole 5-H), and 6.15(m, 2H, pyrrole 3- and 4-H; m/z(%) 169(M^+, 100), 140(15), 114(19), 88(6) and 75(3).

4-Methylidene-6-acetyl-6-azatricyclo[6.2.1.$0^{3,7}$] undec-2-ene(10). Cyclisation of (9b) occured over 3 h at 80°C. Work up followed by crystallisation from ether-petroleum ether afforded the *product* (60%) as pale yellow needles, m.p. 75-77°C(Found: C, 77.0; H, 8.55; N, 7.05. $C_{13}H_{17}NO$ requires C, 76.8; H, 8.45; N, 6.9%); δ 6.52(dd, 1H, J 7.6 and 2Hz, C=CH), 5.17 and 4.77(2 x t, 2 x 1H, $C=CH_2$), 4.08(m, 2H, NCH_2), 3.8(d, 1H, J 2.4 Hz, NCH), 3.38(br s, 1H, 1-H), 2.67(br s, 1H, 8-H), 2.05(s, 3H, Me), and 1.87-1.08(m, 6H); m/z(%) 203 (M^+, 100), 175(21), 162(30), 161(33), 160(37), 133(29), 132(32), 120(99) and 43(30); ν_{max}. 3030, 2950, 2860, 1640 and 1450 cm^{-1}.

Diethyl 3-methylidenebicyclo[4.3.0]nona-4-ene-1,1-dicarboxylate(13) and diethyl 3-methylbicyclo[4.3.0]nona-2,4-diene-1,1-dicarboxylate(14). Cyclisation of (12) occured over 1 h at 80°C. Work up by

preparative t.l.c., eluting with 1:1 v/v ether-petroleum ether, afforded a 1.3:1 mixture of (13) and (14) in 53% combined yield as a pale yellow viscous oil [Found: (mixed isomers) C, 69.05; H, 7.8. $C_{16}H_{22}O_4$ requires C, 69.05; H, 7.95%]; m/z(%)(mixed isomers) 278(M^+, 23), 205(26), 204(61), 175(28), 173(45), 132(15), 131(100), 130(37) and 91(35). The p.m.r. spectra (below) are assigned from the spectrum of the mixed isomers.

(13) δ 6.23(m, 1H, C=CH), 5.75(m, 2H, C=CH_2), 5.29 and 5.85(2 x s, 2 x 1H), 4.28 -4.06(2 x q, 4H, CH_2Me), 3.53-1.78(m, 7H) and 1.3-1.1(2 x t, 6H, CH_2Me).

(14) 6.27(m, 1H, C=CH), 6.07(q, 1H, CH=CMe), 4.28-4.06(2 x q, 4H, CH_2Me), 3.53-1.78(m, 7H), 1.73(s, 3H, Me) and 1.3-1.1(2 x t, 6H, CH_2Me).

5,6,7,12a-Tetrahydro-5-oxo-7-cyanoisoindolo[2,1-b]isoquinoline(16). Cyclisation of (15) was carried out in DMF at 100°C for 1 h and no tetraethylammonium chloride was added in this instance. The *product* (59%) crystallised from ethanol as yellow rods, m.p. 157-161°C (Found: C, 79.1; H, 4.0; N, 10.85. $C_{17}H_{10}N_2O$ requires C, 79.05; H, 3.9; N, 10.85%); δ 7.66 (m, 8H, ArH), 6.59(s, 1H, CHCN), and 6.39(s, 1H, C=CH); m/z(%) 258(M^+, 68), 233(19), 232(100), 231(13), 203(11), 147(30), 91(69) and 77(5).

4,5-Dihydro-4-oxopyridino[2,1-a]isoindole(19). Cyclisation of (18) occurred over 12h. The *product* (60%) crystallised from methanol as colourless plates, m.p. 168-170°C (Found: C, 78.0; H, 5.3; N, 7.7. $C_{12}H_9$NO requires, C 78.65; H, 4.95; N, 7.65%); δ 7.78-7.45(m, 5H, ArH), 6.73 and 6.55(2 x d, 2 x 1H, ArH), and 5.09(s, 2H, NCH_2); m/z(%) 183(M^+, 100), 155(18), 154(44), and 127(13).

Tetrahydro-5-oxopyridino[2,1-a]isoindoles(22)-(24). Cyclisation of (21) was carried out in DMF for 2 h at 100°C without addition of tetraethylammonium chloride. Work up afforded the *product* (82%) as a colourless solid whose p.m.r. spectrum showed it to comprise a 1.45:1.27:1 mixture of (22), (23) and (24) [Found (mixed isomers) C, 79.35; H, 6.55; N, 7.4. $C_{13}H_{13}$NO requires C, 79.35; H, 6.6; N, 7.05%); m/z(%)(mixed isomers) 199(M^+, 47), 184(100), 170(10), 158(42), 156(10), 128(10), 104(54), 115(12), 103(10), and 91(10). The p.m.r. spectra (below) are assigned from the spectrum of the isomeric mixture.

(22) δ 7.65(m, 4H, ArH), 6.0 and 5.72 (2 x m, 2 x 1H, CH=CH), 4.50 and 3.22 (q and m, 2 x 1H, NCH_2), 2.27 and 2.11 (2 x m, 2 x 1H, CH_2), and 1.55(s, 3H, Me).

(23) δ 7.65(m, 4H, ArH), 5.83(m, 2H, CH=CH), 4.72 and 3.72(2xm, 2 x 1H, NCH_2), 2.54 and 2.11(2 x m, 2 x 1H, CH_2), and 1.47(s, 3H, Me).

(24) δ 7.65(m, 4H, ArH), 7.04(m, 1H, NCH=CH), 5.25(m, 1H, NCH=CH), 2.58(m, 3H, HC=CHCH_2CHH), 1.58(m, 1H, CH=CHCH_2 CHH), and 1.39(s, 3H, Me).

4b,9,11,12-Tetrahydro-4b-ethenyl-9-oxoisoindolo[2,1-a]isoquinoline(26) and 13-methyl-8-oxoprotoberberine(27). Cyclisation of (25) by the general procedure was complete in 1 h. Work up afforded a colourless solid (91%) whose p.m.r. spectrum showed it to comprise a 10:1 mixture of (26) and (27). Crystallisation from ether afforded (26) (57%) as colourless plates, m.p. 94-96.5°C (Found: C, 82.45; H, 5.6; N, 5.2. $C_{18}H_{15}$NO requires C, 82.75; H, 5.8; N, 5.35%); δ 7.52(m, 8H, ArH), 5.95(q, 1H, J 16.9 and 10.3 Hz, CH=CH_2), 5.29 and 5.05(2 x d, 2 x 1H, CH=CH_2), 4.47 and 3.44(2 x m,

2 x 1H, NCH_2), and 2.98(m, 2H, $ArCH_2$); m/z(%) 261(M^+, 35), 234(100) and 232(16); ν_{max} 3045, 2990, 2950, 2910, 1680, 1455, 1440, 1393, 1285, 928 and 765 cm^{-1}. The mother liquors afforded 13-methyl-8-oxoprotoberberine (27) whose spectroscopic data accorded with literature.[21]

N-Benzyl-1-oxo-3-propenylidene-2,5-dihydroisoindole (35). Prepared from (34) by the general method with a reaction time of 7 h. The *product* (34%) was obtained as a colourless solid by preparative t.l.c. (silica) eluting with 1:4 v/v ether-petroleum ether, m.p. 123-125°C. Accurate mass 261.1156. $C_{18}H_{15}NO$ requires 261.1154. δ 7.93-7.13(m, 10H, ArH and C<u>H</u>=CH_2), 6.05(d, 1H, J 11.5Hz, C=CH), 5.38-5.28(m, 2H, CH=C<u>H</u>$_2$), and 5.05(s, 2H, NCH_2); m/z(%) 261(M^+, 4), 237(100), 105(18), 104(32), 91(19), and 77(20).

6-Endo-Trig Cyclisations.

2,3-Dimethoxy-8-oxoprotoberberine(29a). Cyclisation of (28a) was carried out in DMF at 100°C for 4 h without addition of tetraethylammonium chloride. Work up afforded the *product* (51%) as colourless needles (MeOH), m.p. 187-188°C(lit.[27] 187-190°C); δ 8.43(d, 1H, ArH), 7.61-7.43(m, 3H, ArH), 7.27 and 6.88(2 x s, 2 x 1H, ArH), 6.75(s, 1H, C=CH), 4.37(t, 2H, NCH_2), 3.99 and 3.94(2 x s, 2 x 3H, OMe), and 2.94(t, 2H, $ArCH_2$).

2,3-Methylenedioxy-8-oxoprotoberberine(29b). Prepared by the general procedure but using 15 mol % $Pd(OAc)_2$ and 30 mol % PPh_3 together with a reaction time of 14 h. The *product* (43.5%) crystallised as pale yellow needles from ethanol, m.p. 176-178°C(lit.[27] 183-184°C). δ 8.44(d, 1H, ArH), 7.54(m, 3H, ArH), 6.85 and 6.73(2 x s, 2 x 1H, ArH), 6.02(s, 2H, OCH_2O), 4.35(t, 2H, NCH_2) and 2.91(t, 2H, $ArCH_2$).

2,3-Methylenedioxy-8-oxo-9,10-dimethoxyprotoberberine(29c). The aryl iodide (28c) was dissolved in dry DMF(20 ml) and added over 45 min. to the stirred catalyst mixture in DMF(20 ml) at 100°C. The mixture was then stirred at room temperature for a further 4 h. before working up in the usual way. The *product* (55%) crystallised from chloroform-ether as plates, m.p. 238-240°C (lit.[28] 240-241°C). δ 7.3(m, 3H, ArH), 6.7 and 6.72(2 x s, 2 x 1H, ArH), 6.01(s, 2H, OCH_2O), 4.29(t, 2H, NCH_2), 3.95 and 4.01(2 x s, 2 x 3H, OMe), and 2.89(t, 2H, $ArCH_2$).

2,3,9,10-Tetramethoxy-8-oxoprotoberberine(29d). Prepared by the standard procedure with a reaction time of 24 h. The *product* (38%) crystallised from methanol as needles, m.p. 183-184°C(lit.[29] m.p. 183°C). δ 7.32, 7.31, 7.23, 6.76 and 6.73(5 x s, 5 x 1H, ArH + C=CH); 4.32(t, 2H, NCH_2), 4.02, 3.99, 3.95 and 3.94(4 x s, 4 x 3H, OMe), and 2.89(t, 2H, $ArCH_2$).

8,13-Dihydrobenzo[g]indolo[2,3-a]quinolizin-5(7H)-one(31). Prepared from (30) by the general procedure with a reaction time of 24 h. The *product* (32%) crystallised from methanol as pale yellow prisms, m.p. 299-300°C (lit.[25] m.p. 299°C). δ(1:1 $CDCl_3$ - pyridine d_5) 7.6-7.11(m, 8H, ArH), 6.87(s, 1H, C=CH), 4.55(t, 2H, NCH_2), and 3.14(t, 2H, $ArCH_2$).

5,11-Dihydro-5-oxo-11,11-dimethylindolo[1,2-b]isoquinoline(33). Prepared from (32) by the standard procudure with a reaction time of 12 h. The *product* (62%) crystallised from ether-petroleum ether as orange plates, m.p. 99-101°C(Found: C, 82.25; H, 5.75; N, 5.15. $C_{18}H_{15}NO$ requires C, 82.75; H, 5.8; N, 5.35%); δ 8.79-7.2(m, 8H, ArH), 6.59(s, 1H, C=CH), and 1.55(s, 6H, 2 x Me); m/z(%) 281(M^+, 6),

247(18), 246(100), 217(10) and 91(15); ν_{max} 1660, 1640, 1600, 1480 and 1350 cm^{-1}.

6-Exo-Trig Cyclisations.

Methyl 5-benzyl-6-oxo-3,4,4a,5,6,10b-hexahydrophenanthridine-4-carboxylate(37) and methyl 5-benzyl-6-oxo-2,3,4,4a,5,6-hexahydrophenanthridine-4-carboxylate(38). Prepared from (36) by the general procedure with a reaction time of 3 h. The *product* (78%) comprised a 1.8:1 mixture (p.m.r.) of (37) and (38). The mixture was separated by flash chromatography (silica) eluting with 1:1 v/v ether - petroleum ether.

(37). Colourless prisms from methylene chloride-petroleum ether, m.p. 105-107°C(Found: C, 76.0; H, 6.2; N, 4.45. $C_{22}H_{21}NO_3$ requires C, 76.05; H, 6.1; N, 4.05%); δ 8.10(dd, 1H, ArH), 7.48-7.22(m, 8H, ArH), 6.19 and 5.95(2 x m, 2 x 1H, CH=CH), 5.73 and 4.11(2 x d, 2 x 1H, NCH_2), 3.87(m, 2H, 4a-H and 10b-H), 3.0(t, 1H, C<u>H</u>CO_2Me), 2.93(s, 3H, OMe), and 2.52 and 2.18(dd and m, 2 x 1H, CH_2); m/z(%) 347(M^+, 69), 288(6), 274(15), and 91(100); ν_{max} (nujol) 1730, 1630, 1600, and 1575 cm^{-1}.

(38) Colourless prisms from methanol, m.p. 125-127°C(Found: C, 75.8; H, 6.3; N, 3.95 %); δ 8.08(dd, 1H, ArH), 7.39 and 7.31(2 x m, 2 x 1H, ArH), 7.19-7.08(m, 6H, ArH), 7.0(t, 1H, J3.7 Hz, C=CH), 4.93, 4.90 and 4.54(3 x d, 3 x 1H, NCH_2 and NCH), 3.48(s, 3H, OMe), 2.71(m, 1H, C<u>H</u> CO_2Me), and 2.23, 2.05, 1.85 and 1.62(4 x m, 4 x 1H, CH_2CH_2); m/z(%) 347(M^+, 100), 256(18), 243(20), 242(48), 211(64), 210(45), 165(27), 106(54) and 91(94); $\nu_{max}(CHCl_3)$ 1710, 1640, 1600, and 1580 cm^{-1}.

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17. This work was completed before the efficacy of silver salts in suppressing isomerisation was apparent.
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