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NEW ANTIOXIDANTS INCORPORATING INDOLE AND INDOLINE CHROMOPHORES

DAVID W BROWN[a], PAUL R GRAUPNER[a], *MALCOLM SAINSBURY[a] AND HOWARD G SHERTZER[b]

[a]School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, U K
[b]Department of Environmental Health, University of Cincinnati, 3223, Eden Avenue, Cincinnati, Ohio, 45267-0056, U S A

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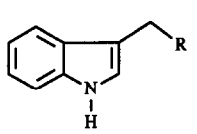
Summary Syntheses of potent antioxidants utilising indenoindole or indenoindoline pharmacophores are described The antioxidant behaviour and the oxidation potentials of these compounds are correlated, and some of their reactions with radicals are noted

Indol-3-ylmethanol (1, R=OH), the nitrile (1, R=CN) and di-(indol-3-yl)methane (1, R=indol-3-yl) originating from vegetable sources are eaten as part of the normal human diet These compounds offer some protection against chemically induced carcinogenesis [1] Certain phenols such as 2,6-di-^{t}butyl-4-methylphenol (BHT) (2) and 2-^{t}butyl-4-methoxyphenol (BHA) (3) protect in the same manner[2,3] and because the last two compounds are antioxidants it seemed possible that the indoles could exert their activity by functioning as radical scavengers For the indoles the disparate nature of the C-3 substituents could be explained if a hydrogen atom were to be abstracted from the methylene bridge In this way the radical so formed would then be stabilised by delocalization with either the electron withdrawing cyanide function of the nitrile (1, R=CN), or with the electron donating indol-3-yl or hydroxyl groups of the di-(indolyl)methane (1, R=indol-3-yl) and the alcohol (1, R=OH) respectively

In order to develop better chemoprotective indoles with lower intrinsic toxicities than the dietary indoles, we have synthesised a number of structurally related compounds (see table) and tested them in a screening model developed by Shertzer[4] to rank antioxidant ability through their inhibition of iron/ascorbate initiated lipid peroxidation in liposomes We note that 3-benzylindoles (4) with electron donating substituents in the 4-position of the benzyl unit shows greater activity than the dietary indoles and 3-(4-*N*,*N*-dimethylaminobenzyl)indole[5] is far superior to α-tocopherol (vitamin

E) (5) and almost as good as BHT in the Shertzer assay Significantly, however, the presence of two methyl groups at the methylene bridge does not impair antioxidant behaviour and 3-(2-methylphenylethyl)indole (6, R=Me) is a better antioxidant than 3-benzylindole (6, R=H) The effect is, however, destroyed by the presence of a carbonyl group at this site and 3-benzoylindole (7) is unresponsive in the iron/ascorbate test



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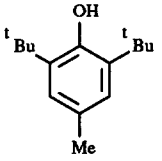

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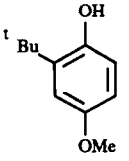

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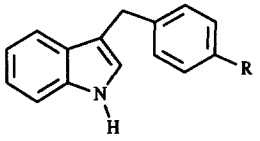

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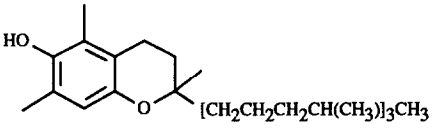

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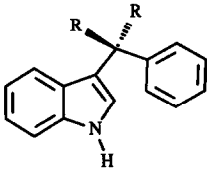

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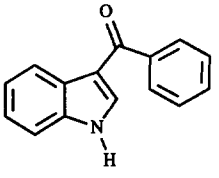

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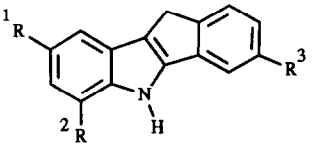

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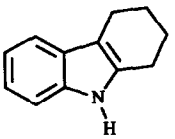
A major increase in activity is demonstrated once the benzylic ring of 3-benzylindole is fused to the indolic system, as in 5,10-dihydroindeno[1,2-*b*]indole (DHII) (8, $^{1}R=^{2}R=^{3}R=H$),[6] and this extra activity is further enhanced by the presence of electron releasing groups in ring A of the tetracycle at sites conjugated with the indolic nitrogen atom Indeed 8-methoxy-DHII (8, $^{1}R=OMe, R^{2}=R^{3}=H$) is a superior antioxidant in this test to BHT

1,2,3,4-Tetrahydrocarbazole (9), 1,2,3,4-tetrahydropent[*b*]indole (10),[7] and indeno[2,1-*b*]indole (iso-DHII, 11)[8] all show relatively good antioxidant properties, and in the assay the iso-DHII is as effective as DHII (see the table)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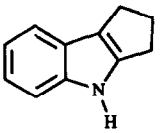
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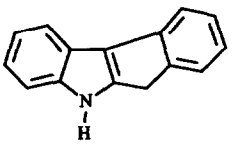
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We observed that there is some correlation between the activity of the early entries in the table in the iron/ascorbate assay and their first ionisation potential as measured by cyclic voltammetry, this caused us to consider 4b,5,9b,10-tetrahydroindenoindoles (THIIs) (12) as potential antioxidants Such compounds, which have the *cisoid* geometry shown, contain an indoline rather than an indole chromophore and would be expected to be more easily oxidised This is the case and the ionisation potential of THII itself (12, $^{1}R=^{2}R=^{3}R=H$) is +0 67 volts (versus S C E) compared with +0 74 volts for DHII THII exhibits a high efficiency in the iron/ascorbate test with a IC_{50} value 0 14μM This is further improved by the substitution of electron donating groups in ring A For example, 6,8-dimethyl-THII (12, $^{1}R=^{2}R=Me,^{3}R=H$), which is oxidised at +0 46 volts, has a iron/ascorbate rating of 0 05μM, which is only bettered by the commercially available, but toxic, substance ethoxyquin (13)(IC_{50} 0 03μM) Thus, certain THII derivatives are remarkably effective antioxidants which in the iron-ascorbate assay show activity levels as low as any of the known antioxidants Furthermore, in mammals the THII compounds appear to be non-toxic and have a protective effect against a variety of hepatopathogenic chemicals [9]

An ethanol solution of THII exposed to sunlight becomes coloured, and when THII in various solvents is treated with radicals coloured solutions form which exhibit weak poorly resolved e s r signals The colour and the e s r signals persist over many weeks We have also demonstrated that THII inhibits the autoxidation of cumene Thus after a week, the ^{1}H n m r spectrum of a solution of cumene (1 mol eq), containing THII (1 mol eq) and AIBN (0 1 mol eq) in deuteriochloroform sealed under an atmosphere of oxygen showed no resonances due to cumene hydroperoxide, but some conversion (less than 5%) of THII into DHII was observed The colour of the solution changed from colourless to dark red during the course of the experiment When the experiment is repeated and THII is omitted cumene hydroperoxide is progressively formed and, after 20h, the relative integral height of the singlet resonance of the hydroperoxide methyl protons indicates that a 8-10% conversion has taken place The oxidation product of DHII might be thought to be dibenz[*b,f*,-1]azapentalene (14), however, this antiaromatic compound has never been observed [10] We note that when DHII is treated with dimethylamino radical cations, in the presence of sulphuric acid the colourless dehydrodimer (15) is formed, but in only 20% yield In order to define more closely the behaviour of THII and its analogues we have examined their electroxidation The parent compound THII undergoes a rapid e c e process leading in part to DHII However, the initial oxidative event is rapidly followed by another two electron oxidation step On a preparative scale these two oxidative steps cannot be differentiated and a dark green intractable resin is formed as the overall product This material exhibits a broad e s r signal which is still observable after the material has been stored for many weeks

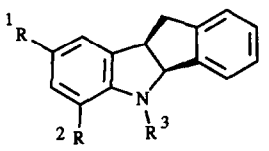
Table *Correlation between iron-ascorbate data and ionisation potential*

Compound	$IC_{50}\mu M$	Ox Pot(vs S C E)
Indol-3-ylacetonitrile	>1250	-
Indole	800	-
Indol-3-ylmethanol	300	-
3-Benzylindole	36	1 06
3-(4-Methoxybenzyl)indole	24	1 07
3-(1-Methyl-1-phenylethyl)indole	18	1.02
Di(indol-3-yl)methane	15	1 03
3-(4-Hydroxybenzyl)indole	12	1 01
3-(2,4,6-Trimethylbenzyl)indole	11	1 00
α-Tocopherol	10	1 00
Tetrahydrocarbazole	8 5	-
5-Methyl-DHII	8 5	-
6-Chloro-DHII	7 0	1 08
1,2,3,4-Tetrahydrocyclopent[*b*]indole	4 6	-
8-Fluoro-DHII	2 5	1 04
8-Methyl-DHII	2 0	0 63
DHII	1 5	0 62
iso-DHII	1 5	0 98
3-(4-Dimethylaminobenzyl)indole	1 5	0 65
BHT	1 2	1 56
10,10-Dimethyl-DHII	0 9	0 77
6,8-Dimethyl-DHII	0 8	0 65
8-Methoxy-DHII	0 7	0 65
1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]indole	0 23	-
THII	0 14	0 67
iso-THII	0 13	0 89
10,10-Dimethyl-THII	0 13	0 68
8-Methoxy-5-methyl-THII	0 12	0 40
4b,9b-Dimethyl-THII	0 07	0 71
8-Methoxy-THII	0 06	0 46
6,8-Dimethyl-THII	0 05	0 57
Ethoxquin (santoquin)	0 03	-

It seems probable that the initial site of electron loss is from the pi system of the indoline unit and to prevent the formation of DHII from THII we have synthesised the 4b,9b-dimethyl-THII derivative (16, $^1R=^2R=^3R=H$) The cyclic voltammogram of this compound now exhibits a partial redox couple and this becomes a perfect couple when further methyl groups are present at N-5, C-6 and C-8 s as in

compound (16, $^1R=^2R=^3R=Me$), indicating that the radical cation (17, $^1R=^2R=^3R=Me$) survives the timescale of the experiment, typically 6-20 seconds.

Interestingly, for the THII (12, $^1R=Et_2N, ^2R=H, ^3R=Et$) the oxidation potential is so low (+0 14 volts) that the compound is oxidised merely by passage through a silica gel column, and the product is a mixture of the THII and its radical cation, which appear to be in equilibrium The lifetime of the radical cation is at least several days, but further oxidation then leads to second product which is presumably the dication (18) Similar behaviour has been noted for 1,4-di-(*N,N*-dimethylamino)benzene (19) which on oxidation affords a stable radical cation known as Wurster's blue [11]



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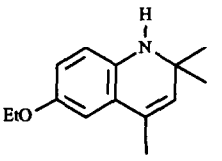

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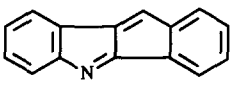

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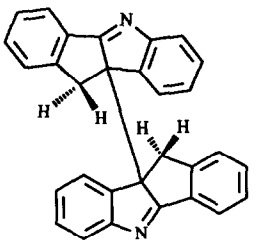

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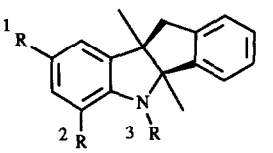

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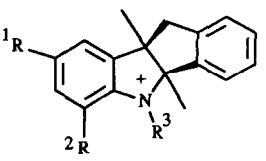

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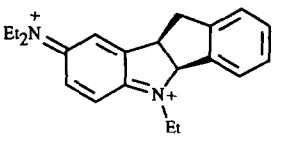

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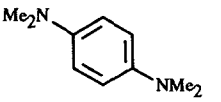


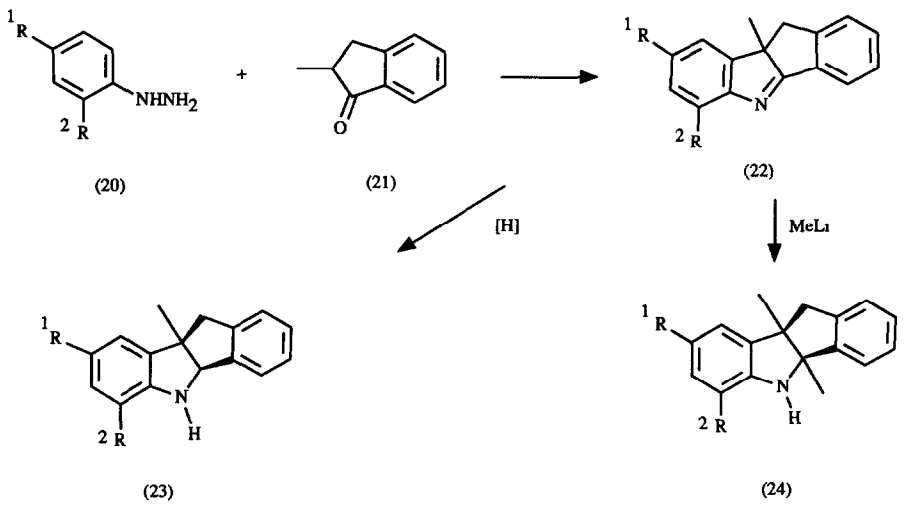
(19)

DHII and its derivatives were normally prepared by Fischer indolisation reactions using the appropriate phenylhydrazine hydrochloride and indanone [12] Most frequently, heating these reagents in ethanol containing 2-5% concentrated hydrochloric acid (by vol.) for up to 4h was sufficient to provide acceptable yields of the tetracycles. In some cases the phenylhydrazines were used and now

the reactions were conveniently carried out by heating the reagents in glacial acetic acid, or under Dean Stark conditions, isolating the intermediate hydrazone, and effecting ring closure in a separate step through the agency of phosphorus oxychloride, polyphosphoric ester or a Lewis acid In some instances the hydrazone was ring closed simply by adsorption onto silica gel and heating the material at 140°C The tetracycle was then eluted from the silica Reduction of the DHIIs to the corresponding THII derivatives was effected by reduction with either sodium cyanoborohydride in glacial acetic acid,[13] triethylsilane, or morpholino borane Catalytic hydrogenation was not effective Care had to be exercised during reductions with sodium cyanoborohydride for if the temperature of the reaction was allowed to rise above 18°C significant amounts of *N*-boranyl-, or *N*-ethyl- THIIs were formed

4b-Methyl-THIIs were synthesised by a method developed by Katritzky and Sengupta[14] for the methylation of indolines thus the THII was reacted with ^{n}butyllithium and then with carbon dioxide The product lithium carbamate was not isolated, but reacted further with ^{t}butyllithium-potassium ^{t}butoxide and then with methyl iodide

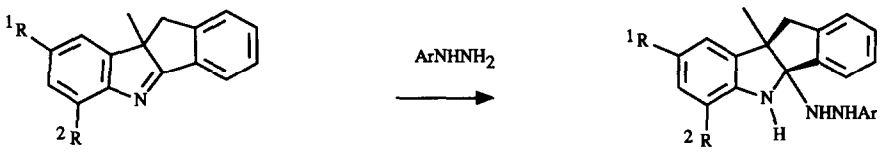
9b-MethylTHIIs (23) were obtained through the Fischer indolisation of 2-methylindanones (21), followed by sodium borohydride reduction of the intermediate indolinenes (22), and 4b,9b-dimethyl analogues (24) were formed from the indolinenes by reaction with methyllithium (scheme 1)



SCHEME 1 *Indolisations of 2-methylindanone*

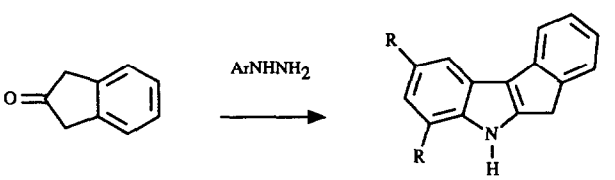
On two occasions phenylhydrazones were heated in diethylene glycol solution at reflux[15] in attempts to effect thermal cyclisations In one such example the phenylhydrazone of 2-methylindanone afforded a complex mixture of products from which 4b,5,9b,10-tetrahydro-9b-methylindeno[1,2-*b*]indole (23, ^{1}R=^{2}R=H) was isolated (28%), the source of the hydride ion equivalent necessary to convert the anticipated product (22, ^{1}R=^{2}R=H) into this compound is unknown We note, however, that indolinenes of this type are prone to nucleophilic attack,[12] and if

excess phenylhydrazine was used in the formation of the indolinene (25) from 2-methylindanone the adduct (26) was produced In the other example, the hydrazone of 6-acetamidoindanone, when heated, gave the indenoindole (8, $^{1}R=^{2}R=H,R^{3}=NHCOMe$) in 53% yield, compared to a 20% yield using polyphosphoric ester as the acidic "catalyst" in a Fischer indolisation reaction



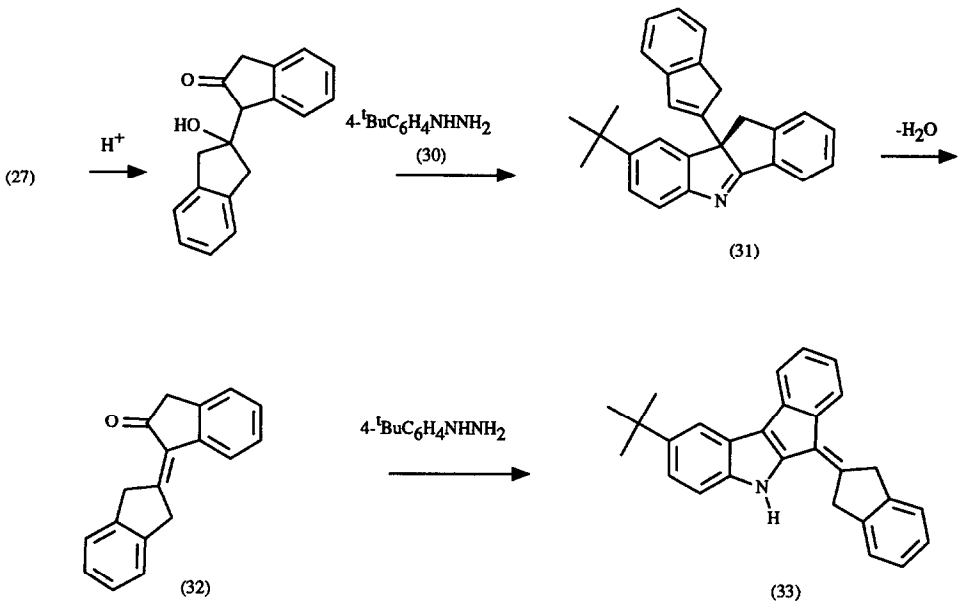
(25) (26)

Iso-DHIIs (28) were sometimes prepared through the Fischer indolisation of indan-2-ones,[8] however, yields were inferior to those from indan-1-ones One reason for this is the propensity of the indanone (27) to undergo acid catalysed aldolisation This problem was first detected during a reaction with indan-2-one and 4-^{t}butylphenylhydrazine (30) In addition to the required DHII (28, R=^{t}Bu,R=H) the 9b-inden-2-ylindolinene (31) was obtained If the enone (32) was preformed, reaction with 4-^{t}butylphenylhydrazine led to the isomer (33) as the only compound isolated (31%) This suggests that in the first reaction the substrate is indeed the aldol compound (28), and that the regioselectivity of the reaction is determined by the retention of the tertiary hydroxyl group until after the heterocyclic ring is formed

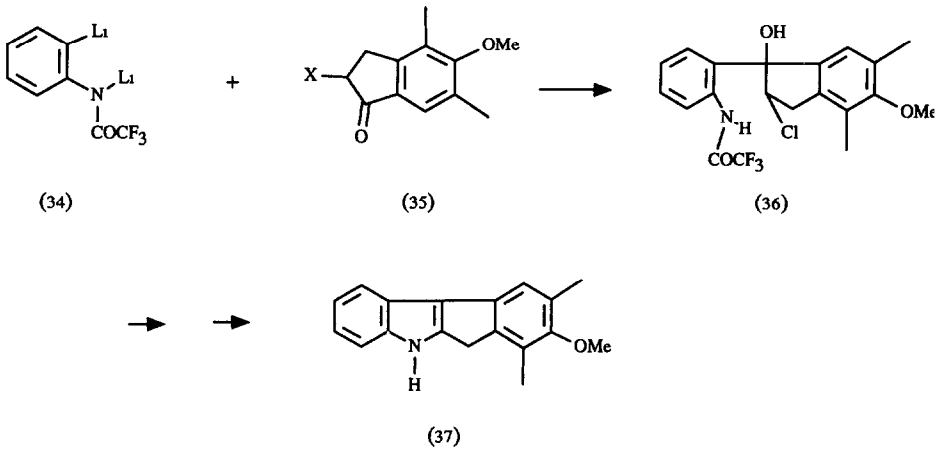


(27) (28)

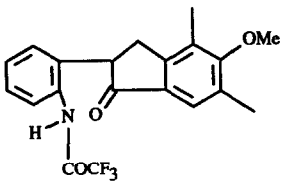
As an alternative route to the iso-DHII series of compounds, we investigated the Wender synthesis of indoles [16] Thus, 2,4-dimethyl-3-methoxy-iso-DHII (37) was prepared by reacting the dilithio derivative (34) of 2-bromo-*N*-trifluoroacetylaniline with the 2-chloroindanone (35, X=Cl) An intermediate in this preparation is the hydroxyphenylindane (36), which cyclised to the iso-DHII when it was treated with potassium ^{t}butoxide, followed by an aqueous work up procedure However, if the bromoindanone (35, X=Br) was reacted with the dilithio compound the regioselectivity of the first nucleophilic attack was altered to give the indanone (38) as the reaction product Obviously the use of the bromoindanone allows an alternative approach to the DHII compounds, and indeed a small amount of the 1,3-dimethyl-2-methoxy-DHII (39)[17] was isolated from the reaction mixture in this case



SCHEME 2 *Indolisation of 2-indanone*



SCHEME 3 *Modified Wender synthesis of indeno- and iso-indenoindoles*



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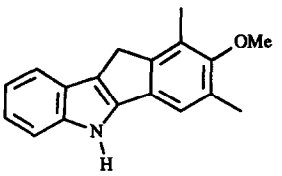

(39)

We expected the modified Wender procedure to provide a general route to both DHIIs and iso-DHIIs, however, the presence of an electron donating group at C-5 in the bromoindanone seems to be important When it is absent the reaction fails, trifluoroacetanilide is returned and products resulting from an aldolisation reaction between two molecules of the bromoindanone are formed

EXPERIMENTAL

Petrol refers to petroleum ether b p 60-80°C, it and all other solvents were distilled prior to use and where necessary dried and purified by standard methods Medium pressure (flash) column chromatography was used in general for the purification of reaction mixtures "Silica gel" refers to Amicon 84072 silica gel (230-400 mesh), or Merck 9385 silica gel Thin layer chromatography (t.l c) was performed on aluminium plates coated with Kieselgel 600 F_{254} Electronic spectra were recorded in 95% ethanol solution with a Perkin Lambda 3 spectrometer, infra red spectra were recorded using a Perkin Elmer 938G instrument and n m r spectra were obtained with either JEOL GX FT 400 or 270 instruments, or with a Bruker AM 200 spectrometer Mass spectra were measured with a VG 7070E spectrometer linked to a 2000 data system

Cyclic voltametric data were recorded with a EG&G 362 Scanning Potentiostat and Condecon^{TM}300 software Anodic potentials were measured for solutions in acetonitrile containing 5% sodium perchlorate as supporting electrolyte at a platinum bead electrode versus S C E as reference

3-(1-Methyl-1-phenylethyl)indole

3-Methyl-3-phenylbutanal (from 3-methyl-3-phenylbutanoic acid[18]) (490mg), phenylhydrazine hydrochloride (460mg) and ethanol (10cm^3) were stirred under nitrogen atmosphere at room temperature and triethylamine (0 4cm^3) added The solvent was then removed and the residue heated at reflux with polyphosphoric ester in chloroform (16cm^3,20% w/v) for 5min The solvent was removed and the residue stirred with water (30cm^3), after 3h, the reaction mixture was extracted with diethyl ether (3x20cm^3) The combined ether extracts were washed with water (10cm^3), dried and evaporated to yield a pale yellow gum This was chromatographed on silica eluting with 5% ethyl acetate in petrol to give the title compound as a gum (560mg, 80%) [Found C, 86 7, H, 7 1, N, 5 9 $C_{17}H_{17}N$ requires C, 86 7, H, 7 3, N, 5 95].

*5,10-Dihydroindeno[1,2-*b*]indole* (DHII) (8, ^{1}R=^{2}R=^{3}R=H)

A mixture of 1-indanone (13.2g, 0.1mol), and phenylhydrazine hydrochloride (14.5g, 0.1 mmol), was heated in glacial acetic acid (150cm^3). As the temperature of the solution approached reflux, the hydrazine hydrochloride dissolved. Soon after, a brown solid precipitated out of solution. The heat was immediately removed, and the reaction mixture allowed to cool. The solid was filtered off, washed with water, and allowed to dry on a sinter, it was then redissolved in hot ethanol (150cm^3) and the solution filtered. On cooling the title compound crystallised as beige prisms, it was collected, washed with cold ethanol (150cm^3), and dried in a vacuum oven (18.5g, 90%), m.p. 258-9°C (dec.) (chloroform) (lit.,[19] 245°C [dec]); υ_{max}(Nujol) 3400 cm^{-1}; δ_H(DMSO-d_6) 3.67 (2H, s), 7.07 (1H, ddd), 7.14 (1H, ddd), 7.20 (1H, ddd), 7.36 (1H, dd), 7.51 (1H, d), 7.52 (1H, d), 7.57 (1H, d), 7.67 (1H, d), 11.6 (1H, br). δ_C(DMSO-d_6): 30.0 (t), 112.6 (d), 117.9 (d) 118.7 (d), 119.5 (d), 120.0 (s), 121.2 (d), 124.3 (s), 124.7 (d), 125.6 (d), 126.8 (d), 135.3 (s), 140.9 (s), 143.7 (s), 147.8 (s); *m/z* (%) 205 (100 M), 204 (73), 102 (33), 103 (20), 206 (16) [Found: C, 87.8; H, 5.35; N, 6.85 calc. for $C_{15}H_{11}N$: C, 87.8; H, 5.4; N, 6.8%].

*5,10-Dihydro-5-methylindeno[1,2-*b*]indole* (5-Methyl-DHII)

Sodium hydride (375mg, 15.6mmol) was added to DMSO (13cm^3) under an atmosphere of nitrogen, and the solution then heated to 70°C until no more gas evolved. The solution was cooled to room temperature and 5,10-dihydroindeno[1,2-*b*]indole (2.7g, 13.1mmol) dissolved in the minimum amount of DMSO was added. After stirring at room temperature for 1 h, dimethyl sulphate (1.5cm^3, 15mmol) was introduced, and the stirring continued for a further 1 h. Water (3cm^3) was cautiously added, and the reaction then poured into ice/water. The solid thus formed was collected, washed with water, dried on the water pump, and then washed with petrol. Crystallisation from ethanol yielded colourless needles (1.5g 53%), m.p. 152°C (lit.,[20] 153.5°C) [Found: C, 87.5; H, 6.0; N, 6.4 calc. for $C_{16}H_{13}N$: C, 87.65; H, 5.95; N, 6.4%]

*5,10-Dihydro-10-methylindeno[1,2-*b*]indole* (10-Methyl-DHII)

3-Methyl-1-indanone (500mg, 3.42mmol) and phenylhydrazine (0.35cm^3, 3.5mmol), were heated to reflux in glacial acetic acid (20cm^3). After 2 minutes, conc. hydrochloric acid (1cm^3) was added *via* the reflux condensor. Boiling was continued for 75 minutes, and then the reaction was cooled. The solution was poured into ice/water, and extracted into ethyl acetate. The combined extracts were washed with brine and then with water, and dried ($MgSO_4$). Evaporation of solvent *in vacuo*, and column chromatography of the residue (10% EtOAc/petrol) yielded a cream solid [R_F (30% EtOAc/petrol) 0.7], (320mg, 43%) m.p. 153-155°C (from $CHCl_3$); $\lambda_{max}(\epsilon)$ (EtOH) 246 (18,700), 324.5 (20,100)nm; υ_{max}(Nujol) 3420cm^{-1}; δ_H(DMSO-d_6) 1.50 (3H, d, *J*=7.3Hz), 3.85 (1H, q, *J*=7.3Hz), 7.0-7.6 (8H, m), 11.55 (1H, s); δ_C(DMSO-d_6) 17.8 (q), 36.8 (d), 112.5, 117.8, 118.4, 119.4, 121.0, 124.3, 125.9, 126.8 (d), 123.9, 125.8, 134.4, 140.8, 142.1, 153.5 (s); *m/z* (%) 204 (100), 219 (52, M) [Found: C, 87.6; H, 5.9; N, 6.2 $C_{16}H_{13}N$ requires: C, 87.6; H, 6.0; N, 6.4%].

*8-Fluoro-5,10-dihydroindeno[1,2-*b*]indole* (8-Fluoro-DHII) (8, ^{1}R=F;^{2}R=^{3}R=H)

A mixture of 4-fluorophenylhydrazine hydrochloride (1.8g, 11.25 mM) and 1-indanone (1.5 g) in ethanol (20 cm^3) was heated to reflux, and concentrated hydrochloric acid (1cm^3) added. Heating

was continued for 5 h, and then the reaction mixture was cooled The product which crystallised from the cold solution as coloured platelets, was collected by filtration and dried (1 9g, 75%), m p 225-227°C (ethyl acetate/petrol), υ_{max}3400cm^{-1}, δ_H 8 3 (1H, br s), 7 6-6 9 (7H, m), 3.70 (2H, s), *m/z* (%) 223 (100 M), 222 (85), 111 (18) [Found C, 80 5, H, 4 6, N, 6 2 $C_{15}H_{10}NF$ requires· C, 80 7, H, 4 5, N, 6 3%]

5,10-Dihydro-8-methoxyindeno[1,2-b]indole (8-Methoxy-DHII) (8, ^{1}R=OMe,^{2}R=^{3}R=H)

To a stirred solution of *p*-methoxyphenylhydrazine hydrochloride (3 5g, 20mmol), and 1-indanone (2 35g, 20mmol) in absolute ethanol (80cm^3), was added dropwise triethylamine (2 01cm^3, 20mmol) Stirring was continued until the t l c analysis of the reaction mixture indicated that no starting materials remained (about 1 h) The solvent was removed, and the yellow residue heated at reflux in a solution of polyphosphoric ester in chloroform (made by boiling phosphorus pentoxide (50g) in chloroform (100cm^3) and ether (50cm^3) for 12 h) After 1 h, the solvent was removed, and the black residue stirred in water (200cm^3) This mixture was extracted 3 times with diethylether, the combined organic phases were washed with water, and dried ($MgSO_4$) Removal of the solvent yielded a beige solid, which was crystallised from ethyl acetate/petrol to give platelets (3 8g, 78%), m p 207°C (lit ,[21] 206°C) [Found C, 81 4, H, 5 6, N, 5 8 calc for $C_{16}H_{13}NO$ C, 81 6, H, 5 6, N, 5 95%]

6-Chloro-5,10-dihydroindeno[1,2-b]indole (6-Chloro-DHII) (8, ^{1}R=^{3}R=H,^{2}R=Cl)

The *o*-chlorophenylhydrazone of 1-indanone (650mg, 2 5mmol) was heated at reflux in a chloroform solution of polyphosphonate ester for 30 minutes The solvent was removed, and the residue stirred in water (75cm^3) for 1 h Extraction into diethylether gave a green solution which was washed with water, dried ($MgSO_4$), and evaporated Purification by column chromatography (R_F 5% EtOAc/petrol 0.5), yielded a colourless solid (500mg, 82%), m p 139°C, υ_{max}(Nujol) 3460cm^{-1}, δ_H($CDCl_3$) 3 72 (2H, s), 7 0-7 6 (7H, m), 8 5 (1H, br), δ_C($CDCl_3$) 30 3 (t), 117 5, 117 7, 120.8, 120 9, 125 2, 125 5, 126 7 (d) 117 0, 122 4, 126 1, 134 5, 137 5, 143 8, 147 7 (s), *m/z* (%) 239 (100, M), 204 (57), 238 (42), 241 (36), 240 (29), 102 (25), 203 (21) [Found C, 75 3, H, 5 6, N, 4 3 $C_{15}H_{10}ClN$ requires C, 75 2, H, 5 8, N, 4 2%)

5,10-Dihydro-6,8-dimethylindeno[1,2-b]indole (6,8-Dimethyl-DHII) (8, ^{1}R=^{2}R=Me,^{3}R=H)

A solution of 2,4-dimethylhydrazine hydrochloride (1 27g, 7 35mmol), and 1-indanone (1g, 1 1eq), in glacial acetic acid (15cm^3), was heated to reflux for 30 minutes The reaction was cooled, and poured into ice/water (200cm^3) This solution was saturated with salt, and extracted into diethylether The ethereal solution was dried ($MgSO_4$), and evaporated *in vacuo* The excess acetic acid was removed by azeotropic distillation *in vacuo* with toluene and petrol (60-80°C), to leave a dark coloured solid The product was purified first by "suction flash" chromatography, and then crystallisation from petrol to yield a colourless solid (R_f [30% EtOAc/petrol] 0 8), (0 53g, 31%), m p 182°C [Found· C, 87 4; H, 6 35, N, 5 9 $C_{17}H_{15}N$ requires C, 87 5, H, 6 5, N, 6 0%]

5,10-Dihydro-10,10-dimethylindeno[1,2-b]indole (10,10-Dimethyl-DHII)

A solution of 3,3-dimethyl-1-indanone[22] (20 0g, 0 125mol) and phenylhydrazine (12 3cm^3, 0 125mol) in glacial acetic acid (200cm^3) was heated to reflux Concentrated hydrochloric acid (10cm^3) was added *via* the condensor, and the heating continued for a further 2 h The solution was allowed to cool, and then poured into water (500cm^3) The aqueous phase was extracted with diethylether (3x50cm^3), the combined extracts were washed with brine and water, and then dried ($MgSO_4$) The solvent was removed, and petrol added to the residue The suspension was heated until boiling, the solid remaining was discarded, and the mother liquor concentrated. On cooling, the title compound crystallised out as colourless needles Further concentration of the mother liquor, and recrystallisation of the product afforded the title compound (10 2g, 35%), m p 160°C, υ_{max}(Nujol) 3410cm^{-1}, δ_H($CDCl_3$) 1 60 (6H, s), 7 1-7 7 (8H, m), 8 16 (1H, s), δ_C($CDCl_3$) 25 8 (q), 43 2 (s), 112 1, 117 4, 118 4, 120 0, 121 5, 122 4, 125 2, 126 5 (d), 123.6, 131 7, 133 0, 139 9, 140.7, 158 6 (s), *m/z* (%) 218 (100), 233 (46, M), 217 (31), 108 5 (18), 219 (16), 109 (15) [Found C, 87 5, H, 6 4, N, 5 85 $C_{17}H_{15}N$ requires· C, 87 5, H, 6 5, N, 6 0%]

9b,9b'-Bis-(10H-indeno[1,2-b]indole (15)

5,10-Dihydroindeno[1,2-*b*]indole (1 02g, 5 0mmol) was added to a mixture of glacial acetic acid (50cm^3), sulphuric acid (98%, 150cm^3), and chlorodimethylamine (0 33g, 1eq), at 0°C The solution was stirred, and iron(II)sulphate heptahydrate (0 34g, 0 25eq) added portionwise Stirring was continued for 30 minutes, and then the reaction was poured onto ice/water (150cm^3) The solution was neutralised (NaOH), causing a white solid to precipitate This was collected by vacuum filtration, and washed with water Column chromatography of this product (20% EtOAc/petrol) yielded a colourless solid which was shown to be 9b,9b'-bis-(10*H*-indeno[1,2-*b*]indole), (205mg, 20%) m p >280°C (softens at *ca* 220°C), υ_{max}(Nujol) 1620-1580cm^{-1}, λ_{max}(EtOH) (ϵ) 240 (33,190), 248 (34,720), 287 (24,510) 315 (27,060), δ_H(DMSO-d_6) 2 72 (2H, d, *J*=17 6Hz), 3 46 (2H, d, *J*=17.6Hz), 6.8-8 1 (16H, m), *m/z* (%) 408 (100 M), 409 (30), 407 (29), 204 (19) [Found C, 88 3, H, 5 15, N, 6 72 $C_{30}H_{20}N_2$ requires C, 88 2, H, 4 95, N, 6 86%]

cis-*4b,5,9b,10-Tetrahydroindeno[1,2-b]indole* (THII) (12, ^{1}R=^{2}R=^{3}R=H)

To a suspension of 5,10-dihydroindeno[1,2-*b*]indole (19 16g, 93mmol) in glacial acetic acid (300cm^3) was added sodium cyanoborohydride (24g, 400mmol) in small portions over 0 5h The mixture was stirred for 3 h, until all the material had dissolved The solution was poured into ice/water (500cm^3) and stirred for 1 h to break down the borohydride complex The clear solution was carefully neutralised with sodium hydroxide causing a white precipitate to form This was collected and washed with water until the washings were free from cyanide ion After drying the title compound was obtained a colourless prisms (19g, 98%), m p 107°C (ethyl acetate/petrol), λ_{max}(EtOH) 243, 297nm, υ_{max}($CHCl_3$) 3740, 1600cm^{-1}, δ_H($CDCl_3$) 3 20 (1H, dd, *J*=16 3, 2 0Hz), 3 51 (1H, dd, *J*=16 3, 8 4Hz), 3 99 (1H, br), 4 18 (1H, ddd, *J*=8 4, 8 4, 2 0Hz), 5 25 (1H, d, *J*=8 4Hz), 6 60 (1H, d, *J*=7 8Hz), 6 74 (1H, dd, *J*=7 4Hz), 6 99 (1H, dd, *J*=7 6Hz), 7 15-7 22 (4H, m), 7 32 (1H, d, *J*=7 5Hz), δ_C($CDCl_3$) 39 1 (t), 45 7 (d), 67 3 (d), 110 3, 119 3, 123 8, 124 4, 125 0, 126 9, 127 7, 127 9 (d), 132 8, 142 3, 143 9, 149 7 (s), *m/z* (%) 207 (100, M), 206 (65), 208 (16), 102 5 (9) [Found C, 86 5, H, 6 25, N, 6 75 $C_{15}H_{13}N$ requires C, 86 9, H, 6 3, N, 6 75%]

cis-*4b,5,9b,10-Tetrahydro-5-methylindeno[1,2-b]indole* (5-Methyl-THII) (12, ^{1}R=^{2}R=H,^{3}R=Me)

A flame dried flask was charged with sodium hydride (60mg, 2 5mmol), and THF (5cm^3) protected under an atmosphere of nitrogen To the stirring suspension was added 4b,5,9b,10-tetrahydroindeno[1,2-*b*]indole (500mg, 2 4mmol) in THF (5cm^3) dropwise The reaction mixture was stirred for 1h, iodomethane (0 2cm^3) was added, and the solution was stirred overnight Water (5cm^3) was introduced and the THF removed *in vacuo* to leave a colourless solid which was dried in a vacuum desiccator This product was redissolved in 5% ethyl acetate/petrol and filtered through a pad of flash silica to yield, after evaporation of the solvent *in vacuo*, the title compound (450mg, 85%) m p 76-77°C (DCM/petrol) (lit ,[23] 79 5-80 0°C), υ_{max}(CHCl$_3$) 1600cm^{-1}, δ_H(CDCl$_3$) 3 0 (3H, s), 3 1 (1H, dd, *J*=16 4, 5 2Hz), 3 4 (1H, dd, *J*=16 3, 9 2Hz), 4 1 (1H, ddd, *J*=8 8, 9 2, 5 2Hz), 4 9 (1H, d, *J*=8 8Hz), 6 4 (1H, d, *J*=7 7Hz), 6 7 (1H, dd, *J*=7 8Hz), 7 1-7 5 (6H, m), δ_C(CDCl$_3$) 33 5 (q), 39 9 (t), 45 6 (d), 75 8 (d), 106 4, 117 3, 124 1, 125 1, 126 6, 128 0, 128 2 (d), 132 8, 142 2, 144 2, 152 0 (s) *m/z* 221 (100%, M), 220 (60), 206 (19), 222 (15) [Found C, 86 9, H, 6 8, N, 6 35 calc for $C_{16}H_{15}N$ C, 86 85, H, 6 8, N, 6 35%]

cis-*5-Ethyl-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* (5-Ethyl-THII) (12, ^{1}R=^{2}R=H;^{3}R=Et)

5,10-Dihydroindeno[1,2-*b*]indole (60 0g, 0 29M) was vigorously stirred in glacial acetic acid (1000cm^3) and to it was added sodium cyanoborohydride (79g, 1 25M) portionwise over 40 min After 3h stirring the reaction mixture was poured onto ice-water (2000cm^3) and the gelatinous solid which formed was separated and stirred with a mixture of ethyl acetate (75cm^3) and water (100cm^3) A colourless solid remained this was found to be unreacted starting material (19 0g) The original filtrate was extracted with ethyl acetate (2x75cm^3) and the combined organic phases dried and evaporated The residue was then partly dissolved in a mixture of petrol (20cm^3) and ethyl acetate (40cm^3) The residual solid was removed and shown to be impure starting material (2 5g) The filtrate was extracted with 2M hydrochloric acid (8x25cm^3) and the combined acid extracts were washed with ethyl acetate (2x15cm^3), prior to basification with 0 89 ammonia The oil which separated was extracted into ethyl acetate (6x25cm^3) and the combined organic layers were then dried and evaporated to give the title compound as a colourless oil (34g, 75% corrected for unreacted starting material), υ_{max} 3080-3010, 2960, 1595cm^{-1}, δ_H 1 20 (3H, t, *J*=7 0Hz), 3 05(1H, dd, *J*=16 5 and 5 0Hz), 3 38(2H, q, *J*=7 0Hz), 3 40(1, dd, *J*= 16 5 and 9 0Hz), 4 12(1H, ddd, *J*=9 0,5 0 and 5 0Hz), 5 11 (1H, d, *J*=9 0Hz), 6 33(1H, d, *J*=7 0Hz), 6 57(1H, dt, *J*=7 5 and 1 0Hz), 7 02(1H, t, *J*=8 0Hz), 7 08(1H, d, *J*=8 0Hz), 7 14-7 20(3H, m), 7 34-7 40(1H, m) [Found (for the HI salt) C,56 3, H, 5 0, N, 3 85 $C_{17}H_{18}NI$ requires C, 56 2, H, 5 0, N, 3 9%]

cis-*8-^{t}Butyl-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* (8-^{t}Butyl-THII) (12, ^{1}R=^{t}Bu,^{2}R=^{3}R=H)

A solution of 8-^{t}butyl-5,10-dihydroindeno[1,2-*b*]indole* (0 57g, 2 2mM) in trifluoroacetic acid (5cm^3) was stirred rapidly, and triethylsilane (0 7cm^3, 2 eq) added in one portion The reaction was stirred overnight, poured into water (10cm^3) and neutralised by the addition of sodium hydroxide The product was extracted into diethyl ether (2x5cm^3), and the combined extracts were washed with water, dried (Na_2SO_4) and evaporated to yield a pink solid This was washed with cold petrol, and then crystallised from petrol to yield a colourless solid (0 47g, 81%), m p 103-105°C, υ_{max} (CHCl$_3$

solution) 3380cm^{-1}, δ_H 7 4-6 9 (6H, m), 6 58 (1H, d, *J*=8Hz), 5 25 (1H, d, *J*=8 5Hz), 4 15 (2H, br m) 3.5 (1H, dd, *J*=16 0 and 9Hz), 3 2 (1H, d, *J*=16Hz), 1 2 (9H, s), *m/z* (%) 248 (100), 263 (34, M) [Found C, 87 0, H, 8 1, N, 5 4 $C_{19}H_{21}N$ requires C, 86 65; H, 8 05, N, 5 3%].

*From 4-^{t}butylphenylhydrazine hydrochloride and 1-indanone, m p 202°C [Found C, 87 3, H, 7 3, N, 5 7 $C_{19}H_{19}N$ requires C, 87 3, H,7 3, N, 5 9]

cis-*8-^{t}Butyl-4b,5,9b,10-tetrahydro-5-methylindeno[1,2-b]indole* (8-^{t}Butyl-5-methyl-THII) (12, ^{1}R=^{t}Bu,^{2}R=Me,^{3}R=H)

A flame dried flask was charged with 8-^{t}butyl-4b,5,9b,10-tetrahydroindeno[1,2-*b*]indole (309mg, 1 17mM), and tetrahydrofuran (2 5cm^3) The solution was cooled to -78°C, and a solution of ^{n}butyllithium (0 75cm^3 of 1 6M solution in hexanes, 1 1 eq) added dropwise The reaction mixture was stirred at -78°C for 1h, and iodomethane (0 1cm^3 , 1 3eq) was then added After allowing the reaction to warm slowly to room temperature, a saturated solution of ammonium chloride was introduced, and the organic material extracted into diethyl ether The organic phase was washed with brine, and dried ($MgSO_4$) Evaporation of the solvent yielded a light brown oil, which solidified on cooling as a beige solid (311mg, 96%), m p 74°C, υ_{max} (liquid film) 1605cm^{-1}, δ_H 7 5-7 0 (6H, m), 6 32 (1H, d, *J*=8 3Hz), 4 91 (1H, d, *J*=8 8Hz), 4 16 (1H, ddd, *J*=9 0, 8 8 and 5 3Hz), 3 44 (1H, dd, *J*=16 3 and 9 1Hz), 3 10 (1H, dd, *J*=16 3 and 5 3Hz), 2 95 (3H, s), 1 29 (9H, s), *m/z* (%) 277 (37, M), 262 (100), 263 (20), 217 (15) [Found C, 86 7, H, 8 3, N, 5 0 $C_{20}H_{23}N$ requires C, 86 6, H, 8 4, N, 5 05%]

cis-*8-^{t}Butyl-4b,5,9b,10-tetrahydro-4b-methylindeno[1,2-b]indole* (8-^{t}Butyl-4b-methyl-THII)

A flame-dried flask was purged with nitrogen and charged with 8-^{t}butyl-4b,5,9b,10-tetrahydroindeno[1,2-*b*]indole (240mg, 0 91mM) and freshly distilled tetrahydrofuran (3cm^3) The solution so formed was cooled to -78°C, and ^{n}butyllithium (0 60cm^3 of 1 6M solution in hexane, 1 1 eq) added dropwise The pale yellow solution was allowed to warm to room temperature, and dry carbon dioxide gas was bubbled through the solution until it became virtually colourless The solvent was carefully removed at reduced pressure and an atmosphere of dry nitrogen introduced The colourless residue was redissolved in dry tetrahydrofuran (3cm^3), and the solution cooled to -78°C, and 1 1 equivalents of ^{n}butyllithium added The reaction mixture was stirred at -78°C for 2 h, and then treated with iodomethane (0 06cm^3, 1 1 eq) After allowing the reaction to warm to room temperature, the solvents were removed and 2M HCl solution (20 cm^3) added When the gas evolution had ceased (*ca* 20 minutes), the solution was neutralised with solid sodium carbonate The organic material was extracted into dichloromethane (3x5cm^3), and the combined extracts were washed with brine, and dried (Na_2SO_4) After removal of solvent, the solid product remaining was purified by flash chromatography [R_F = 0 4 (10% EtOAc/60-80°C petrol)] eluting with 10% ethyl acetate/petrol This afforded a pale yellow oil which solidified at -20°C as a waxy solid (0 86mg, 34%), m p 82-84°C, υ_{max} (liquid film) 3360 (br), 1600cm^{-1}, δ_H 7 4-7 0 (6H, m), 6 49 (1H, d, *J*=9 0Hz), 4 15 (1H, br m), 3 71 (1H, br m), 3 51 (1H, dd, *J*=16 0 and 9 0Hz), 3 17 (1H, dd, *J*=16 0 and 5Hz), 1 61 (3H, s), 1 27 (9H, s), *m/z* (%) 262 (100), 277 (40, M) [Found C, 86 4, H, 8 4, N, 5 2 $C_{20}H_{23}N$ requires C, 86 6, H, 8 4, N, 5 05%]

9b,10-dihydro-9b-methylindeno[1,2-b]indole (22, ^{1}R=^{2}R=H)

A flame dried flask was charged with a solution of the hydrazone of 2-methyl-1-indanone (1 47g, 6 22mmol) in DCM (30cm^3), followed by phosphorus trichloride (3 4cm^3 of 2 0*M* solution in DCM) The solution was heated to reflux for 2h, cooled, and poured into a saturated solution of sodium hydrogen carbonate After stirring for 1h, the organic material was extracted with more DCM The basic components were back-extracted into 2M hydrochloric acid This aqueous solution was made basic, and re-extracted with DCM Evaporation of the combined extracts and column chromatography of the residue (20% EtOAc/petrol) gave a clear gum (R_f 10% EtOAc/petrol 0 1) which could be further purified by bulb to bulb distillation (0 4g, 30%) to afford an unstable gum, b p 170°C (0 2mmHg), δ_H($CDCl_3$) 1 39 (3H, s), 2 84 (1H, d, ^2J 14 6Hz), 3 11 (1H, d, ^2J 14 5Hz), 6 4-8 0 (8H, m), *m/z* (%) 218 (100), 219 (82, M), 204 (40), 217 (34), 108 5 (20), 219 (14)

cis-*4b,5,9b,10-Tetrahydro-9b-methylindeno[1,2-b]indole* (9b-Methyl-THII) (23, ^{1}R=^{2}R=H)

The phenylhydrazone of 2-methyl-1-indanone (1 44g, 6 1mmol) was heated in diethylene glycol (20cm^3) to near its reflux temperature, until ammonia started to evolve from the air condenser Heating was continued overnight, or until the ammonia ceased to evolve The solution was cooled, poured into an equal volume of water, and extracted into diethylether The ethereal solution was back-extracted with 2M hydrochloric acid, the aqueous extract was made basic with sodium hydroxide, and re-extracted with diethylether The first extract contained no major products (t l c 30% EtOAc/petrol) The basic component contained many products, the least polar of which (R_f 30% EtOAc/petrol 0 8) was purified by column chromatography (5% EtOAc/petrol) to yield a colourless solid (0 38g, 28%), m.p 72°C (from petrol), υ_{max}(melt) 3400 (br), 1610 cm^{-1}, δ_H($CDCl_3$) 1 46 (3H, s), 3 10 (1H, d, ^2J 16 2Hz), 3 30 (1H, d, ^2J 16 3Hz), 4 05 (1H, s), 4 69 (1H, s), 6 52 (1H, dd, ^3J 7 7Hz, J 0 55Hz), 6 71 (1H, ddd, ^3J 7 3, 7 3Hz, ^4J 0 55, 1 0Hz), 6 95 (1H, ddd, ^3J 7 9, 7.3Hz, ^4J 1 3Hz), 7 0-7 2 (5H, m), δ_C($CDCl_3$) 26 5 (q), 46 5 (t), 53 3 (s), 74 2 (d), 110 1, 119 0, 122 8, 123 9, 124 6, 126 8, 127 6, 127 7 (d), 137 1, 142 3, 144 0, 149 0 (s), *m/z* (%) 221 (100 M), 220 (52), 130 (20), 204 (17), 222 (16), 206 (10) [Found C, 87 0, H, 6 8, N, 6 25 $C_{16}H_{15}N$ requires C, 87 0, H, 6 8, N, 6 3%]

cis-*4b,5,9b,10-Tetrahydro-8-methoxyindeno[1,2-b]indole* (8-Methoxy-THII)
(12, ^{1}R=OMe,^{2}R=^{3}R=H)

5,10-Dihydro-8-methoxyindeno[1,2-*b*]indole (770mg, 3 3mmol) was reacted with sodium cyanoborohydride (1 0g, 16mmol), in glacial acetic acid (17cm^3) solution After 30 minutes, the solution was poured into ice/water, stirred for 1h, and neutralised with sodium hydroxide The colourless suspension was extracted into diethylether, the organic layers dried (Na_2SO_4), and concentrated *in vacuo* The residue was column chromatographed (10% ethyl acetate/petrol) to yield the product (R_f [30% EtOAc/petrol] 0 5) as a colourless solid (520mg, 66%), m p 101°C (EtOAc/petrol), υ_{max} ($CHCl_3$) 3330cm^{-1}, δ_H($CDCl_3$) 3 28 (1H, dd, ^2J 16 1Hz, ^3J 1 9Hz), 3 57 (1H, dd, ^2J 16 1Hz, ^3J 8 4Hz), 3 80 (3H, s), 3 85 (1H, br), 4 24 (1H, ddd, ^3J 8 4, 8 4, 1 9Hz), 5 30 (1H, d, ^3J 8 4Hz), 6 6-7 4 (7H, m), δ_C($CDCl_3$) 38 8 (t), 46 3 (d), 55.8 (q), 67 9 (d), 110 9, 111 2, 112 9, 123 9, 124 9, 126 9, 127 9 (d), 134 6, 142 1, 143 5, 144 2, 154 1 (s), *m/z* (%) 237 (100, M), 222 (65), 238 (18)) [Found C, 81 0, H, 6 35, N, 5 9 $C_{16}H_{15}NO$ requires C, 81 0, H, 6 4, N, 5 9%]

cis-*8-Fluoro-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* (8-Fluoro-THII) (12, ^{1}R=F,^{2}R=^{3}R=H)

A solution of 8-fluoro-5,10-dihydroindeno[1,2-*b*]indole (0 8g, 3 6mM) in trifluoroacetic acid (5cm^3) was stirred rapidly, and triethylsilane (0 86cm^3, 1 5eq) added in one portion The reaction was stirred for 4h and the excess trifluoroacetic acid removed *in vacuo* Water (10cm^3) was added to the solid, and the suspension neutralised by the addition of sodium hydroxide The product was extracted into diethyl ether, which was washed with water, dried and evaporated to yield an off white solid This was crystallised from ethyl acetate/petrol to yield a colourless solid (0 53g, 81%), m p 92-94°C, υ_{max}($CHCl_3$) 3380, 1605cm^{-1}, δ_H 7 34 (1H, m), 7 8-7 2 (3H, m), 6 87 (1H, m) 6 69 (1H, m), 6 52 (1H, dd, *J*=8 4 and 4 4Hz)), 5 27 (1H, d, *J*=8 8 Hz), 4.16 (1H, ddm, *J*=8 8 and 8.3Hz), 4 1 (1H, br *s*), 3 51(1H, dd, *J*=16 5 and 8 3Hz)), 3 18 (1H, dd, *J*=16 5 and 2 0Hz) [Found C, 79 5, H, 5 4, N, 6 15, $C_{15}H_{12}NF$ requires C, 80 0, H, 5 4, N, 6 2%]

cis-*8-Nitro-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* (8-Nitro-THII) (12, ^{1}R=NO_2,^{2}R=^{3}R=H)

5-Acetyl-8-nitro-4b,5,9b,10-tetrahydroindeno[1,2-*b*]indole (200mg) was vigorously stirred in a solution of concentrated sulphuric acid (8cm^3) and water (20cm^3) for 6h at 90°C On cooling, a solid was obtained, this was filtered off and treated with dilute ammonium hydroxide solution to give the title compound as a bright orange prisms This was collected and crystallised from ethanol (120mg, 68%), m p 181-182°C, υ_{max} 3340, 1610cm^{-1}, δ_H 3 20(1H, dd, *J*=16 5 and 2 0Hz), 3 58(1H, dd, *J*=16 5 and 8 5Hz), 4 25(1H, dddd, *J*=8 5, 8 5, 2 0, and 1 5Hz), 5 13(1H, s), 5.46(1H, d, *J*=8 5Hz), 6 44(1H, d, *J*=8 5Hz), 7 24-7 26(3H, m), 7 30(1H, m), 7 97(1H, ddd, *J*=8 5, 2 0, and 0 5Hz), 8 03(1H, *J*=2 0, and 1 5Hz [Found C, 71 7, H, 4 70 , N, 11 1 $C_{15}H_{12}N_2O_2$ requires C, 71 4, H, 4 8, N, 11 1%]

cis-*(E)- and (Z)-5-Acetyl-8-amino-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* (*E*- and Z- 5-Acetyl-8-amino-THII (12, ^{1}R=NH_2,^{2}R=H, ^{3}R=Ac)

(*E*)- and (Z)-5-Acetyl-8-nitro-4b,5,9b,10-tetrahydroindeno[1,2-*b*]indole (4 2g) in glacial acetic acid (250cm^3) and water (25cm^3) were stirred and treated with 30% aqueous titanium trichloride (42cm^3) over a period of 5 min After a further 15 min , the reaction mixture was poured on to ice and water (800cm^3) and the pH of the solution adjusted to 4 5 with 0 89 ammonium hydroxide The product was then extracted as rapidly as possible into dichloromethane (6x75cm^3) The combined extracts were dried and evaporated to give a solid which was triturated with diethyl ether to afford the title compounds as a colourless solid (2 9g, 77%), m p 196-198°C, υ_{max}3500-3100, 1600cm^{-1}, δ_H 2 42(3H,s), 2 55(3H,), 3 16(1H, d, *J*=16Hz), 3 22(1H, d, *J*=16Hz), 3 45(2H, m), 3 65(4H, exchanged by D_2O), 4 01(1H, dd, *J*==8Hz), 4 13(1H, dd *J*==7 5Hz), 5 72(1H, d, *J*=7 5Hz), 6 26(1H, d, *J*=8Hz), 6 46(2H, d, *J*=8 5Hz), 6 57(1H, s), 6 64(1H,), 6 82(1H, d, *J*=8 5Hz), 7 16-7 25(6H, m), 7 38(1H, d, *J*=7 5Hz), 7 64(1H, d, *J*=7 5Hz), 7 85(1H, d, *J*=8 5Hz), *m/z* 264, 222, 221, 91 The same mixture of isomers can be obtained in similar yield by catalytic hydrogenation of the mixed isomeric nitro compounds over 10% palladium on carbon catalyst using chloroform as the solvent. These compounds were analysed as the 8-acetates cis-(E)- and (Z)-5-Acetyl-8-(*N*-acetyl-amino)-4b,5,9b,10-tetrahydroindeno[1,2-b]indoles [Found 74 1, H, 5 8, N, 9 0 $C_{19}H_{18}N_2O_2$ requires C, 74 5, H, 5 9, N, 9 2%]

cis-*(E)- and (Z)-5-Acetyl-8-(N,N-diethylamino)-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* [E- and Z-5-Acetyl-8-(*N,N*-diethylamino)-THII] (12, ^{1}R=NEt,^{2}R=H,^{3}R=Ac)

(E)- and (Z)-5-Acetyl-8-amino-4b,9b-tetrahydroindeno[1,2-*b*]indole (1 0g) sodium carbonate (1g) and ethyl iodide (2 0cm^3) were heated together at reflux in a mixture of tetrahydrofuran (80cm^3) and water (15cm^3), with stirring, for 24h More ethyl iodide (0 5cm^3) was then added and the heating continued for a further 3h The solvents were evaporated and dichloromethane added to the residue Solids were removed by filtration and these were then washed thoroughly with diethyl ether Filtrate and washings were combined and reduced in volume to about 15cm^3 On cooling, the title compounds separated as pale yellow prisms (0 75g, 62%), m p 176-178°C, υ_{max}1635 cm^{-1}, δ_H 1 10(6H, t, *J*=7 0Hz), 1.13(6H, t, *J*=7 0Hz), 2 43(3H, s),2 54(3H, s), 3 21(1H, d, *J*=16Hz), 3 29(10H, m), 4 06(1H, dd, *J*=*J*=8Hz), 4 16(1H, dd, *J*=*J*=7 5Hz), 5 56(1H, d, *J*=2Hz), 5 72(1H, d, *J*=7 5Hz), 6 27(1H, d, *J*=8Hz), 6 47(2H, ddd, *J*=7 5, *J*=2Hz), 6 63(1H, d, *J*=2Hz), 6 90(1H, d, *J*=9Hz), 7 15-7 23(6H, m), 7 41(1H, m), 7 60(1H, m), 7 89(1H, d, *J*=9Hz) [Found C, 78 9, H, 7 6, N, 8 7 $C_{21}H_{24}N_2O$ requires C, 78 7, H, 7 55, N, 8 7%]

cis-*5-Ethyl-8-(N,N-diethylamino)-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* [5-Ethyl-8-(*N,N*-diethylamino)-THII] (12, ^{1}R=NEt$_2$,^{2}R=H;^{3}R=Et)

cis-(E)- and (Z)-5-Acetyl-8-(*N,N*-diethylamino)-4b,5,9b,10-tetrahydroindeno[1,2-*b*]indoles (0 32g, 1mM) in dry tetrahydrofuran (60cm^3) were treated with lithium aluminium hydride (0 38g, 10mM) in portions over a period of 30min The reaction mixture was then heated at reflux for 3h and then excess reagent was destroyed by the addition of 30% sodium ammonium tartrate The organic solvent was then decanted and the residue extracted with tetrahydrofuran (3x10cm^3) Solvent and extracts were combined, dried and evaporated to yield an oil which was absorbed onto silica (1g) and added to the top off a column of silica (5g), prior to elution with 10% ethyl acetate in petrol The colour of the column became dark blue but the title compound was eluted off as a colourless oil (0 2g, 65%) The compound is unstable in air becoming blue and then dark red δ_H 1 09 (6H, t, *J*=7 0Hz), 1 27(3H, t,*J* =7 0Hz), 3 1-3 3(5H, m), 3 3-3 5(3H, m), 4 18(1H, br s), 5 07(1H, br.s), 6 40(1H, d, *J*=7 0Hz), 6 57(1H, d, *J*=7 0Hz), 6 74(1H, s), 7 22(3H, s), 7 43(1H, m), *m/z* (%) 306(100), 291(43), 27(20) [Found 306 21052 $C_{21}H_{26}N_2$ requires 306 20960]

cis-*4b,5,9b,10-Tetrahydro-4b,9b-dimethylindeno[1,2-*b*]indole* (4b,9b-Dimethyl-THII) (16, ^{1}R=^{2}R=^{3}R=H)

Methyllithium (1 5cm^3, 2eq of 1 5*M* solution in hexane) was added dropwise at -78°C to a solution of 9b,10-dihydro-9b-methylindeno[1,2-*b*]indole (260mg, 1 19mmol) in THF (10cm^3) After stirring at -78°C for 1h, water (1cm^3) was added to the dark red solution, and the reaction allowed to warm The reaction mixture was quenched with saturated ammonium chloride solution (10cm^3), the organic phase separated, and dried (Na_2SO_4) Evaporation of solvent, and flash chromatography (10% EtOAc/petrol) of the residue gave a colourless gum (R_f [10% EtOAc/petrol 0.5) which solidified to a colourless solid (87mg, 31%), m p 79°C, υ_{max} (liq film) 3400 (br), 1600cm^{-1} (s), δ_H($CDCl_3$) 1 35 (3H, s), 1 46 (3H, s), 3 07 (1H, d, ^2J 15 9Hz), 3 36 (1H, d, ^2J 15 9Hz), 4 27 (1H, br), 6 53 (1H, d, ^3J 7 8Hz), 6 71 (1H, ddd, ^3J 7 3Hz, ^4J 1 1Hz), 6 96 (1H, ddd, ^3J 7 7Hz, *J* 1 5Hz), 7 1-7 3 (5H, m),

$\delta_C(CDCl_3)$ 22 3, 22 4 (q), 45 3 (t), 54 8 (s), 75 2 (s), 109 7, 119 0, 121 9, 123.0, 124.4, 126 9, 127 4, 127 5 (d), 137 7, 140 8, 148 4, 148 8 (s), *m/z* (%) 220 (100), 235 (95, M), 204 (31), 205 (28), 234 (26), 236 (17) [Found C, 86 7, H, 7.3, N, 6 0 $C_{17}H_{17}N$ requires C, 86.8, H, 7 3, N, 5 95%].

cis-*4b,5,9b,10-Tetrahydro-6,8-dimethylindeno[1,2-b]indole* (6,8-Dimethyl-THII) (12, ^{1}R=^{2}R=Me,^{3}R=H)

6,8-Dimethyl-DHII (323mg, 1 38mmol) was reacted with sodium cyanoborohydride (400mg, 5eq) in glacial acetic acid solution (7cm^3) for 30 minutes The solution was poured into ice/water, and stirred for a further 30 minutes The aqueous solution was neutralised with sodium hydroxide, and the suspension was extracted into diethylether The combined organic extracts were washed with water, dried (Na_2SO_4) and evaporated *in vacuo* Purification of the residue by suction flash chromatography, gave a colourless solid (244mg, 75%), m p 147°C (EtOAc/petrol), $\upsilon_{max}(CHCl_3)$ 3400, 1600 cm^{-1}, $\delta_H(CDCl_3)$ 2 03 and 2 07 (3H, s), 3 18 (1H, dd, ^2J 16 3Hz, ^3J 2 0Hz), 3 48 (1H, dd, ^2J 16 3Hz, ^3J 8 4Hz), 4 16 (1H, ddd, ^3J 8 4, 8 4, 2 0Hz), 5 24 (1H, d, ^3J 8 4Hz), 6 66 (1H, s), 6 84 (1H, s), 7 1-7 4 (4H, m), $\delta_C(CDCl_3)$ 16 8 and 20 8 (q), 39 2 (t), 46 2 (d), 67 7 (d), 122 5, 123 9, 125 1, 127 0, 127 9, 129 4 (d), 119 7, 129 0, 132 5, 142 4, 144 5, 146 1 (s), *m/z* (%) 235 (100 M), 234 (37), 220 (24), 236 (16) [Found C, 86 5, H, 7 35, N, 5 8 $C_{17}H_{17}N$ requires C, 86 75, H, 7 3, N, 5 95%]

cis-*4b,5,9b,10-Tetrahydro-10,10-dimethylindeno[1,2-b]indole* (10,10-Dimethyl-THII)

5,10-Dihydro-10,10-dimethylindeno[1,2-*b*]indole (1 00g, 4 29mmol) was treated with sodium cyanoborohydride (1 0g, 16mmol) in glacial acetic acid (20cm^3) After 10 minutes, the reaction mixture was poured into water, stirred for 30 minutes, and extracted into diethylether (3x10cm^3) The combined organic extracts were washed with water (10x5cm^3), dried (Na_2SO_4), and the solvent removed *in vacuo* The residue was dissolved in 5% ethyl acetate/petrol and filtered through a pad of "flash" silica, yielding, on removal of solvent, a gum which solidified to give a colourless solid (0 98g, 98%), m p 57-59°C (DCM/petrol), υ_{max}(melt) 3360 cm^{-1}, $\delta_H(CDCl_3)$ 1 17 (3H, s), 1 43 (3H, s), 3 86 (1H, d, ^3J 8 8Hz), 3 9 (1H, br), 5 29 (1H, d, ^3J 8 8Hz), 6 59 (1H, d, ^3J 7 7Hz), 6 71 (1H, ddd, ^3J 7 3, 7.4Hz), 7 02 (1H, ddd, ^3J 7 3Hz), 7 2-7 3 (5H, m), $\delta_C(CDCl_3)$ 27 2 (q), 32 2 (q), 47 5 (s), 59 1 (d), 66 8 (d), 110 1, 118 5, 122 8, 124 2, 126 2, 127 1, 127 8, 128 3 (d), 129 5, 142 3, 151 3, 153.0 (s), *m/z* (%) 235 (100 M), 106 (99), 220 (49), 204 (21), 234 (20), 236 (16) [Found C, 86 75, H, 7 3, N, 5 9 $C_{17}H_{17}N$ requires C, 86 75, H, 7 3, N, 5 95%]

cis-*4b,5,9b-Trimethyl-4b,5,9b,10-tetrahydroindeno[1,2-b]indole* (4b,5,9b-Trimethyl-THII) (16, ^{1}R=^{2}R=H,^{3}R=Me)

The preparation of 4b,9b-dimethyl-THII was repeated using 9b-methyl-9b,10-dihydroindeno-[1,2-*b*]indole (0 86g, 4 0mmol), THF (8cm^3), and methyl lithium (4 0cm^3 of 1 4M solution), quenching the anion with iodomethane instead of with water After work-up, the least polar component was separated by column chromatography (1% EtOAc/petrol), to give a gum which was further purified by bulb to bulb distillation (0 46g, 46%), b p 175°C (0 02mmHg), υ_{max}(liq film) 1605 cm^{-1}, $\delta_H(CDCl_3)$ 1 32 (3H, s), 1 40 (3H, s), 2 86 (3H, s), 2 94 (1H, d, ^2J 15 9Hz), 3 27 (1H, d, ^2J 15 9Hz), 6 30 (1H, d, ^3J 7 7Hz), 6 65 (1H, ddd, ^3J 7 3Hz), 7 05 (1H, ddd, ^3J 7 7Hz), 7 10 (1H, dd,

^3J 7 3Hz, 9-H), 7 15-7 4 (4H, m); $\delta_C(CDCl_3)$ 17 0 (q), 21.1 (q), 28 8 (q), 46 2 (t), 54 9 (s), 80 2 (s), 105 6, 116.9, 122 1, 123 8, 124 7, 126 2, 127 6, 127 7 (d), 127 1, 136 3, 142 6, 144.8 (s), *m/z* (%) 234 (100), 249 (93, M), 219 (49), 218 (34), 56 (30), 235 (21), 250 (18), 158 (16), 109 (12), 110 (12) [Found 249 1520 $C_{18}H_{19}N$ requires 249 1517]

cis-*4b,5,9b,10-Tetrahydro-8-methoxy-5-methylindeno[1,2-*b*]indole* (8-Methoxy-5-methyl-THII) (12, ^{1}R=OMe,^{2}R=H,^{3}R=Me)

Using the same procedure as for 4b,5,9b,10-tetrahydro-5-methylindeno[1,2-*b*]indole, 8-methoxy-THII (239mg, 1 0 mmol) was methylated with iodomethane, using sodium hydride (25mg, 1 1mmol) as the base, in THF (2cm^3) Extraction work-up (into diethylether), and purification by suction flash chromatography, yielded a clear gum (158mg, 63%) which solidified after bulb to bulb distillation (180°C at 0 2mmHg), m p 72°C, υ_{max}(liquid film) 1600cm^{-1}, $\delta_H(CDCl_3)$ 2 87 (3H, s), 3 03 (1H, dd, ^2J 16 3Hz, ^3J 5 5Hz), 3 36 (1H, dd, ^2J 16 2Hz, ^3J 9 2Hz), 3 70 (3H, s), 4 08 (1H, ddd, ^3J 8 6, 9 2, 5 5Hz), 4 80 (1H, d, ^3J 8 6Hz), 6 28 (1H, d, ^3J 8 4Hz), 6 61 (1H, dd, ^3J 8 4Hz, ^4J 2 7Hz), 6 77 (1H, dd, ^4J 2 7, 0 6Hz), 7 1-7 5 (4H, m), $\delta_C(CDCl_3)$ 34 7 (q), 39 2 (t), 45 6 (d), 55 8 (q), 76 4 (d), 107 0, 111.4, 112 1, 124 7, 125 0, 126 3, 127 9 (d), 134 0, 142 1, 143 8, 146 4, 152 6 (s), *m/z* (%) 251 (100, M), 236 (95), 237 (19), 252 (17) [Found C, 81 6; H, 6 8, N, 5 55 $C_{17}H_{17}NO$ requires C, 81 25, H, 6 8, N, 5 55%]

cis-*4b,5,9b,10-Tetrahydro-8,9b-dimethyl-4b-(4-methylphenylhydrazin-*N_b*-ylindeno[1,2-*b*]indole* (26, ^{1}R=^{2}R=H, Ar= 4-MeC_6H_5)

To a suspension of 4-methylphenylhydrazine hydrochloride (8 15g, 0 051mol) in water (30cm^3) was added dropwise 2M sodium hydroxide solution until pH 11 was achieved The mixture was extracted with diethyl ether (3 x 50cm^3), the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated The residue was then dissolved in glacial acetic acid (100cm^3) and 2-methyl-1-indanone (5 0g, 0 034mol) added in small portions to the solution The mixture was stirred at room temperature for $^1/_2$ h Saturated sodium bicarbonate solution was then added until pH 9 was attained The mixture was then extracted with diethyl ether (3 x 50cm^3). The combined organic extracts were washed with brine (2 x 20cm^3), dried (Na_2SO_4) and evaporated The residue was crystallized from methanol/water to yield pale yellow prims (2 18g, 27%) A small sample was recrystallized from ethyl acetate/petrol for analytical purposes, m p 156°C υ_{max}(Nujol) 3450, 3360, 3290, 1600 cm^{-1}, δ_H ($CDCl_3$) 7 80 (1H, m), 7 42 (1H, s, D_2O exchanged), 7 35 (1H, s), 7 27 (3H, m), 6 99 (1H, s), 6 94 (2H, d, *J* = 8 5Hz), 6 59 (2H, d, *J* = 8 5Hz) 6 50 (1H, d, *J* = 7 9Hz), 3 63 (1H, d, *J* = 16 9Hz), 3.38 (2H, s(br), exchanged by D_2O), 2 86 (1H, d, *J* = 16 9Hz), 2 36 (3H, s), 2 20 (3H, s), 1 72 (3H, s), *m/z* (%) 355 (M, 5) 234 (100) 232 (80) 218 (30) 122 (40) [Found, C, 81 10, H, 7 06, N, 11 70 $C_{24}H_{25}N_3$ requires C, 81 10, H, 7 09, N, 11 82%]

cis-*9b,10-Dihydro-8,9b-dimethylindeno[1,2-*b*]indole* (22, ^{1}R=Me,^{2}R=H)

To a solution of 4-methylphenylhydrazine hydrochloride, (9 73g, 0 061mol) in absolute ethanol (240cm^3) was added dropwise 2-methyl-1-indanone, (8 14g, 0 056mol), followed by concentrated hydrochloric acid (3cm^3) The mixture was boiled for 2h, the solvents removed, and the residue portioned between diethyl ether and water, and the layers separated The aqueous phase was

extracted with diethyl ether (3 x 50cm^3) The combined organic phases were washed sequentially with saturated sodium bicarbonate solution and brine, dried (Na_2SO_4), and evaporated The crude material thus obtained was purified by flash chromatography on silica gel, eluting with 7-12% ethyl acetate/petrol to yield a low m.p solid (5 05g, 39%), δ_H ($CDCl_3$) 7 87 (1H, m) 7 51 (1H, d, J = 7 9Hz), 7 39 (3H, m), 7 25 (1H, s), 7 15 (1H, d, J = 8 0Hz), 3 07 (1H, d, J = 14 7Hz), 2 81 (1H, d, J = 14.7Hz), 2 41 (3H, s), 1 37 (3H, s)

*9b,10-Dihydro-9b-methyl-8-^{i}propylindeno[1,2-*b*]indole* (22, ^{1}R=^{i}Pr;^{2}R=H)

To a solution of 4-^{i}propylphenylhydrazine hydrochloride, (6 50g, 0.035mol) in absolute ethanol (140cm^3) was added dropwise 2-methyl-1-indanone, (4 6g, 0 032mol) followed by concentrated hydrochloric acid (2 5cm^3) The mixture was refluxed for 2h and the ethanol evaporated The residue was partitioned between diethyl ether (100cm^3) and water (100cm^3) and the layers separated The aqueous phase was extracted with diethyl ether (2 x 30cm^3) and the combined organic extracts were washed sequentially with saturated sodium bicarbonate solution and brine, and then dried (Na_2SO_4) Removal of the solvent gave the title compound which was purified by flash chromatography on silica gel eluting with 10% ethyl acetate/petrol, to yield a yellow gum, (1 62g, 25%), δ_H ($CDCl_3$) 7 88 (1H, m), 7 55 (1H, d, J = 8 1Hz), 7.41 (3H, m), 7 30 (1H, d, J = 1 8Hz), 7 23 (1H, dd, J = 1 8Hz and 7 1Hz), 3 10 (1H, d, J = 14 7Hz), 2 98 (1H, sept , J = 7 0Hz), 2 85 (1H, d, J = 14 7Hz), 1 39 (3H, s), 1 30 (6H, d, J = 7 0Hz)

cis-*4b,5,9b,10-Tetrahydro-4b,8,9b-trimethylindeno[1,2-*b*]indole* (4b,8,9b-Trimethyl-THII) (24, ^{1}R=Me,^{2}R=H)

To a solution of 9b,10-dihydro-5,9b-dimethylindeno[1,2-*b*]indole, (5 05g, 0.022mol) in dry tetrahydrofuran (100cm^3) at -78°C, under nitrogen, in a flame dried flask, was added dropwise methyllithium, (1 4*M* solution in diethyl ether, 23 2cm^3, 0 032mol) The mixture was stirred at -78°C for 2h, and then at -15°C for a further 1h Saturated ammonium chloride solution (3cm^3) was then added and the mixture allowed to warm to room temperature The reaction mixture was portioned between ether and saturated ammonium chloride solution and the layers separated The aqueous phase was extracted with diethyl ether (2 x 25cm^3) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to afford the title compound as an off white solid This was purified by flash chromatography on silica gel eluting with 3-10% ethyl acetate/petrol to yield a colourless solid, 2 73g (51% overall yield, or 78% based on recovered starting material), m p 208-212°C, υ_{max} (liquid film) 3340, 2900, 1600cm^{-1}, δ_H ($CDCl_3$) 7 1-7 3 (4H, m), 6 94 (1H, m), 6 77 (1H, d, J = 7 8Hz), 6 46 (1H, d, J = 7 8Hz), 3 35 (1H, d, J = 15 9Hz) 3 06 (1H, d, J = 15 9Hz), 2.22 (3H, s), 1 46 (3H, s), 1 34 (3H, s), *m/z* (%) 249 (M, 100) 234 (70) [Found, C, 86 6, H, 7 99, N, 5 5 $C_{18}H_{19}N$ requires C, 86 7, H, 7 7, N, 5 6%]

cis-*4b,5,9b,10-Tetrahydro-4b,9b-dimethyl-8-^{i}propylindeno[1,2-*b*]indole*(4b,9b-Dimethyl-8-^{i}propyl-THII) (24, ^{1}R=^{i}Pr;^{2}R=H)

To a solution of methyllithium (1 4M in ether, 14 5cm^3, 12 4mmol) in dry tetrahydrofuran (20cm^3), at -78°C, under nitrogen, in a flame dried flask, was added dropwise over 1h a solution of 9b, 10-dihydro-9b-methyl-8-^{i}propylindeno[1,2-*b*]indole (1 62g, 6 20mmol) in dry tetrahydrofuran

($30cm^3$) After addition, the mixture was stirred for a further 0.5h at -78°C Saturated ammonium chloride solution ($2cm^3$) was then added and the mixture allowed to warm to room temperature The reaction mixture was then portioned between diethyl ether ($50cm^3$) and saturated ammonium chloride solution ($25cm^3$), and the layers separated. The aqueous phase was extracted with diethyl ether (2 x $10cm^3$) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated The crude material thus obtained was purified by flash chromatography on silica gel eluting with 3-10% ethyl acetate/petrol to yield a pale yellow gum (0 77g 45%), υ_{max} (liquid film) 3340, 2900, 1600 cm^{-1}, δ_H ($CDCl_3$) 7 1-7 3 (4H, m), 6 98 (1H, d, J = 1 8Hz), 6 82 (1H, dd, J = 1 8Hz and 7 9Hz), 6 47 (1H, d, J = 7 9Hz), 3 36 (1H, d, J = 15 9Hz), 3 06 (1H, d, J = 15 9Hz), 2 78 (1H, sept J = 6 8Hz), 1 45 (3H, s) 1 34 (3H, s), 1 18 (6H, dd, J = 1 3Hz and 6 9Hz), *m/z* (%) 277 (M, 75) 262 (100) 105 (30) [Found 277 1821 $C_{20}H_{23}N$ requires 277 1829]

cis-*(E)- and (Z)-5-Acetyl-4b,5,9b,10-tetrahydro-8-nitroindeno[1,2-b]indole* (E- and Z- 5-Acetyl-8-nitro-THII) (12, ^{1}R=NO_2,^{2}R=H,^{3}R=Ac)

5-Acetyl-4b,5,9b,10-tetrahydroindeno[1,2-*b*]indole* (5 7g) in glacial acetic acid ($25cm^3$) was treated dropwise over 5 min with concentrated nitric acid ($11.5cm^3$), during this time the reaction mixture was vigorously stirred The solution was then heated with stirring for 1 5h at 55-60°C, before it was poured onto ice and the mixture left stirring overnight. The yellow solid which formed was then collected and crystallised from hot ethanol ($350cm^3$) as needles (5 5g, 82%), m p 210°C, υ_{max}1655 cm^{-1}, δ_H 2 55,2 65 (2x3H, br s), 3 36(2H, br d, J=16Hz), 3 58(2H, dd, J=16 and 8Hz), 4 20, 4 30(2x1H, br s), 5 95, 6 35(2x1H, br s), 7 0-7 6(9H, m), 8 05-8 13(5H, m), *m/z* 294, 252, 206, 204 [Found C, 69 4, H, 4 7, N, 9 4 $C_{17}H_{14}N_2O_3$ requires C, 69 4, H, 4 8, N, 9 5%]

*Obtained from THII by treatment with sodium hydride and then acetyl chloride as a mixture of E- and Z- isomers, R_f (30% EtOAc in hexane) 0 33, m p 150°C [Found C, 81 9, H, 6 1, N, 5 6 $C_{17}H_{15}NO$ requires C, 81 9, H, 6 1, N,5 6%]

5,6-Dihydroindeno[2,1-b]indole (iso-DHII) (28, ^{1}R=^{2}R=H)

2-Indanone (5 25g, 39 7mmol) and phenylhydrazine hydrochloride (5 74g, 39 7mmol) were heated to reflux in glacial acetic acid ($60cm^3$) for 1h, and then cooled The solution was poured into ice/water, and the solid precipitate collected by filtration After partial purification by column chromatography [R_F (30% EtOAc/petrol) 0 6], and crystallisation (charcoal) from ethyl acetate, the product was recrystallised from chloroform to yield colourless needles (0 64g, 8%) m p 205°C (dec) (lit ,[8] 200°C), υ_{max}(Nujol) 3400, 1600 cm^{-1}, δ_H(DMSO-d_6) 3 65 (2H, s), 7 0-7 2 (8H, m), 10 40 (1H, br), *m/z* 205 (%) (100 M), 204 (69), 88 (22), 102 (19), 206 (17)

5,6-Dihydro-9-methoxyindeno[2,1b]indole (9-Methoxy-iso-DHII) (28, ^{1}R=MeO,^{2}R=H)

4-Methoxyphenylhydrazine hydrochloride (3 5g) and 2-indanone (2 6g) were dissolved in ethanol ($25cm^3$) containing concentrated hydrochloric acid (0 $5cm^3$) and the solution was heated at reflux for 2h The solvent was then removed under reduced pressure to give a black residue which was treated with ethyl acetate and filtered The filtrate was mixed with silica (25g) and the solvent removed under reduced pressure, the residue was then placed at the top of a silica column and eluted with ethyl acetate petrol (1 10) to afford the indole (2 35g, 50%) as pale brown needles, m p 170-171°C,

υ_{max} 3370, 1605 cm^{-1}, δ_H 3 65(2H,s), 3 90(3H,s), 6 84(1H, dd, *J*=8 5 and 2 5Hz), 7 08 (1H, ddd, *J*=7 5, 7 5 and 1 0Hz), 7 20 (1H, d, *J*=8 5Hz), 7 24(1H, ddd, *J*=7 5, 7 5 and 0 5Hz), 7 30(1H, d, *J*=2 5Hz), 7 39(1H, d, *J*=7 5Hz), 7 61(1H, d, *J*=7 5Hz), 8.09(1H, br s), *m/z* (%) 235 (100), 220 (25), 192 (30), 191 (20) [Found C, 81 6, H, 5 7, N, 6 0 $C_{16}H_{13}NO$ requires C,81 7, H,5 6, N,5.95%]

5,6-Dihydro-9-isopropylindeno[2,1-b]indole (9-^{t}Propyl-iso-DHII) (28, ^{1}R=^{t}Pr,^{2}R=H)

A suspension of 4-isopropylphenylhydrazine hydrochloride (3 13g, 16 8mM) and 1-indanone (2 22g, 1eq) was heated to reflux in absolute ethanol (20cm^3) containing concentrated hydrochloric acid (0 5cm^3) for 4h The ethanol was removed *in vacuo*, and the product partially purified by column chromatography, eluting with 10% ethyl acetate/petrol and finally purified by crystallisation from ethyl acetate/petrol This gave pale green needles (0 84g, 18 7%), m p 144°C, δ_H 8 05 (1H, br s), 7 7-7 0 (7H, m), 3 65 (2H, s), 3 07 (1H, septet, *J*=7 0Hz), 1 35 (6H, d, *J*=6 9Hz) [Found C, 87 7, H, 6 95, N, 5 6, $C_{18}H_{17}N$ requires C, 87 4, H, 6 95, N, 5 65%]

5,6-Dihydro-9-^{t}butylindeno[2,1-b*]indole* (9-^{t}Butyl-iso-DHII) (28, ^{1}R=^{t}Bu,^{2}R=H)

2-Indanone (2 0g, 15 2mM) in ethanol (25cm^3) containing 30% aqueous hydrochloric acid (0 5cm^3) was stirred and heated with 4-^{t}butylphenylhydrazine hydrochloride (3 0g, 15 2mM) for 4h Silica gel (3 0g) was then added and the solvents removed under reduced pressure The residue was then added to the top of a column of silica (28g) and eluted with 5% ethyl acetate in petrol Early fractions gave *9-^{t}Butyl-5,10b-dihydro-10b-(inden-2-yl)indeno[2,1-b]indole* (31), m p 220°C, $\upsilon_{max}$$cm^{-1}$ 1620, 1595, δ_H 1 46 (9H, s), 3 89(2H, s), 4 02(2H, s), 6 87(1H, s), 7 13(1H, ddd, *J*=6 5, 6 5, and 1 0Hz), 7 19(1H, ddd, *J*=6 5, 6 5, and 1 0Hz), 7 32(1H, dd, *J*=7 5 and 7 5Hz), 7 35-7 42(3H, m), 7 45(1H, d, *J*=7 5Hz), 7 47(1H, d, *J*=7 5Hz), 7 70(1H, d, *J*=7 5Hz), 7 76(1H, d, *J*=7 0Hz), 7 86 (1H, d, *J*=2 0Hz), *m/z* (%), 375(15, M), 237(12), 57 (100) [Found C, 89 6, H, 6 7, N, 3 7 $C_{28}H_{25}N$ requires C, 89 6, H, 6 7, N, 3 7%], whereas later fractions afforded a mixture of this compound and the title compound These fractions were combined and rechromatographed to give *5,6-Dihydro-9-^{t}butylindeno[2,1-b]indole* (28, ^{1}R=^{t}Bu,^{2}R=H), (0 35g, 9%), m p 182°C, υ_{max} 3390, 1610 cm^{-1}, δ_H 1 44(9H, s), 3 71(2H, s), 7 10(1H, ddd, *J*=7 5, 7 5, 1 5Hz), 7 22-7 42(4H, m), 7 68(1H, br d, *J*=7 0Hz), 7 84(1H, br s), 8 15(1H,s), *m/z* (%) 261 (100, M), 246(95), 204 (25) [Found C, 87 2 , H, 7 2 , N, 5 35 $C_{19}H_{19}N$ requires C, 87 3, H, 7 3, N, 5 4%]

5,6-Dihydro-9^{t}butyl-5-(2-indanylidene)indeno[2,1-b]indole (33)

The enone (32)[24] (0 25g) was heated in boiling ethanol (5cm^3) containing 4-^{t}butylphenylhydrazine (0 2g) and concentrated hydrochloric acid (0 1cm^3) for 4h The solvent was then removed and the residue chromatographed on silica (10g) eluting with 7% ethyl acetate in petrol to yield the title compound as yellow-geen prisms (0 13g, 35%), m p 232-235°C sinters, υ_{max} 3420, 1600 cm^{-1}, δ_H 1 44(9H, s), 4 40(2H, s), 4 45(2H, s), 7 10(1H, ddd, *J*=7 5, 7 5, 2 0Hz), 7 24-7 32(4H, m), 7 38-7 46(3H, m), 7 56(1H, d, *J*=7 0Hz), 7 59(1H, d, *J*=8 0Hz), 7 77(1H, d, *J*=2 0Hz), 8 16(1H, br s), *m/z*(%) 375(100), 360(20), 318(30) [Found C, 87 2 , H, 7 2 , N, 5 35 $C_{19}H_{19}N$ requires C, 87 3, H, 7 3, N, 5 4%]

cis-*5,5a,6,10b-Tetrahydroindeno[2,1-b]indole* (iso-THII)

6-Dihydroindeno[2,1-*b*]indole (185mg, 0 9mmol) was reacted with sodium cyanoborohydride (310mg, 5mmol), in glacial acetic acid (5cm^3), for 6h. The solution was poured into ice/water, and stirred for 1h It was then neutralised with sodium hydroxide, and the white solid which formed was collected by filtration, washed with water, dried and purified by flash chromatography (10% EtOAc/petrol, R_F 30% EtOAc/petrol 0 6) to yield a colourless solid (81mg, 43%), m p 85-86°C, υ_{max}($CHCl_3$) 3380, 1600 cm^{-1}, δ_H($CDCl_3$) 3 09 (1H, dd, *J*=16 3, 1 5Hz), 3 33 (1H, dd, *J*=16 4, 6 2Hz), 3 45 (1H, br), 4 74 (1H, d, *J*=8 5Hz), 4 82 (1H, ddd, *J*=8 5, 6 2, 1 8Hz), 6.55 (1H, d, *J*=7 7Hz), 6 73 (1H, ddd, *J*=7.5, 7.5, 1 1Hz), 7 00 (1H, ddd, *J*=7 5, 7 5, 1 1Hz), 7 1-7 4 (4H, m), δ_C($CDCl_3$) 41 1 (t), 53 7 (d), 63 7 (d), 109 2, 118 8, 124 0, 124 2, 125 1, 127 0, 127 1, 127 8 (d), 141 5, 143 2, 150 3 (s), m/z (%) 207 (100, M), 206 (84), 204 (18), 178 (17), 208 (15), 103 (10) [Found C, 87 2, H, 6 3, N, 6.75 $C_{15}H_{13}N$ requires C, 86 9, H, 6 3, N, 6 75%]

cis-*5,5a,6,10b-Tetrahydro-9-methoxyindeno[2,1-b]indole* (9-Methoxy-iso-THII)

5,6-Dihydro-9-methoxyindeno[2,1*b*]indole (0 56g), as a suspension in glacial acetic acid (25cm^3) at 16°C, was treated with sodium cyanoborohydride (1 0g) in small portions over 6h The resulting solution was stirred for a further 1h , and then poured into ice-water (100cm^3) The solution was separated from a small amount of resinous material and the filtrate treated with sodium carbonate (2 5g) in small portions with vigorous stirring The colourless solid which separated was collected and crystallised from ethanol as needles (0 31g, 55%), m p 129-130°C, υ_{max} 3340, 2730, 1600 cm^{-1}, δ_H 3 06 (1H, dd, *J*=16 5 and 1 5Hz), 3 2-3 8(1H, br s), 3 31(1H, dd, *J*=16 5 and 6 0Hz), 3 76(3H, s), 4 71(1H, d, *J*=8 0Hz), 4 80(1H, ddd, *J*=8 0, 6 0 and 2 0Hz), 6 5(1H, d, *J*=8 5Hz), 6 58(1H, dd, *J*=8 5 and 2 5Hz), 6 99(1H, d, *J*=2 5Hz), 7 15-7 24(3H, m), 7 33-7 36 (1H, m) [Found C, 80 6; H, 6 3, N, 5 9 $C_{16}H_{15}NO$ requires C, 81 0, H, 6 4, N, 5 9%]

cis-*5,5a,6,10b-Tetrahydro-9-isopropylindeno[2,1-b]indole* (9-^{i}Propyl-iso-THII) and cis-*5-Ethyl--5,5a,6,10b-tetrahydro-9- isopropylindeno[2,1-b]indole* (5-Ethyl-9-^{i}propyl-iso-THII)

To a suspension of 5,6-dihydro-9-isopropylindeno[2,1-*b*]indole (2 3g, 9 3mmol) in glacial acetic acid (30cm^3) was added sodium cyanoborohydride (2g) in small portions over 30 min The mixture was stirred for 3h , and the solution then obtained was poured into ice/water (50cm^3) and stirred for 1 h The clear solution was carefully neutralised with sodium carbonate causing a white precipitate to form This was extracted into diethyl ether (3x10cm^3), and the combined extracts were washed copiously with water, dried (Na_2SO_4) and evaporated Tlc analysis of the residue indicated two products had formed these were isolated by column chromatography eluting with 10% ethyl acetate/petrol to yield first a small amount of *cis*-5-Ethyl-5,5a,6,10b-tetrahydro-9-isopropyl-indeno[2,1-*b*]indole (0 07, 3%), and then the title product (0 93g, 40%), both as colourless oils) Further purification of the latter product was achieved by distillation, υ_{max}(liquid film) 3380, 2960, 1610 cm^{-1}, δ_H 7 4-7 1 (5H, m), 6 87 (1H, dd, *J*=8 1, 1 8Hz), 6 50 (1H, d, *J*=8 1Hz), 4 81 (1H, ddd, *J*=8 1, 6 2 and 2 0Hz), 4 73 (1H, d, *J*=8 1Hz), 3 32 (1H, dd, *J*=16 6 and 6 2), 3 08 (1H, dd, *J*=16 6 and 2 0Hz), 2 83 (1H, septet, *J*=6 9Hz), 1 23 (6H, d, 6 9Hz) [Found C, 86 6, H, 7 8, N, 5 5 $C_{18}H_{19}N$ requires C,86 7, H, 7 7, N, 5 6%]

cis-*5,5a,6,10b-Tetrahydro-9-fluoroindeno[2,1-b]indole* (9-Fluoro-iso-THII)

5,6-Dihydro-9-fluoroindeno[2,1-*b*]indole (0.55g, 2 5mM) in glacial acetic acid (25cm^3) was stirred and treated with sodium cyanoborohydride (2 1g, 36 5 mM) in small portions over 10 h, maintaining the temperature below 18°C The amount of the reducing agent appears crucial since mixtures form if more is added The reaction mixture was then added to ice-water (100cm^3) and the yellow o il which was formed was separated from the aqueous phase

The pH of the aqueous phase was then adjusted to 6 by the addition of sodium carbonate (30g), and the colourless oil which was liberated was extracted into diethyl ether (4x20cm^3) The combined extracts were dried and evaporated to yield an oil which was extracted with hot petrol (6x10cm^3) and the residue triturated with ethanol (1cm^3) This treatment caused the compound to crystallise as colourless prisms which recrystallised from ethanol to give the title compound (60mg, 11%) , m p 116-117°C, υ_{max} 3380 cm^{-1}, δ_H 3 06(1H, dd, *J*=16 5 and 1 5Hz), 3 06(1H, dd, *J*=16 5 and 1 5Hz), 3 31(1H, dd, *J*=16 5 and 6 0Hz), 3 67(1H, br s), 4 70(1H, d, *J*=8 0Hz), 4 82(1H, ddd, *J*=8.0, 6 0 and 1 5Hz), 6 43(1H, dd, *J*=8 5, and 4 0Hz), 6 70(1H, ddd, *J*=8 5, 8 5 and 2 5Hz), 7 07(1H, dd, *J*=8 5 and 2 5Hz), 7 16-7 25(3H, m), 7 33(1H, m) [Found C, 80 0, H, 5 45, N, 6 0 $C_{15}H_{12}NF$ requires C, 80 0, H, 5 4, N, 6 2%]

cis-*9-^{t}-Butyl-5,5a,6,10b-tetrahydroindeno[2,1-b]indole* (9-^{t}Butyl-iso-THII)

9-^{t}Butyl-5,6-dihydroindeno[2,1-*b*]indole (0 16g, 0 6mM) in glacial acetic acid (25cm^3) was stirred and treated with sodium cyanoborohydride (0,7g, 11 mM) in small portions over 3 h, maintaining the temperature below 18°C The reaction mixture was then added to ice-water (80cm^3) and the yellow oil which was formed was separated from the aqueous phase The pH of the aqueous phase was then adjusted to 6 by the addition of sodium carbonate (25g), and the colourless oil which was liberated was extracted into diethyl ether (6x10cm^3) The combined extracts were dried and evaporated to yield an oil which was chromatographed on silica eluting with 5% ethyl acetate in petrol This gave the title compound as colourless prisms (0 11g, 7%), m p 92°C, υ_{max} 3380 cm^{-1}, δ_H 1 30(9H, s), 3 05(1H, d, *J*=16 5 Hz), 3 28(1H, dd, *J*=16 5 and 6 0Hz), 3 79(1H, s), 4 70(1H, d, *J*=8 0Hz), 4 75(1H, ddd, *J*=8 0, 6 0 and 2 0Hz), 6 48(1H, d, *J*=8 0Hz), 7 03(1H, dd, *J*=8 0, and 2 0Hz), 7 14-7 24(3H, m), 7 34(1H, m), 7 40(1H, d, *J*=2 0Hz) [Found C, 86 5, H, 8 3, N, 5 5 $C_{19}H_{21}N$ requires C, 86 65, H, 8 0, N, 5 3%]

2-Chloro-5-methoxy-4,6-dimethylindan-1-one (35, X=Cl)

Sulphonyl chloride (*ca* 1 eq) was added dropwise over 30 minutes to a solution of 5-methoxy-4,6-dimethylindan-1-one (0 65g, 3 4mmol) in dry diethyl ether (10cm^3), with stirring and in absence of light at O°C After the addition was complete, the reaction was allowed to warm up to room temperature, and stirring continued for a further 2h The solvents were removed and the solid residue chromatographed, eluting with 50% dichloromethane/petrol and then with dichloromethane, to yield the dichloro derivative [R_F(DCM) 0 85, 0 14g, 14%] which was discarded, and the required product [R_F(DCM) 0 7] The latter is a colourless solid (0 65g, 85%) m p 109-110°C, υ_{max} ($CHCl_3$) 2960, 1730, 1600 cm^{-1}, δ_H($CDCl_3$) 7 53 (1H, s), 4 54 (1H, dd, *J*=7 8, 3 7Hz), 3 79 (3H, s), 3 64 (1H, dd, *J*=17 5, 7 8Hz), 3 13 (1H, dd, *J*=17 5, 3 5Hz), 2 33 (3H, s), 2 25 (3H, s) [Found C, 63 9, H, 5 85 $C_{12}H_{10}ClO_2$ requires C, 64 15, H, 5 83%]

2-Bromo-5-methoxy-4,6-dimethylindan-1-one (35, X=Br)

Bromine (0 4cm^3) was added dropwise over 30 minutes to a solution of 5-methoxy-4,6-dimethylindan-1-one (1 25g, 6 6mmol) in dry diethylether (10cm^3), with stirring and in the absence of light at 0°C After the addition was complete, the reaction mixture was allowed to warm to room temperature, and stirring was continued for a further 20 min. The solvents were removed in the absence of light and the solid residue chromatographed, eluting first with 10% ethyl acetate/petrol and then with dichloromethane, to yield the title compound as a pale yellow solid (1 08g), m p 72°C

5-Methoxy-4,6-dimethyl-2-(2'-trifluoroacetamidophenyl)indan-1-one (38) and *5,10-Dihydro-2-methoxy-1,3-dimethylindeno[1,2-b]indole* (1,3-Dimethyl-2-methoxy-DHII) (39)

A solution of *o*-bromotrifluoroacetanilide (565 mg, 2 1 mM) in tetrahydrofuran (40cm^3) was cooled to -78°C and to this was added methyl lithium (1 molar equivalent of a 1.4M solution in pentane) This addition was followed 10 minutes later by the introduction of *tert*-butyllithium (2 molar equivalents of a 1 7*M* solution in pentane) The reaction mixture was stirred for 1h at -78°C, and then a solution of 2-bromoindanone (567 mg) in tetrahydrofuran (5cm^3) added dropwise, the reaction mixture was stirred for 2h and then allowed to warm slowly to room temperature, and stirred for a further 24h After this time, a 10% solution potassium hydroxide in methanol (5cm^3) was introduced and the reaction mixture stirred for 90 minutes It was then poured into 2M HCl containing some ice, and extracted with dichloromethane (3x20cm^3) The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford a solid residue which was chromatographed on silica, eluting with dichloromethane/ petrol mixtures of increasing polarity to yield firstly unchanged trifluoroacetanilide (R_F 0 4) (16 mg), and a pale brown solid This was rechromatographed to give firstly 5,10- dihydro-2-methoxy-1,3-dimethylindeno[1,2-*b*]indole (30mg)[R_F 0 8 (30% EtOAc/petrol)], m p 177°C (EtOAc/petrol) (lit ,[17] 184 2-184 5°C), υ_{max} (Nujol) 3290 cm^{-1}, δ_H ($CDCl_3$) 8 20 (1H, br), 7 6-7 1 (5H, m), 3 76 (3H, s), 3 56 (2H, s), 2 36 (6H, s), δ_C ($CDCl_3$) 154 8 (s), 146 0 (2), 143 5 (s), 140 0 (s), 130 4 (s), 128 9 (s), 121 2 (d), 120 1(d), 118 6 (d), 117 2 (d), 111 9 (d), 60 2 (q), 29 4 (t), 16 5 (q), 12 4 (q), *m/z* (%) 263 (75, M), 249 (20), 248 (100), 205 (15),204 (20) [Found C, 82 0, H, 6 4, N, 5 2 calculated for $C_{18}H_{17}NO$ C, 82 1, H, 6 5, N, 5 3%], and then 5-Methoxy-4,6-dimethyl-2-(2'-trifluoroacetamidophenyl)indan-1-one, m p 182°C (130mg, 16 5%), υ_{max} ($CHCl_3$) 1735, 1690cm^{-1}, δ_H($CDCl_3$) 10 4 (1H, br), 7 82 (1H, dd), 7 46 (1H, s), 7 46-7 17 (4H, m), 4 27(1H, m), 3 83(3H, s), 3 73(2H, 2 x 2nd order multiplets), 2 37 (3H, s), 2 33 (3H, s), δ_C 185 3, 155 1, 132 4, 129 7, 128 0, 127 1, 126 0, 125 8, 124 7, 60 0, 48 7, 30 1, 16 5, *m/z* (%) 377(100, M), 205(25), 177(48)

5,6-Dihydro-3-hydroxy-2,4-dimethylindeno[2,1-b]indole (1,2-Dimethyl-2-hydroxy-DHII)

5,6-Dihydro-2,4-dimethyl-3-methoxyindeno[2,1-*b*]indole (50mg) in dichloromethane (1cm^3) was cooled to -78°C and treated with boron tribromide (0 1cm^3) After stirring for a few minutes, the reaction mixture was allowed to warm to room temperature and poured onto crushed ice After the addition of excess sodium hydrogen carbonate the product was extracted from the reaction mixture with dichloromethane and the combined dried extracts were evaporated to give a colourless solid This was chromatographed on silica eluting with dichloromethane to afford the title compound as a

microcrystalline solid, m p 192-194°C, δ_H 10 2(1H, br s), 7 8(1H, br s), 7 5-7 0 (5H, br m), 3 62(2H, s), 2 35(3H, s), 2 30(3H, s), *m/z* (%) 249(100, M), 234(55), 204(15)

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