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THE CHEMISTRY OF THE PYRIDO[4,3-*b*]CARBAZOLES PART 15[1]

THE SYNTHESIS OF UNSYMMETRICALLY 1,4-DISUBSTITUTED CARBAZOLES AND THEIR USE IN THE SYNTHESIS OF 6H-PYRIDO-[4,3-*b*]CARBAZOLES

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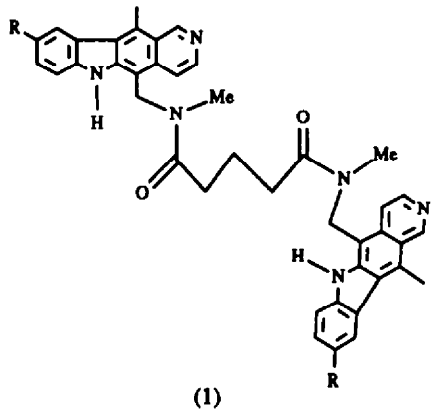
Abstract: A new construction of unsymmetrically 1,4-disubstitued carbazoles has been devised and used in the synthesis of the alkaloid olivacine. The starting materials are gramines and the sodium salts of 2-cyano-4-oxopentanonitriles. These afford 4-cyano-5-(indol-3-yl)pentan-2-ones, which can be cyclised by treatment with acetic acid and then aromatised to yield carbazoles suitably functionalised for subsequent conversion into 6*H*-pyrido[4,3-*b*]carbazoles unsymmetrically substituted at C-5 and C-11. Attempts to develop this as a general approach to 5-alkylamino-6*H*-pyrido[4,3-*b*]carbazoles have, however, encountered a number of unforeseen problems.

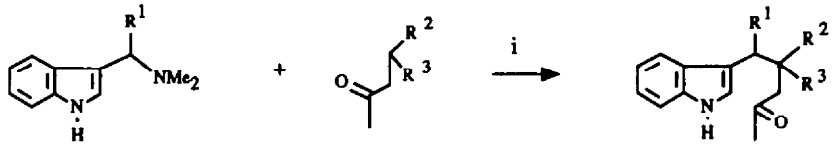
In previous work we described the synthesis of the 9-methoxylated 'dehydrodimer' of ellipticine (1, R=OMe).[2] This compound which shows anticancer activity *in vitro* comparable to 9-hydroxyellipticine, one of the most cytotoxic ellipticines,[3] was to have been *O*-demethylated to the phenol (1, R=OH) in the expectation of a further enhancement of activity. Unfortunately the conditions needed to effect this conversion produce extensive decomposition of the molecule. This caused us to consider alternative syntheses of ellipticine 'monomers' containing the more easily cleaved 9-*O*-benzyloxy group, and rather than use our usual approach to such compounds,[4] we chose to apply the Cranwell-Saxton route to pydrido[4,3-*b*]carbazoles.[5] This synthesis, modified by Birch and Jackson,[6] involves the use of carbazoles as starting materials, which are in turn obtained by the reaction of symmetrical 1,4-diketones with indoles.



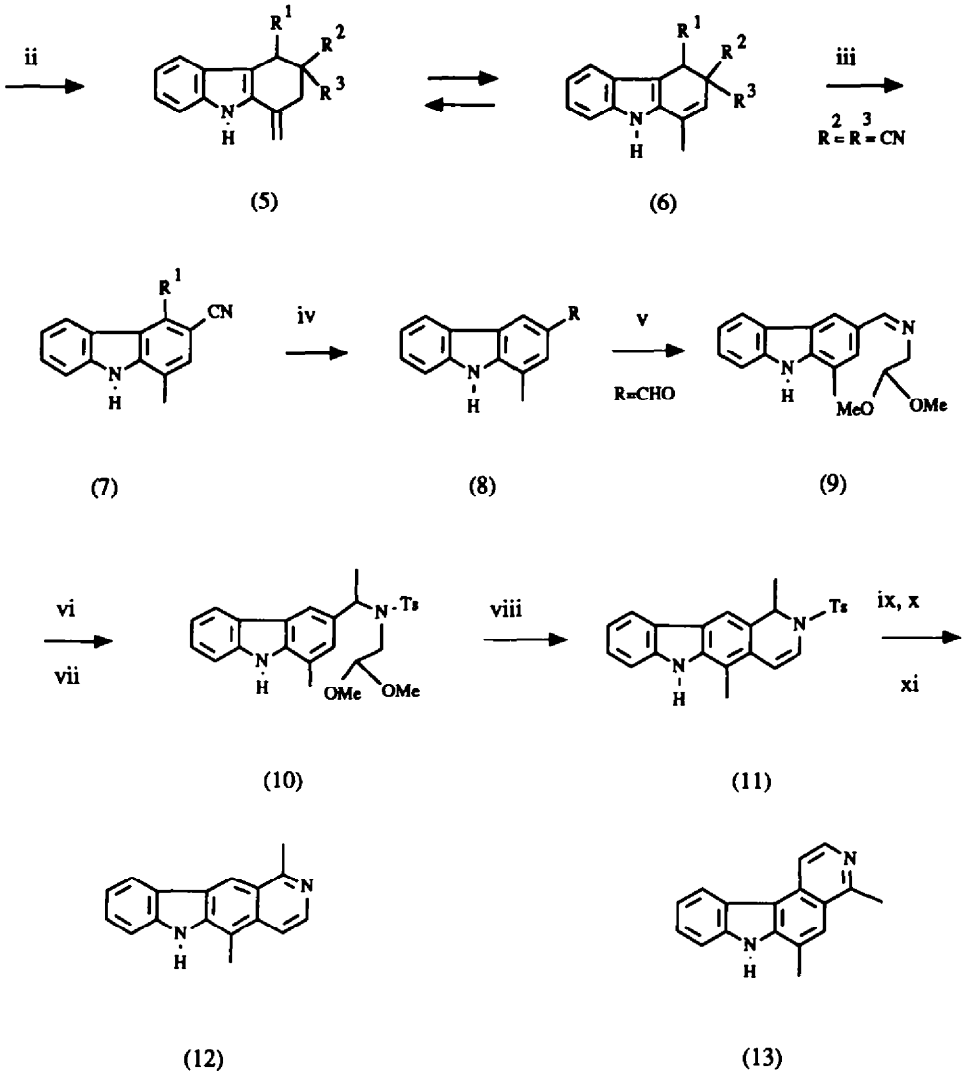
(1)

Unsymmetrical ketones give mixed products, and since we wished to obtain ellipticines with different substituents at C-5 and C-11 we sought first to resolve this problem. Thus a new strategy to unsymmetrically carbazoles was evolved, wherein a gramine derivative (2) is reacted with ethyl 2-cyano-4-oxopentanoate (3, R^2=CN;R^3=CO_2Et) to give the indoles (4, R^2=CN; R^3=CO_2Et). The indoles may be cyclised to the 3,4-dihydro-2*H*-carbazoles (5, R^2=CN; R^3=CO_2Et) by heating with 50% acetic acid, and these products aromatised to the corresponding carbazoles (7) through reactions first with lithium chloride in hot DMSO, and then treatment of the crude reaction products with DDQ. The carbazoles so formed bear a cyano group at C-3 which may then be elaborated into the appropriate substituent to allow final ring closure to the required pyrido[4,3-*b*]carbazoles. This method was tested in a total synthesis of the alkaloid olivacine (12) (Scheme 1).[7]

All steps in this reaction sequence worked well, except that in the final ring-closure reaction the *N*-toluenesulphonyldihydroisoquinoline (11) was isolated rather than the expected fully aromatic pyridocarbazole olivacine. This added an extra step to the synthesis since it became necessary to react this product with sodium in liquid ammonia in order to form olivacine. We did not detect any trace of the angular isomer (13) of the alkaloid, which is possible through ring closure of the acetal (10) at C-4 rather than at C-2.[8]



(2) (3) (4)



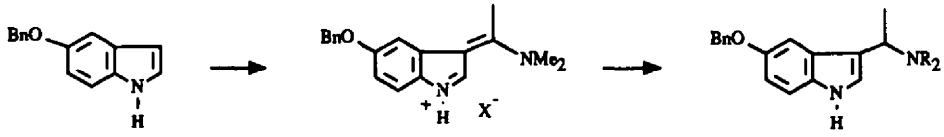
Scheme 1: The synthesis of olivacine

Reagents: i DMAD;ii HOAc/H_2O;iii SiO_2;iv DIBAL;v $NH_2CH_2CH(OMe)_2$;vi MeLi;vii TsCl/Na_2CO_3;viii HCl; ixNa/NH_3.

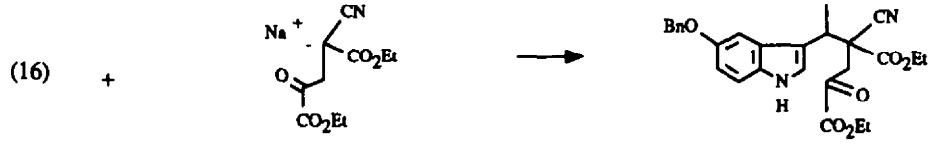
Whether the exocyclic or the endocyclic doubly bonded product (5) or (6), respectively, is formed in the cyclisation of the indoles (4) seems to be a function of the substituent groups R^2 and R^3. Thus, for example, the indole (4, R^1=H; R^2=Ac: R^3=CO_2Et) gives predominantly the endocyclic tricycle (6, R^1=H; R^2=Ac: R^3=CO_2Et), whereas (4, R^1=H; R^2= R^3= CN) affords only the exocyclic product. For the conversion of the last compound into the corresponding carbazole (8, R=CN) it is only necessary to absorb it onto silica and heat this material to 250C°. Contrary to a literature report,[9] we note that the ketone (8, R=COMe) does not react with the dimethylacetal of aminoacetaldehyde to form the methyl derivative of

the imine (9), hence it is necessary to use the aldehyde (8, R=CHO) instead and to introduce the future C-11 methyl group of olivacine by reacting the imine (9) with methyl lithium. Overall the synthesis is not expanded, of course, since the methylated imine does not require reduction.

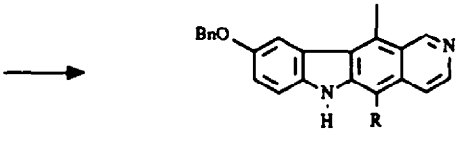
In order to continue this work we next selected the ethoxycarbonylcarbazole (19, R=CO_2Et) as a starting material for further elaboration to the dehydrodimer (1, R=OH). For the preparation of this carbazole the gramine derivative (16, R=Me) was required and this compound was obtained through the reaction of 5-benzyloxyindole (14) with *N,N*-dimethylacetamide in the presence of phosphorus oxychloride. The intermediate (15) was then reduced with sodium borohydride without isolation. If ammonia is added prior to the reduction step the product is the primary amine (16, R=H). The gramine (16, R=H or Me) was then to be reacted with the anion (17) of diethyl 4-cyano-2-keto-1,5-pentandioate and the product (18) converted by a series of reactions, similar to those of scheme 1, into a monomeric ellipticine suitable for elaboration to the dehydrodimer (1, R=OH).



(14) (15) (16)



(17) (18)



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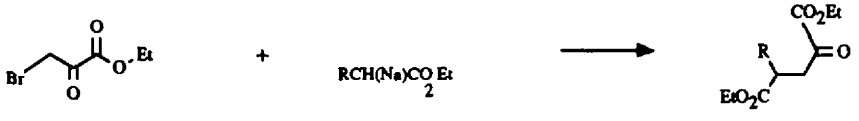
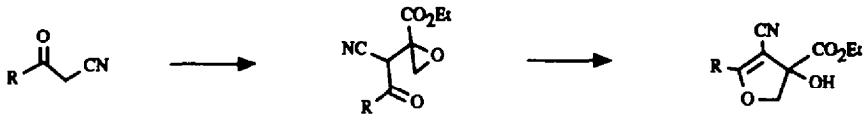


(20) (21) (22)

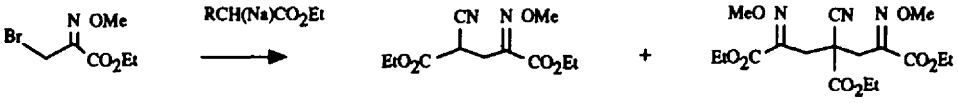
Unfortunately in our hands reactions of the enolate anions (21, R=CN or CO_2Et) with ethyl bromopyruvate (20) failed to give the required diesters (22), instead complex mixtures formed. In line with these results Mansour[10] has recently shown that, although ethyl bromopyruvate alkylates β-ketonitriles (23) under basic conditions, the intermediate products are keto-epoxides (24) which react further to form

isolable dihydrofurans (25).



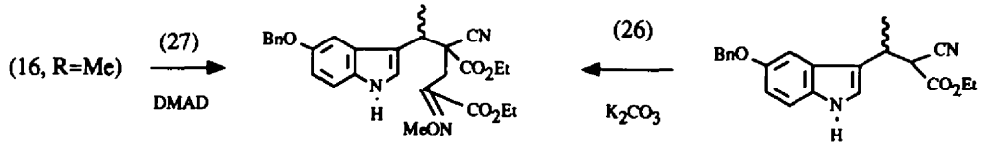
(22) (24) (25)

In order to avoid this problem we next formed the ethylene acetal of ethyl bromopyruvate, but this failed to react with the enolate anions. This is undoubtedly due to steric factors, since the *O*-methyloxime (26)[11] reacts with sodium ethyl cyanoacetate to form a mixtures of the mono- and di-alkylated products (27) and (28) respectively.

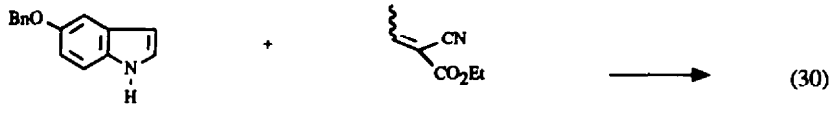


(26) (27) (28)

The first of these was reacted with the gramine (16, R=Me) in the presence of dimethyl acetylenedicarboxylate[12] to give the indole (29) in 17 % yield. An alternative synthesis of this compound through the reaction of the gramine first with the anion of ethyl cyanoacetate, followed by reaction of the product (30) with the *O*-methyloxime of ethyl bromopyruvate was frustrated by the poor yield in the first reaction - 27%. However, the compound (30) is formed in 68% yield by heating ethyl 2-cyanobut-2-enoate (31) and 5-benzyloxyindole (14) in a mixture of acetic anhydride and acetic acid at 90°C. Montmorillite clay in boiling dichloromethane[13] is less satisfactory in promoting this reaction and only affords the indole (30) in 27% yield. When the indole is treated with the bromoester (26) and potassium carbonate in dry DMF the desired compound (29) was formed in 74% yield as a mixture of diastereomers.



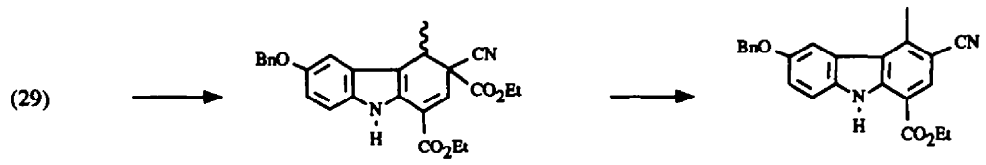
(29) (30)



(14) (31) (30)

Standard methods for the deprotection of the *O*-methyloximo function of this product failed,[14] complex mixtures resulted, and treatment with hot aqueous acids leads to the diester (27) and resin which arises presumably from the polymerisation of 5-benzyoxy-3-vinylindole which must be the second component of

the retro-alkylation reaction. Conversion of the indole (29) to the required dihydrocarbazole (32) does occur when the compound is treated with dioxane saturated with hydrogen chloride, or when it is heated with ethyl polyphosphate. In both cases, however, the yields were 20-25%. Aromatisation of the dihydrocarbazole (32) to the corresponding nitrile (33) was achieved in 45% yield by treating it with lithium chloride in aqueous DMSO.[15]

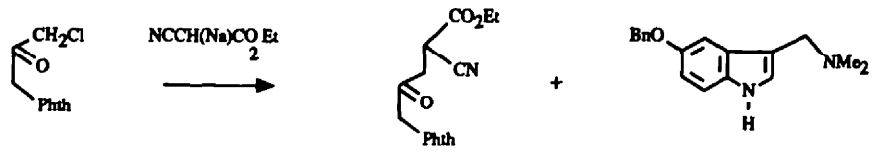


(32) (33)

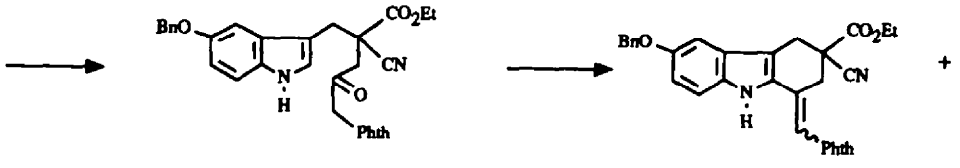
Although the carbazole bears all the appropriate functionalities for subsequent conversion into 5-alkylated ellipticines, several steps are still required and the low productivity of the synthesis caused us to consider a more direct approach in which an aminoalkyl side chain of the target ellipticine is appended to the carbazole precursor early in the procedure. For this purpose we selected the synthon (35), which was obtained from the anion of ethyl cyanoacetate and the chloroketone (34). This compound was then reacted with the 'simple' gramine (36) in the presence of diethyl acetylenedicarboxylate to give the indole (37) in an overall yield of 65%. Cyclisation to a mixture of the dihydrocarbazoles (38) and (39) was achieved by heating this product with 4-toluene sulphonic acid in toluene (combined yield 96%).

The major component of this mixture (38) crystallised out from dichloromethane solution and we hoped that de-ethoxylation and aromatisation would now provide the protected carbazole (40), which would allow us to complete the synthesis of a model for subsequent construction of the dehydrodimer (1, R=OH). However, no reaction occurred between the carbazole (38) and lithium chloride in DMSO and we sought to obtain the corresponding methyl ester by transesterification with a large excess of methanol containing 4-toluenesulphonic acid. Instead of the corresponding methyl ester, however, the ring opened compound (41, R=OMe) was obtained. In another attempt to de-ethoxycarbonylate the carbazole (38), it was treated with potassium cyanide in HMPA at 125°C. In this case the product was the nitrile (44), and it is now clear that the intermediate anion (42) eliminates the phthalide anion to afford the diene (43) which then isomerises to the nitrile (41). In a final attempt to resolve this problem we attempted to remove the phthalimido group which acts as a leaving group. However, reaction of the carbazole (38) with hydrazine in aqueous methanol gave only the semicarbazide (41, R=$NHNH_2$).

Further efforts to hydrolyse and aromatise this product on to the aminocarbazole only served to bring about its decomposition. It is now clear that success in this type of reaction can only be achieved if the substituent at C-1 on the carbazole unit is a poor leaving group, and in further work we hope to solve this problem by selecting appropriate functionalities at this site.

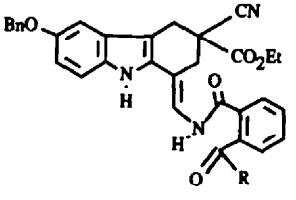


(34) (35) (36)



(37) (38)

(39) (40)



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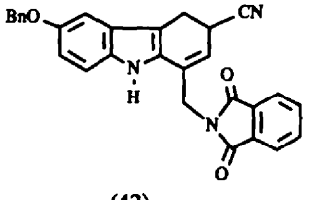
(38) 

(42)

(43) (44)

EXPERIMENTAL

U.v. spectra were recorded on a Perkin-Elmer 402 instrument for solutions in 95% ethanol. ^{1}H N.m.r. spectra were obtained at 270MHz and ^{13}C n.m.r. spectra at 67.8 MHz using tetramethylsilane as internal standard in deuteriochlorform solution, unless stated otherwise. The instrument used was a J.E.O.L. MNGXFT spectrometer. Mass spectra were measured on a VG 7070E instrument. All solvents, other than ethanol, were distilled prior to use. Petroleum ether refers to light petroleum, b.p. 60-80C°.

2-Cyano-4-oxopentanonitrile (3, R^2=R^3= CN)

A solution of malononitrile (3.3g, 50 mmol) in dry THF (10 cm^3) was added, dropwise, to a cooled, stirred suspension of sodium hydride (1.2g, 50 mmol) in dry THF (30 cm^3) under a nitrogen atmosphere. After the addition, the ice bath was removed and the reaction mixture stirred for a further 30 minutes before the resultant suspension was slowly injected, *via* a cannula, into a cooled solution of chloroacetone (5.3 cm^3, 66 mmol) in dry THF (30 cm^3). The reaction mixture was stirred for 1h before the solvent was removed at reduced pressure. The residue was purified by bulb to bulb distillation (220°C, 0.3 mmHg) to yield 4.9g (79%) of colourless crystals which were recrystallised from chloroform/pet. ether; m.p. 55-56°C; υ_{max}CHCl$_3$)cm^{-1} 2200 (C≡N), 1700 (C=O); δ_H (CDCl$_3$) ppm 4.21 (1H, t, *J* = 6Hz, C*H*), 3.25 (2H, d, *J*= 6Hz, CH_2), 2.30 (3H, s, CH_3); *m/z* (70 eV) 43 (100%), (C.I.), 123 [(M+I)$^+$,100%] [Found: C, 58.6; H, 5.0; N, 22.5 $C_6H_6N_2O$ requires: C, 59.0; H, 4.95; N, 22.9%].

4,4-Dicyano-5-(3-indolyl)pentan-2-one (4, R^1=H; R^2=R^3= CN)

A solution of the ketone (3, R^2=R^3= CN) (2g, 16.4 mmol) and dimethyl acetylenedicarboxylate (2.01 cm^3, 16.4 mmol) in dry THF (15 cm^3) was added, dropwise, to a cooled solution of gramine (2.85g, 16.4 mmol) in dry THF (40 cm^3), under a nitrogen atmosphere.The reaction mixture was stirred for 3h. The solvent was removed at reduced pressure and the residue purified by column chromatography (pet. ether: ethyl acetate/ 50:50, R_F = 0.65). The title compound was isolated as white plates (2.90g, 71%), which recrystallised from ethyl acetate/pet. ether, m.p. 125-126°C; ν_{max} (CHCl$_3$) cm^{-1} 3410 (N-H), 2200 (C≡N), 1680 (C=O); δ_H ($d_6$acetone) ppm 10.40 (1H, s, exchanges, N-*H*), 7.70 - 6.90 (5H, m, aromatic protons), 3.52 + 3.35 (2 x 2H, 2 x s, 2 x CH_2), 2.10 (3H, s, CH_3); *m/z* (70eV) 251 (M$^+$, 10%), 130 (100%); λ_{max} nm 289, 280, 219 [Found: C, 71.7; H, 5.2; N, 16.5 $C_{15}H_{13}N_3O$ requires: C, 71.7; H, 5.2; N, 16.7%].

4-Cyano-4-ethoxycarbonyl-5-(3-indolyl)pentan-2-one (4, R^1=H; R^2=CN; R^3= CO_2Et)

The same procedure was used as for the synthesis of the indole (4, R^1=H; R^2=R^3= CN), starting this from the ketone (3, R^2=CN; R^3= CO_2Et)[16] (1.5g, 8.88 mmol). The title compound (2.60g, 98%) was isolated as colourless crystals, which recrystallised from ethyl acetate/pet. ether, m.p. 148°C; R_F = 0.9 (pet. ether:ethyl acetate: triethylamine 4:1:1), ν_{max} (Nujol) cm^{-1} 3420 (N-H), 2250 (C≡N), 1730 (C=O), 1710 (C=O); δ_H (d^6 acetone) ppm 10.50 (1H, s, exchanges, N-*H*), 7.50-6.70 (5H, m, aromatic protons), 3.92 (2H, q, *J* = 6Hz, OCH_2CH$_3$), 3.40-3.20 (4H, m, 2 x CH_2), 2.07 (3H, s, CH_3 C=O), 1.12 (3H, t, *J* = 6Hz, OCH$_2$CH_3); λ_{max} nm (ε)289 (2600), 281 (3000), 221 (1400); *m/z* (70eV) 298 (M$^+$, 10%), 130 (100%), 43 (23%) [Found: C, 68.1; H, 6.2; N, 9.4 $C_{17}H_{18}N_2O_3$ requires: C, 68.5; H, 6.0; N, 9.4%].

4-Acetyl-4-cyano-5-(3-indolyl)pentan-2-one ((4, R^1=H; R^2=CN; R^3= COMe)

To a stirred solution of gramine (4.35g, 25 mmol) in dry THF (30 cm^3), under a nitrogen atmosphere,

was slowly added a solution of freshly distilled dimethyl sulphate (2.4 cm^3, 3.14g, 25 mmol) in dry THF (25 cm^3). On addition, a pink gum formed. In a separate flask, a solution of the ketone (3, R^2=CN; R^3= COMe) (4.23g, 25 mmol) in dry THF (35 cm^3) was slowly added to a stirred cooled suspension of NaH (0.6g, 25 mmol) in dry THF (15 cm^3). After the addition was complete, the ice bath was removed and the mixture stirred at ambient temperature for 30 minutes. The resultant purple solution was then slowly transferred, *via* a cannula, into the first reaction vessel. The mixture was shaken until stirring was possible, and the mixture was then stirred for 16h. The solvent was removed and the residue partitioned between chloroform (25 cm^3) and 2M HCl (25 cm^3). The aqueous layer was washed with chloroform (2 x 15 cm^3) and the combined organic layers were washed with water (2 x 25 cm^3), brine (25 cm^3) and dried ($MgSO_4$). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet. ether/ethyl acetate) to yield the title compound as a pale red oil (6.22g, 79%). R_F = 0.61 (pet.ether:ethyl acetate 4:1). ν_{max} ($CHCl_3$) cm^{-1} 3400 (N-H), 1710 (C=O), 1750 (C=O); δ_H ($CDCl_3$) ppm 8.83 (1H, s, exchanges, N-H), 7.40-6.78 (5H, m, aromatic protons), 4.13 (2H, q, J = 7Hz, OCH_2CH_3), 3.50 (2H, q, J = 4Hz, CH_2), 3.05 (2H, s, CH_2), 2.38 + 1.92 (2 x 3H, 2 x s, 2 x CH_3C=O), 1.16 (2H, t, J = 7Hz, OCH_2CH_3); δ_C ($CDCl_3$) ppm 206.9 (*C*=O), 205.8 (*C*=O), 171.4 (CO_2Et), 135.6 (indole *C*-8), 127.7 (indole *C*-9), 123.1 (indole *C*-2), 121.6, 119, 117, 111 (indole *C*-4, *C*-5, *C*-6, *C*-7), 108 (indole *C*-3), 62.6 [*C* ($COCH_3$) CO_2Et] 61.3 (CH_2), 46.4 (CH_2COCH_3), 29.5 (CH_3 C=O), 28.8 (OCH_2CH_3), 27.4 ($COCH_3$), 13.5 ($CO_2CH_2CH_3$); *m/z* (C.I.) 315 (M^+, 32%), 130 (100%).

The same procedure used for the synthesis of the indole (4, R^1=H;R^2=R^3=CN) was employed to convert the ketone (3, R^2= CN;R^3=COMe)[17] (1.99g, 10.84 mmol) into the indole (4, R^1=H;R^2= CN;R^3=COMe). However, after the work-up procedure and column chromatography (pet.ether/ethyl acetate), the required product was found to be contaminated with dimethyl 2-(*N,N*-dimethyl amino)butenedioate.[18] Extensive column chromatography did not completely separate the two compounds.

3,3-Dicyano-3,4-dihydro-1-methylene-2H-carbazole (5, R^1=H;R^2=R^3=CN)

A solution of the indole (4, R^1=H;R^2=R^3=CN) (1.45g, 5.74 mmol) in 50% aqueous acetic acid (75 cm^3) was heated at reflux for 4h. After cooling, the solvent was removed under reduced pressure and the residue partitioned between saturated $NaHCO_3$ solution (75 cm^3) and ethyl acetate (3 x 50 cm^3). The combined organic layers were washed with water (100 cm^3), brine (50 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the title compound as a colourless solid (1.43g, 99%), which crystallised from ethyl acetate, m.p. 215°C. R_F = 0.84 (pet.ether:ethyl acetate 1:1). υ_{max} ($CHCl_3$) cm^{-1} 2400 (N-H), 2210 (C≡N), 1620 (C=C); δ_H (d^6 acetone) ppm 10.50 (1H, s, exchanges, N-*H*), 7.60-6.92 (4H, m, aromatic protons), 5.66 + 5.20 (2 x 1H, 2 x s, olefinic protons), 3.64 + 3.31 (2 x 2H, 2 x s, 2 x CH_2); λ_{max}nm 305, 272, 212; *m/z* (70eV) 233 (M^+, 100%), 232 (23%), 155 (57%), 149 (30%), 57 (23%) [Found: C, 76.8; H, 4.7; N, 17.7 $C_{15}H_{11}N_3$ requires: C, 77.2; H, 4.8; N, 18.0%].

3-Cyano-3-ethoxycarbonyl-2H-3,4-dihydro-1-methylenecarbazole (5, R^1=H;R^2=CN;R^3=CO_2Et)

The procedure used for the synthesis of the tetrahydrocarbazole (R^1=H;R^2=R^3 CN) was employed to convert the indole (4, R^1=H;R^2=CN;R^3 CO_2Et) (2.0g, 6.71 mmol) into (5, R^1=H;R^2=CN;R^3 CO_2Et) (1.86g, 99%). The title compound was isolated as colourless crystals recrystallised from chloroform/pet.ether, m.p. 133°C. R_F = 0.59 (pet. ether:ethyl acetate 1:1), ν_{max} ($CHCl_3$) cm^{-1} 3400 (N-H), 2250 (C≡N), 1720 (C=O), 1630 (C=C); δ_H ($CDCl_3$) ppm 8.32 (1H, br s, exchanges, N-*H*), 7.50-7.10 (4H,

m, aromatic protons), 5.20-4.96 (2 x 1H, 2 x s, olefinic protons), 4.30 (2H, q, J = 7Hz, OCH_2CH_3), 3.56 + 3.38 (2 x 2H, 2 x s, 2 x CH_2), 1.31 (3H, t, J = 7Hz, OCH_2CH_3); *m/z* (70eV), 280 (M^+, 48%), 207 (100%); λ_{max}nm (ϵ) 309 (54 500), 305 (54 900), 252 (21 700) [Found: C 72.8, H 5.7, N 9.9. $C_{17}H_{16}N_2O_2$ requires: C 72.8, H 5.8, N 10.0%].

3-*Acetyl*-3-*ethoxycarbonyl*-3,4-*dihydro*-1-*methylcarbazole* (6, R^1=H;R^2=CN;R^3= COMe).

The procedure used for the synthesis of the 3,4-dihydro-2*H*-carbazole (5, R^1=H;R^2=R^3=CN;) was employed to convert the indole (4, R^1=H;R^2=CN;R^3= COMe) (2.0g, 6.35 mmol) into a mixture of the 3,4-dihydrocarbazole (6, R^1=H;R^2=CN;R^3= COMe) and the isomeric 3,4-dihydro-2*H*-carbazole (5, R^1=H;R^2=CN;R^3= COMe) (1.36g, overall yield 72%). The mixture was purified by column chromatography (pet.ether/ethyl acetate) to yield a mixture of (6, R^1=H;R^2=CN;R^3= COMe) and (5, R^1=H;R^2=CN;R^3= COMe). δ_H($CDCl_3$)ppm; 8.80 (0.5H, s, N-*H*),8.30 (0.5H, s, N-*H*), 7.60 -7.00 (4H, m, rest of aromatic protons), 5.88 (0.5H, d , J = 1.5 Hz, endocyclic olefinic proton), 5.23 + 5.03 (2 x 0.5H, 2 x s, 2 x exocyclic olefinic protons), 4.52 - 4.04 (2H, m, 2 x OCH_2CH_3), 3.60 - 3.10 (3H, m, 3 x CH_2), 2.21 (3H, s, 2 x $COCH_3$), 2.05 (1.5H, s, H_2C=CCH_3), 1.58 - 1.08 (2 x 1.5H, m, 2 x OCH_2CH_3). The title compound was obtained as colourless crystals by crystallisation of the crude reaction product from ethyl acetate/pet.ether, m.p. 131°C, R_F = 0.74 (pet.ether:ethyl acetate 1:1), ν_{max} ($CHCl_3$) cm^{-1} 3420 (N-H), 1700 (C=O); δ_H($CDCl_3$) ppm 8.10 (1H, s, exchanges, N-*H*), 7.56-7.08 (4H, m, aromatic protons), 5.88 (1H, d, J = 1.5Hz, olefinic proton), 4.24 (2H, q, J = 7Hz, OCH_2CH_3), 3.50 (2H, d, J = 16Hz, CH_2), 2.21 (3H, s, $COCH_3$), 2.11 (3H, d, J = 1.5Hz, CH_2 = CCH_3), 1.23 (3H, t, J = 7Hz, OCH_2CH_3); *m/z* (70eV) 181 (28%), 101 (34%), 73 (23%), 43 (100%) [Found: C, 72.4; H, 6.4; N, 4.6 $C_{18}H_{19}NO_3$ requires: C, 72.7; H, 6.4; N, 4.7%].

3-Cyano-1-methylcarbazole (7, R^1=H)

The tetrahydrocarbazole (5, R^1=H;R^2=R^3=CN) (546 mg, 2.34 mmol) was preabsorbed onto silica gel (5.5g) and heated at 250°C under a stream of nitrogen. After 1h, the silica was allowed to cool and then washed with ethyl acetate (4 x 50 cm^3). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl acetate). The title compound was isolated as a pale yellow solid (198 mg, 41%), which recrystallised from ethyl acetate/pet.ether, m.p. 193°C; R = 0.42 (pet.ether:ethyl acetate/80:20), ν_{max} (Nujol) cm^{-1} 3450 (N-H), 2200 (C≡N); δ_H (d^6 acetone) ppm 10.83 (1H, br.s, exchanges, N-*H*), 8.04 - 6.82 (6H, m, aromatic protons), 2.50 (3H, s, CH_3); λ_{max} (95% ethanol) nm (ϵ) 336 (1200), 324 (1600), 310 (1900), 273 (21900), 261 (17100); *m/z* (70 eV) 206 (M^+, 100%), 205 (44%), 179 (62%), 151 (31%) [Found: C, 81.4; H,4.8; N, 13.6 $C_{14}H_{10}N_2$ requires: C, 81.5; H, 4.9; N, 13.6%].

3-*Ethoxycarbonyl*-1-*methylcarbazole* (8, R=CO_2Et)

The carbazole (5, R^1=H;R^2=CN;R^3=CO_2Et) (0.39g, 1.39 mmol) was preabsorbed onto silica gel (4g) and heated at 250°C under a stream of nitrogen for 2h. The silica gel was then allowed to cool and washed with ethyl acetate (4 x 50 cm^3). The solvent was removed and the residue purified by column chromatography (pet. ether/ethyl acetate). The title compound was isolated as a pale yellow solid (180mg, 50%), recrystallised from chloroform/pet.ether, m.p. 133-135°C, (lit.[19] 151°C) R_F = 0.34 (pet. ether : ethyl acetate 80:20), ν_{max} ($CHCl_3$) ppm 3450 (N-H), 1680 (C=O), 1600 (C=C); δ_H ($CDCl_3$) ppm 8.68 (1H, s,

H-4 of carbazole), 8.30 (1H, s, exchanges, N-*H*), 8.12-7.25 (5H, m, rest of the aromatic protons), 4.37 (2H, q, J = 7Hz, OCH_2CH_3), 2.57 (3H, s, CH_3), 1.45 (3H, t, J = 7Hz, OCH_2CH_3); λ_{max} nm 278, 269, 235; *m/z* (70eV) 253 (M^+, 65%), 208 (65%), 180 (29%), 68 (32%), 43 (100%), 28 (50%) [Found C, 75.9; H, 6.0; N, 5.6 Calc. for $C_{16}H_{15}NO_2$: C, 75.9; H, 5.9; N, 5.5%].

A second product was eluted from the column (R_F = 0.42 (pet. ether:ethyl acetate 80:20) and this was characterised as 3-cyano-1-methylcarbazole (7, R^1=H) (30mg, 10%).

1-Methyl-3-(methylsulphoxy)acetylcarbazole (8, R=$COCH_2SOMe$)

A solution of sodium hydride (103 mg, 4.29 mmol) in dry DMSO (3 cm^3) was stirred at 60-70°C, under a nitrogen atmosphere, until the evolution of hydrogen gas had ceased and the solution had become dark green in colour (approx 1h). Dry THF (4 cm^3) was added to the solution and the mixture cooled in an ice bath. A solution of the ester (8, R=CO_2Et) (363 mg, 1.4 mmol) in dry THF (4 cm^3) was added over a period of 5 minutes and the reaction mixture stirred for a further 30 minutes at room temperature. The reaction mixture was then poured into aqueous HCl (pH 4, 35 cm^3) and the aqueous layer thoroughly extracted with DCM (10 x 50 cm^3). Some yellow product precipitated and was filtered and washed with diethyl ether. The combined organic layers were washed with water (3 x 50 cm^3), brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure to yield a yellow solid which was triturated with diethyl ether, filtered and combined with earlier product (287 mg, 72%), m.p. 231°C, ν_{max} (Nujol) cm^{-1} 3140(N-H), 1650 (C=O), 1015 (S=O); δ_H (d^6 DMSO) ppm 10.00 (1H, s, exchanges, N-*H*), 8.60-7.27 (6H, m, aromatic protons), 4.58 (2H, ABq, J = 14Hz, CH_2),2.64 (3H, s, CH_3), 1.25 (3H, s, CH_3); λ_{max}nm 334, 294, 275, 236, 191; *m/z* (70eV) 285 (M^+, 17%), 208 (45%), 194 (47%), 78 (80%), 63 (100%) [Found: 285.1009 $C_{16}H_{15}NO_2S$ requires: 285.1001].

3-*Acetyl*-1-*methylcarbazole* (8, R=Ac)

Reaction of methyl lithium with the nitrile (8, R=CN)

To a solution of the nitrile (8, R=CN) (50mg, 0.24 mmol) in dry THF (6 cm^3), cooled to -78°C under a nitrogen atmosphere, was slowly added a solution of methyl lithium (0.50 mmol, 1.5m in ether). After the final addition, the reaction mixture was allowed to warm slowly to room temperature (at least 2h). The red solution was then cooled in an ice bath and methanol (1 cm^3) added. Next the solvent was removed at reduced pressure to leave an orange solid, which was redissolved in 50% aqueous acetic acid (9 cm^3) and gently refluxed for 30 minutes. The solvent was removed at reduced pressure, saturated $NaHCO_3$ solution (20 cm^3) added and extracted with ethyl acetate (3 x 10 cm^3). The combined organic layers were washed with water (2 x 15 cm^3), brine (15 cm^3) and dried (Na_2SO_4). The solvent was removed and the residue purified by column chromatography to yield the title compound as a colourless solid (53 mg, 98%), which crystallised from dichlorometane/pet.ether as small prisms, m.p. 178-180°C; R_F = 0.72 (pet.ether:ethyl acetate 1:1). ν_{max} ($CHCl_3$) cm^{-1} 3400 (N-H), 1650 (C=O), 1600 (C=C); δ_H (d^6 acetone) ppm 11.19-10.87 (1H, br.s, exchanges, N-*H*), 8.58-7.10 (6H, m, aromatic protons), 2.64 (3H, s, CH_3), 2.62 (3H, s, CH_3); λ_{max} nm 328, 288, 273, 236, 196; *m/z* (70eV) 223 (M^+, 62%), 208 (100%) [Found: C, 80.6; H, 5.6;, N, 6.2% $C_{15}H_{13}NO$ requires: C, 80.7; H, 5.8; N, 6.3%].

3-*Cyano*-3,4-*dihydro*-1-*methylene*-2*H*-*carbazole* (5, R^1=R^2=H;R^3=CN)

A mixture of the carbazole (5, R^1=H;R^2=CN;R^3=CO_2Et) (300 mg, 1.08 mmol), water (25 mg, 1.39

mmol) and LiCl (45 mg, 1.08 mmol) was stirred in DMSO (2 cm^3) at 160°C, under a nitrogen atmosphere for 48h. The reaction mixture was allowed to cool and then poured into water (20 cm^3). The aqueous layer was extracted with dichlorometane (4 x 15 cm^3) and the combined organic layers were washed with water (3 x 15 cm^3), brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed and the residue purified by column chromatography to yield the title compound as a colourless solid (49 mg, 50%), which crystallised from ethyl acetate/pet.ether, m.p. 145-148°C. R_F = 0.42 (pet.ether:ethyl acetate 4:1), ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2200 (C≡N), 1630 (C=C); δ_H ($CDCl_3$) ppm 8.18 (1H, s, N-*H*), 7.48-7.07 (4H, m, aromatic protons), 5.23 + 5.01 (2 x 1H, 2 x s, olefinic protons), 3.11 (3H, m, CH_2 + *CH*CN), 2.79 (2H, m, CH_2); λ_{max} nm 308, 242, 239, 206; *m/z* (70eV) 208 (M^+, 100%), 207 (28%), 155 (43%), 154 (25%) [Found: C, 80.4; H, 5.7; N, 13.2 $C_{14}H_{12}N_2$ requires: C, 80.8; H, 5.8; N, 13.5%]. This compound (25 mg, 0.12 mmol) can be converted into 3-cyano-1-methylcarbazole (7, R^1=H) by stirring in dry benzene (2 cm^3) under a nitrogen atmosphere with DDQ (30 mg, 0.13 mmol) and the dark green solution heated at reflux for 14h. The solvent was then removed and the residue purified by column chromatography to yield the title compound as a pale yellow solid [20 mg, 75% for the two steps from (5, R^1=H;R^2=CO_2Et;R^3=CN].

3-F*ormyl*-1-*methylcarbazole* (8, R=CHO)

To a stirred suspension of the nitrile (8, R=CN) (345 mg, 1.67 mmol) in dry benzene (5 cm^3), under a nitrogen atmosphere, was slowly added DIBAL (1.2 cm^3, 1.75 mmol, 1.5M). The suspension dissolved after the addition and the reaction mixture was stirred for 14h at room temperature, giving an orange precipitate. Water (2 cm^3) was added to the reaction mixture, the benzene was removed at reduced pressure and the residue gently refluxed in dilute H_2SO_4 (10 cm^3) for 2h. The reaction mixture was allowed to cool, and extracted with ethyl acetate (3 x 30 cm^3). The combined organic layers were washed with brine (30 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure. The residue was purified by column chromatography (pet.ether/ethyl acetate) to yield the title compound as a pale yellow solid (340 mg, 94%), which crystallised from ethyl acetate/pet.ether, m.p. 196°C (lit.,[18] 206-208°C); R_F = 0.70 (pet.ether:ethyl acetate 3:2); ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 1670 (C=O); δ_H (d^6 DMSO) ppm 11.79 (1H, br. s, exchanges, N-*H*), 10.01 (1H, s, *CH*O), 8.59 - 7.26 (6H, m, aromatic protons), 2.62 (3H, s, CH_3); λ_{max} nm (ε) 329 (1300), 290 (2700) 274 (3300), 236 (3000), 200 (3100); *m/z* (70eV) 209 (M^+, 100%), 208 (72%), 180 (46%) [Found: C, 80.0; H, 5.2; N, 7.1 calculated for $C_{14}H_{11}NO$: C, 80.4; H, 5.3; N, 6.7%].

3-([N-2,2-Dimethoxyethyl)iminomethyl]-1-methylcarbazole (9)

A solution of the aldehyde (8, R=CHO) (346 mg, 1.66 mmol) and aminoacetaldehyde dimethylacetal (191 mg, 0.2 cm^3, 1.82 mmol) in dry benzene (40 cm^3) was heated to reflux, using a Dean and Stark trap. After 4h, the reaction mixture was cooled and the solvent removed at reduced pressure to yield the title compound as an orange foam (472 mg, 96%). Attempts to crystallise the product failed and it was used without further purification; ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 1635 (C=N); δ_H ($CDCl_3$) ppm 8.84 (1H, s, ArC*H*=N), 8.28 (1H, s, exchanges, N-*H*), 8.01-7.16 (6H, m, aromatic protons), 4.77 (1H, t, *J* = 5.3Hz, $CH(OCH_3)_2$), 3.83 (2H, d, *J* = 5.3Hz, HC = N-CH_2), 3.45 (6H, s, $(OCH_3)_2$), 2.38 (3H, s, CH_3); λ_{max} nm (ε) 314 (15000), 288 (41800), 274 (48100), 238 (38100); *m/z* (70eV) 296 (M^+, 8%), 75 (100%) [Found: 296.3680 $C_{18}H_{20}N_2O_2$ requires: 296.3682].

3-[N-(2,2-Dimethoxyethyl)-N-(4-tolunesulphonyl)methylamino]-1-methylcarbazole (10)

A solution of the imine (9) (150 mg, 0.51 mmol) in dry THF (3 cm^3) was stirred under a nitrogen atmosphere at -78°C. To this solution was slowly added methyl lithium (0.7 cm^3, 1.11 mmol, 1.5M solution in diethyl ether). The mixture was kept at -78°C for 40 minutes and then allowed to warm slowly to O°C. A solution of saturated ammonium chloride (10 cm^3) was added and the mixture thoroughly stirred for 10 minutes. The two phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 10 cm^3). The combined organic phases were dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (pet.ether/ethyl acetate) to yield the title amine as a pale orange foam, (103 mg, 65%). The product was used without further purification. R_F = 0.23 (pet.ether : ethyl acetate/60:40); ν_{max} ($CHCl_3$) cm^{-1} 3420 (carbazole N-H), 3260 (aliphatic N-H), 2860 (O-CH_3); δ_H ($CDCl_3$) ppm 8.20 (1H, s, carbazole N-*H*), 8.04-7.17 (6H, m, aromatic protons), 4.49 (1H, t, *J* = 5.5Hz, C*H*(OCH_3)$_2$), 3.92 (1H, q, *J* = 6.6Hz, CH_3C*H*NH), 3.35 + 3.29 (2 x 3H, 2 x s, 2 x OCH_3), 2.75-2.60 (2H, m, NHCH_2), 2.51 (3H, s, C-1 CH_3), 1.47 (3H, d, *J* = 6.6Hz, CH_3CHNH), 1.25 (1H, s, CH_3CHN-*H*); λ_{max} nm (ϵ) 339 (3500), 326 (3800), 295 (15000), 260 (19900), 249 (27000), 239 (36600); *m/z* (70eV) 208 (100%), 99(40%), 98 (28%) [Found: 312.1836 $C_{19}H_{24}N_2O_2$ requires: 312.1848].

Tosyl chloride (460 mg, 2.4 mmol) and sodium carbonate (240 mg, 2.6 mmol) were added to a solution of the amine (144 mg, 0.46 mmol) in THF (2 cm^3) and water (4 cm^3). The reaction mixture was stirred at ambient temperature for 48h. However, t.l.c. analysis (pet.ether : ethyl acetate/60:40) indicated the presence of starting material. Additional quantities of tosyl chloride (115mg, 0.6 mmol) and sodium carbonate (60 mg, 0.57 mmol) were added and the mixture stirred for a further 14h. The reaction mixture was diluted with H_2O (14 cm^3) and extracted with ethyl acetate (3 x 10 cm^3). The combined organic layers were washed with 0.1N HCl (10 cm^3) H_2O (10 cm^3), saturated $NaHCO_3$ solution (10 cm^3), water (10 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure to give a pale yellow oil which was purified by column chromatography (pet.ether/ethyl acetate). The title compound was isolated as a very pale yellow solid (185 mg, 84%), and crystallised from chloroform/pet.ether, m.p. 153-154°C. R_F = 0.52 (pet.ether:ethyl acetate 3:2), ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 1590 (C=C); δ_H ($CDCl_3$) ppm 7.96 (1H, s, N-*H*), 7.87-6.81 (10H, m, aromatic protons), 5.24 (1H, q, *J* = 7.0Hz, CH_3C*H*NTs), 4.32 (1H, m, C*H*(OCH_3)$_2$), 3.33+ 3.16 (2 x 3H, 2 x s, 2 x OCH_3), 3.14 (2H, m, NCH_2CH), 2.47 (3H, s, C-1 CH_3), 2.40 (3H, s, tosyl CH_3), 1.65 (3H, d, *J* = 7.1Hz, CH_3CHNTs); λ_{max}nm (ϵ) 339 (6300), 324 (6900), 295 (27500), 260 (52700), 249 (69000), 239 (91000), 234 (81500), 201 (59100); *m/z*(70 eV) 466 (M^+, 5%), 208 (87%), 75 (100%) [Found C, 66.6; H, 6.4; N, 5.8 $C_{26}H_{30}N_2O_4S$ requires: C, 66.9; H, 6.5; N, 6.0%].

1,2-Dihydro-1,5-dimethyl-2-(4-toluenesulphonyl)-6H-pyrido[4,3-b]carbazole (11)

6M HCl (2 drops) was added to a stirred solution of the acetal (10) (97 mg, 0.21 mmol) in dry dioxane (2 cm^3), under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 16h. The reaction mixture was heated at 60°C for 6h., then added to 2M NaOH solution (15 cm^3) and extracted with ethyl acetate (3 x 15 cm^3). The combined organic layers were washed with water (3 x 15 cm^3), brine (15 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure. The residue was purified by column chromatography (pet. ether:ethyl acetate) to yield the title compound as a colourless oil (34 mg, 45%); R_f = 0.79 (pet.ether:ethyl acetate 7:3); ν_{max} ($CHCl_3$) cm^{-1} 3460 (N-H); δ_H ($CDCl_3$) ppm 7.96 (1H, s, N-*H*), 7.93-6.97 (9H, aromatic protons), 6.80 (1H, dxd, *J* = 6.2Hz, TsN-C*H*=CH), 6.31 (1H, dxd, *J* = 7.3Hz, TsN-CH=C*H*), 5.35 (1H, m, CH_3C*H*NTs), 2.45 (3H, s, C-5 CH_3), 2.25 (3H, s,TsCH_3), 1.43 (3H, d, *J* = 6.6Hz,

CH_3CHNTs); λ_{max} nm (ϵ) 331 (7600), 258 (10600); *m/z* (70eV), 402 (M^+, 10%), 387 (30%), 247 (23%), 232 (30%), 91 (38%), 73 (26%), 42 (100%) [Found: 402.1400 $C_{24}H_{22}N_2O_2S$ requires: 402.1391].

1,5-*Dimethylpyrido*[4,3-*b*]*carbazole* (12) (Olivacine)

A solution of the dihydroisoquinoline (11) (20 mg, 0.05mmol) was stirred in liquid ammonia (3 cm^3) at -78°C, under a nitrogen atmosphere. Sodium metal (2.0 mg, 0.075 mmol) was added and the mixture was stirred for 40 minutes. Ammonium chloride (10 mg) was added and the ammonia evaporated at room temperature, under a stream of nitrogen gas. The mixture was dissolved in methanol(5 cm^3) and 2M H_2SO_4(1 cm^3) and warmed at 50 °C for 1h. The methanol was then removed at reduced pressure, and the yellow residue was partitioned between diethyl ether (5 cm^3) and 2M HCl (5 cm^3). The acidic layer was basified with solid NaOH (with cooling) and extracted with DCM (2 x 10 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated to yield the title compound as a yellow solid (8.5 mg, 70%). The product was found to be identical with an authentic sample.[20] m.p. 315-320°C (lit.,[17] 320-324°C); R_F = 0.39 (DCM:ethanol:ammonia 200:8:1) [Found: 246.1151 Calculated for $C_{17}H_{14}N_2$: 246.1155].

1-(5-Benzyloxy-3-indolyl)-N,N-dimethylaminoethane (16, R=Me)

A solution of acetaldehyde (217 mg, 4.93 mmol) in benzene (1 cm^3) was added to a mixture of 5-benzyloxyindole (1.0g, 4.48 mmol), dimethylamine hydrochloride (402 mg, 4.93 mol), K_2CO_3 (124 mg, 0.9 mmol), acetic acid (2 cm^3) and propenoic acid (1 cm^3) at -5°C. The mixture was kept at -5°C for 1h then stirred at 4°C for 5 days. The mixture was poured into ice water (20 cm^3) and extracted with diethyl ether (2 x 20 cm^3). The aqueous layer was made basic with 10 M NaOH and extracted with ethyl acetate (2 x 30 cm^3). The solvent was dried (Na_2SO_4) and removed at reduced pressure to give an off-white solid (0.43 g, 33%), which was crystallised from ethyl acetate/pet.ether, m.p. 93-96°C. R_F = 0.35 (DCM:methanol:triethylamine 98:2:1); ν_{max} (Nujol) cm^{-1} 1580 (C=C); δ_H ($CDCl_3$) ppm 8.69 (1H, br s, N-*H*), 7.46-6.87 (9H, m, aromatic protons), 5.04 (2H, s, $OCH_2C_6H_5$), 3.80 (1H, q, *J* = 7.5Hz, CH_3CH NMe_2), 2.23 (6H, s, $N(CH_3)_2$), 1.48 (3H, d, *J* = 7.5Hz, CH_3CHNMe_2); λ_{max} nm (ϵ) 304 (7700), 294 (8400), 214 (31000); *m/z* (70eV) 249 (42%), 158 (66%), 91 (77%), 44 (100%), (C.I.) 292 (10%), 250 (100%), 249 (98%), 158 (48%), 91 (51%) [Found C, 77.5; H, 7.5; N, 9.4 $C_{19}H_{22}N_2O$ requires: C, 77.5; H, 7.5; N, 9.5%].

1-(5-Benzyloxy-3-indolyl)aminoethane (16, R=H)

Phosphorus oxychloride (10.7 cm^3, 0.115 mol) was added dropwise to a cooled, stirred solution of *N,N*-dimethylacetamide (10.7 cm^3, 0.115 mol) in dry toluene (300 cm^3), under a nitrogen atmosphere. After the addition, the mixture was stirred for 1h. 5-Benzyloxyindole (25.6g, 0.115 mol) was added and the mixture stirred for 17h. On leaving to settle, the mixture separated into two layers. The top layer was decanted off and the bottom, orange layer was washed with diethyl ether (4 x 150 cm^3), decanting each time. The solvent was removed at reduced pressure and the remaining orange oil was dissolved in Analar methanol (800 cm^3). 0.89 NH_3 (16.5 cm^3) was added and the solution became pale green. Sodium borohydride (16.5g) was carefully added, portionwise, and the mixture stirred for a further 2.5h. The solvent was removed at reduced pressure and the residue partitioned between 2M HCl (400 cm^3) and DCM (200 cm^3). The layers were separated, the aqueous layer made basic with solid KOH (with cooling) and extracted with DCM (3 x 200 cm^3). The organic layers were combined, dried (Na_2SO_4) and evaporated to give a brown solid. Crystallisation from ethyl acetate/pet. ether gave the title compound as a colourless solid (16.4g, 54%), m.p. 125-128°C; R_F = 0.21 (DCM:methanol:triethylamine 96:4:2); ν_{max} (Nujol)cm^{-1}

3345 (indole N-H), 3280 (aliphatic N-H); δ_H (d^6 DMSO) ppm 10.66 (1H, br s, exchanges, indole N-*H*), 7.49-6.76 (9H, m, aromatic protons), 5.08 (2H, s, $OCH_2C_6H_5$), 4.22 (1H, q, J = 7.5Hz, CH_3CH NH_2), 1.79 (2H, br s, exchanges NH_2), 1.26 (3H, d, J = 7.5Hz, CH_3CH NH_2); λ_{max}nm (ϵ) 274(10 100), 250(8 700); *m/z* (70eV) 249 (50%), 158 (81%), 130 (28%), 91 (100%) [Found: C, 76.3; H, 6.8; N, 10.3 $C_{17}H_{18}N_2O$ requires: C, 76.7; H, 6.8; N, 10.5%].

Ethyl-3-bromo-2-methoxyiminopropananoate (26)

A mixture of methoxyamine hydrochloride (3.30 g, 39.46 mmol), ethyl bromopyruvate (7.70 g, 39.46 mmol), chloroform (120 cm^3) and methanol (80 cm^3) was vigorously stirred at ambient temperature for 16h. The solvent was removed at reduced pressure, and the residue dissolved in DCM (100 cm^3). This was washed with water (50 cm^3), brine (50 cm^3) and dried (Na_2SO_4). The solvent was evaporated at reduced pressure to give a clear oil which was purified by bulb to bulb distillation (120°C/1.2 mmHg) to yield the title compound as a colourless oil (7.8g, 88%). R_F = 0.61 (pet.ether:ethyl acetate 4:1); ν_{max} (thin film) cm^{-1} 1720 (C=O), 1592 (C=N); δ_H ($CDCl_3$) ppm 4.38 (2H, q, J = 7.5Hz, OCH_2CH_3), 4.20 (2H, s, $BrCH_2$), 4.17 (3H, s, $NOCH_3$), 1.38 (3H, t, J = 7.5Hz, OCH_2CH_3); λ_{max} nm (ϵ) 234 (3,600); *m/z* (70ev) 225 (37%), 223 (37%), 181 (60%), 179 (100%), 177 (34%), 144 (89%), 29 (100%) [Found: C, 31.7; H, 4.5; N, 5.6 $C_{16}H_{10}BrNO_3$ requires C, 32.2; H, 4.5; N, 6.3 %].

Diethyl 2-cyano-4-methoxyimino-1,5-pentadioate (27)

and *Diethyl 4-cyano-4-ethoxycarbonyl-2,6-di(methoxyimino)-1,7-heptadioate* (28)

Ethyl cyanoacetate (504 mg, 0.47 cm^3, 4.46 mmol) was added dropwise to a stirred, cooled suspension of sodium hydride (107 mg, 4.46 mmol), in dry DMF (10 cm^3), under a nitrogen atmosphere. After the final addition, the ice-bath was removed and the mixture stirred at ambient temperature for 30 minutes. This pale green solution was then slowly injected, *via* a cannula, into a solution of the methoxime (26) (1.0g, 4.46 mmol) in dry DMF (10 cm^3). The reaction mixture was stirred for 10 minutes at ambient temperature and then poured into water (60 cm^3). The aqueous phase was extracted with ethyl acetate (60 cm^3) and the separated organic phase washed with water (3 x 30 cm^3) and brine (30 cm^3). The solvent was dried (Na_2SO_4) and evaporated to give 972 mg (85%) of a yellow oil. T.l.c. analysis (hexane:ethyl acetate 2:1) showed the oil to be a mixture of 2 components. The mixture was separated by column chromotography using the same solvent mixture and the first compound eluted was shown to be the monoalkylated product (27). (R_F = 0.56, hexane:ethyl acetate 2:1). However, the product was contaminated by ethyl cyanoacetate, but was obtained pure by bulb to bulb distillation (160°C/0.3 mmHg). Subsequently, the diester (27) was obtained as colourless crystals (302 mg, 26%), which recrystallised from chloroform/pet.ether, m.p. 32-33°C. ν_{max} ($CHCl_3$) cm^{-1} 2250 (C≡N), 1745 (C=0), 1715 (C=O), 1600 (C=N); δ_H ($CDCl_3$) ppm 4.36 (2H, q, J = 7.5Hz, $N{=}C{-}CO_2CH_2CH_3$), 4.26 (2H, q, J = 7.5Hz, $NCCHCO_2CH_2CH_3$), 4.12 (3H, s, $NOCH_3$), 4.02 (1H, t, J = 7.5Hz, $NCCHCO_2Et$), 3.19 (2H, d, J = 7.5Hz, $CHCH_2C{=}NOCH_3$), 1.37 (3H, t, J = 7.5Hz, $N{=}CCO_2CH_2CH_3$), 1.32 (3H, t, J = 7.5Hz, $NCCHCO_2CH_2CH_3$); λ_{max} nm (ϵ) 227 (4100); *m/z* (70eV), 225 (84%), 183 (100%), 155 (83%), 153 (52%), 137 (60%), 125 (94%), (C.I.) 257 [$(M+1)^+$, 100%], 211 (28%), 153 (22%), 125 (43%), 114 (96%) [Found: C, 51.5; H, 6.6; N, 10.6 $C_{11}H_{16}N_2O_5$ requires: C, 51.6; H, 6.3; N, 10.9%].

The second compound eluted from the column: R_F = 0.42 (hexane:ethyl acetate 2:1), was shown to be the dialkylated product (28). This product was obtained as a colourless oil and was purified by bulb to bulb distillation (220°C/0.4 mmHg), (527 mg, yield 60%). ν_{max} (thin film) cm^{-1} 2250 (C≡N), 1720 (C=O), 1690

(C=O), 1590 (C=N); δ_H ($CDCl_3$) ppm 4.35 (4H, q, J = 7.5Hz, 2 x CH_3ON=$CCO_2CH_2CH_3$), 4.21 (2H, q, J = 7.5Hz, $NCCCO_2CH_2CH_3$), 4.07 (6H, s, 2 x $NOCH_3$), 3.28 (4H, ABq, J = 14Hz, 2 x CH_3ON = CCH_2), 1.35 (6H, t, J = 7.5Hz, 2 x CH_3ON = $CCO_2CH_2CH_3$), 1.30 (3H, t, J = 7.5Hz, $NCCCO_2CH_2CH_3$); λ_{max} nm (ϵ) 227 (7200); *m/z* (70eV) 399 (M^+, 4%), 145 (100%), 29 (100%) [Found: C, 51.2; H, 6.6; N, 10.1 $C_{17}H_{25}N_3O_8$ requires: C, 51.1; H, 6.3; N, 10.5%].

Ethyl 4,4-*dicyano*-2-*methoxyiminobutanoate* and

Diethyl 4,4-*dicyano*-2,6-*di(methoxyimino)*-1,7-*heptadioate.*

A solution of malononitrile (221 mg, 3.35 mmol) in dry DMF (4 cm^3) was added, dropwise, to a stirred, cooled suspension of sodium hydride (80 mg, 3.35 mmol) in dry DMF (4 cm^3), under a nitrogen atmosphere. After the final addition, the ice bath was removed and the mixture stirred at ambient temperature for 30 minutes. The anion solution was then cooled again and injected into a cooled solution of the methoxime (26) (750 mg, 3.35 mmol) in dry DMF (8 cm^3), under a nitrogen atmosphere. The mixture was stirred at O°C for 1h and then added to water (50 cm^3). This was extracted with ethyl acetate (60 cm^3) and the organic layer washed with H_2O (3 x 30 cm^3), brine (40 cm^3) and dried (Na_2SO_4). T.l.c. analysis of the residue revealed it to be a mixture of two components which were separated by column chromatography. The first product eluted (R_F = 0.51, hexane:ethyl acetate 2:1) was shown to be the monoalkylated product, and this was purified by bulb to bulb distillation (150°C/1.1 mmHg). The product was isolated as a colourless oil (181 mg, 29%); ν_{max} (thin film) cm^{-1} 2230 (C≡N), 1700 (C=O), 1590 (C=N); δ_H ($CDCl_3$) ppm 4.38 (2H, q, J = 7.5Hz, OCH_2CH_3), 4.32 (1H, t, J = 7.5Hz, $CH(CN)_2$), 4.17 (3H, s, C=$NOCH_3$), 3.31 (2H, d, J = 7.5Hz, $CH_2CH(CN)_2$), 1.37 (3H, t, J = 7.5Hz, OCH_2CH_3); λ_{max}nm(ϵ) 254(3100); *m/z* (70eV) 149 (20%), 136 (58%), 106 (100%), 29 (100%)[Found: 209.0799 $C_9H_{11}N_3O_3$ requires: 209.0804].

The second product eluted (R_F = 0.35, hexane:ethyl acetate 2:1) was an off white solid (312 mg, 54%), which crystallised from chloroform/pet.ether, m.p. 83-85°C. This compound was characterised as the dialkylated product; ν_{max} ($CHBr_3$) cm^{-1} 1720 (C=O), 1600 (C=N); δ_H ($CDCl_3$) ppm 4.38 (4H, q, J = 7Hz 2 x OCH_2CH_3), 4.18 (6H, s, 2 x $NOCH_3$), 3.40 (4H, s, 2 x $CH_2(CN)_2$), 1.41 (6H, t, J = 7Hz, 2 x OCH_2CH_3); λ_{max}nm(ϵ) 252(10 100); *m/z* (70eV) 145 (60%), 71 (100%), (C.I.) 353 [$(M+1)^+$, 100%], 145 (40%) [Found C, 51.4; H, 5.8; N, 15.7 $C_{15}H_{20}N_4O_6$ requires: C, 51.1; H, 5.7; N, 15.9%].

Ethyl 5-(5-*benzyloxy*-3-*indolyl*)-4-*cyano*-4-*ethoxycarbonyl*-2-*(methoxyimino)hexanoate* (29)

Dimethyl acetylenedicarboxylate (333 mg, 0.29 cm^3, 2.34 mmol) was added to a cooled, stirred solution of the gramine (16, R=Me) (760 mg, 2.59 mmol) and the diester (27) (600 mg, 2.34 mmol) in dry THF (10 cm^3), under a nitrogen atmosphere. The ice bath was removed and the mixture was stirred at ambient temperature for 16h. The solvent was removed and the residue partitioned between 2M HCl (40 cm^3) and ethyl acetate (40 cm^3). The organic layer was washed with water (2 x 30 cm^3), brine (30 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl acetate). The title compound was isolated as a light brown oil (487 mg, 41%). ^1H n.m.r. indicated that the product was an equal mixture of two diastereomers. R_F = 0.32 (hexane:ethyl acetate 2:1); ν_{max} ($CDCl_3$) cm^{-1} 3450 (N-H), 2200 (C≡N), 1720 (C=O); δ_H ($CDCl_3$) ppm 8.44 + 8.31 (2 x 0.5H, 2 x br. s, 2 x N-H), 7.51- 6.87 (9H, m, other aromatic protons), 5.12 + 5.10 (2 x 1H, 2 x s, 2 x $OCH_2C_6H_5$), 4.37 (1H, q, J = 7.5Hz, OCH_2CH_3), 4.19 (1H, q, J = 7.5Hz, OCH_2CH_3), 4.07 + 3.93

(2 x 1.5H, 2 x s, 2 x NOCH_3), 3.68 (2H, m, 2 x CH_2), 3.43 (1H, m, 2 x CH_3C*H*), 1.67 (1.5H, d, *J* = 7.5Hz, CH_3CH), 1.46 (1.5H, d, *J* = 7.5Hz, CH_3CH), 1.21 (1.5H, t, *J* = 7.5Hz, OCH_2CH_3), 0.70 (1.5H, t, *J* = 7.5Hz, OCH_2CH_3); λ_{max} nm(ε) 307(10 100), 285(13 250), 276(15 800), 251(13 700); *m/z* (70eV) 505 (M^+, 2%), 354 (8%), 250 (50%), 145 (72%), 91 (100%), 43 (70%), 29 (100%) [Found: 505.2162 $C_{28}H_{31}N_3O_6$ requires: 505.2211].

Method B:

The indole (30) (150 mg, 0.41 mmol) and K_2CO_3 (57 mg, 0.41 mmol) were stirred in dry DMF (3 cm^3) under a nitrogen atmosphere. The methoxime (26) (93 mg, 0.41 mmol) was added and the mixture stirred at ambient temperature for 24h. However, t.l.c. analysis (pet.ether : ethyl acetate/60:40) indicated the presence of starting material (30). A further amount of the methoxime (26) (50 mg, 0.22 mmol) was added and the reaction mixture was heated at 100°C for 7h. The reaction mixture was allowed to cool and then poured into water (15 cm^3). The aqueous phase was extracted with ethyl acetate (2 x 20 cm^3) and the combined organic layers were washed with water (3 x 15 cm^3), brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed and the residue purified by column chromatography (pet.ether/ethyl acetate) to yield a light beige oil which proved to be the title compound as a diastereomeric mixture (154 mg, 74%).

Ethyl 3-(5-*benzyloxy*-3-*indolyl*)-2-*cyanobutanoate* (30)

The olefin (31) (1.20 g, 8.6 mmol) was added to a solution of 5-benzyloxyindole (0.9 g, 4.31 mmol) in acetic acid (3 cm^3) and acetic anhydride (1 cm^3), under a nitrogen atmosphere. The mixture was stirred at 90°C for 8h and then stirred at ambient temperature for 16h. The mixture was poured into water (30 cm^3) and extracted with ethyl acetate (2 x 50 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 50 cm^3), water (2 x 50 cm^3), brine (50 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure. The light brown residue was purified by column chromatography to yield the title compound (30) as a light beige oil (1.04 g, 68%); R_F = 0.65 (pet.ether:ethyl acetate 7:3). The product which is a diastereomeric mixture can be used in subsequent reactions without further purification: δ_H($CDCl_3$)ppm 8.20 (1H, br. s, 2 x N-*H*), 7.49 - 6.93 (9H, m , rest of aromatic protons), 5.11 (2H, s, 2 x OCH_2C$_6$H$_5$), 4.26 (1.3H, q, *J* = 7.2 Hz, OCH_2CH$_3$), 3.98 (0.7H, q, *J* = 7.15Hz, OCH_2CH$_3$), 3.92 - 3.83 [2H, m, (2 x CH_3C*H*CH) + (2 x CH_3CHC*H*)], 1.57 (2H, d, *J* = 7.14 Hz, CH_3CHCH), 1.53 (1H, d, *J* = 6.2 Hz, CH_3CHCH), 1.28 (2H, t, *J* = 7.14 Hz, OCH_2CH_3), 0.98 (1H, t, *J* = 7.14 Hz, CH_2CH_3). Crystallisation from ethyl acetate/pet.ether yielded a single diastereomer as colourless crystals, m.p. 84-87°C; ν_{max} ($CDCl_3$) cm^{-1} 3450 (N-H), 2250 (C≡N), 1720 (C=O); δ_H ($CDCl_3$) ppm 8.25 (1H, s, exchanges with D_2O, N-*H*), 7.48-6.90 (9H, m, aromatic protons), 5.08 (2H, s, OCH_2C$_6$H$_5$), 4.24 (2H, q, *J* = 7.2Hz, OCH_2CH$_3$), 3.83 (2H, m, CH_3C*H* + C*H*(CN)CO_2Et), 1.51 (3H, d, *J* = 7.0Hz, CH_3CH), 1.26 (3H, t, *J* = 7.2Hz, OCH_2CH_3); λ_{max} nm (ε) 308 (2200), 295 (3200), 275 (4100); *m/z* (70eV) 362 (M^+, 41%), 271 (41%), 250 (100%), 159 (59%), 91 (82%), (low eV) 362 (M^+, 100%), 250 (33%) [Found C, 72.8; H, 6.1; N, 7.6 $C_{22}H_{22}N_2O_3$ requires: C, 72.9; H, 6.1; N, 7.7%; %.

6-*Benzyloxy*-3-*cyano*-1,3-*di(ethoxycarbonyl)*-3,4-*dihydro*-4-*methylcarbazole* (32)

A solution of the diastereoisomeric mixture (29) (175 mg, 0.35 mmol) in 4M HCl in dioxane (2 cm^3) was stirred under a nitrogen atmosphere for 36h. The solution was basified with saturated $NaHCO_3$ solution, water (20 cm^3) was added and the mixture extracted with ethyl acetate (30 cm^3). The organic layer was washed with water (3 x 10 cm^3) and dried (Na_2SO_4). The solvent was evaporated and the residue purified

by column chromatography (pet.ether/ethyl acetate). The title compound was isolated as a yellow oil (33 mg, 21%). ^{1}H N.m.r. analysis proved the product to be a mixture of 2 diastereoisomers; R_F = 0.56 (hexane:ethyl acetate 2:1); ν_{max} ($CHBr_3$) cm^{-1} 3440 (N-H), 2200 (C≡N), 1740 (C=O), 1710 (C=O); δ_H ($CDCl_3$) ppm 9.40 + 9.39 (2 x 0.5H, 2 x br. s, 2 x N-*H*), 7.52 - 6.93 (8H, m, aromatic protons), 6.92 + 6.70 (2 x 0.5H, 2 x s, 2 x olefinic protons), 5.11 (2H, s, 2 x $OCH_2C_6H_5$), 4.38 + 4.26 (2H, m, 2 x OCH_2CH_3), 3.94 (1H, m, 2 x CH_3CH), 1.52 (1.5H, d, *J* = 7.5Hz, CH_3CH), 1.41 (1.5H, t, *J* = 7.5Hz, OCH_2CH_3), 1.24 (1.5H, t, *J* = 7.5Hz, OCH_2CH_3), 1.08 (1.5H, d, *J* = 7.5Hz, CH_3CH); λ_{max}nm (ε) 284(2 700), 246(3 000); *m/z* (70eV) 458 (M^+, 28%), 367 (25%), 149 (77%), 91 (100%) [Found: 458.1845 $C_{27}H_{26}N_2O_5$ requires: 458.1840].

6-Benzyloxy-3-cyano-1-ethoxycarbonyl-4-methylcarbazole (33)

A mixture of the dihydrocarbazole (32) (11 mg, 0.024 mmol), LiCl (1 mg, 0.024), water (0.43 mg, 0.024 mmol) and DMSO (0.5 cm^3) was heated at 100°C, under a nitrogen atmosphere. After 26h, the mixture was allowed to cool and water (5 cm^3) added. The mixture was extracted with ethyl acetate (3 x 20 cm^3) and the combined organic layers were washed with water (3 x 10 cm^3), brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl acetate) to yield the title compound as a pale yellow solid (4 mg, 45%), recrystallised from ethyl acetate/petrol, m.p. 178-181°C; R_F = 0.66 (hexane:ethyl acetate 2:1); ν_{max} ($CHCl_3$) cm^{-1} 3350 (N-H), 2210 (C≡N), 1705 (C=O); δ_H ($CDCl_3$) ppm 10.20 (1H, br. s, N-*H*), 8.29 (1H, s, C-2*H*), 7.74-7.23 (8H, m, other aromatic protons), 5.20 (2H, s, $OCH_2C_6H_5$), 4.48 (2H, q, *J* = 7.1Hz, OCH_2CH_3), 3.05 (3H, s, CH_3), 1.48 (3H, t, *J* = 7.1Hz, OCH_2CH_3); λ_{max}nm (ε) 371 (1800), 294 (16600), 263 (10200), 250 (8100); *m/z* (70eV) 384 (M^+, 46%), 293 (89%), 247 (100%), 149 (21%), 91 (90%) [Found: C, 74.9; H, 5.1; N, 7.2 $C_{24}H_{20}N_2O_3$ requires: C, 75.0; H, 5.2; N, 7.3%].

Ethyl 3-(5-benzyloxy-3-indolyl)-2-cyanopropanoate

Method A:

A solution of ethyl cyanoacetate (806 mg, 0.76 cm^3, 7.14 mmol) and dimethyl acetylenedicarboxylate (0.88 cm^3, 7.14 mmol) in dry THF (20 cm^3) was slowly added to a stirred solution of 5-benzyloxygramine (2.0 g. 7.14 mmol) in dry THF (20 cm^3), under a nitrogen atmosphere. The resulting yellow solution was stirred at ambient temperature for 1h. The solvent was removed at reduced pressure and the residue partitioned between 2M HCl (20 cm^3) and ethyl acetate (3 x 20 cm^3). The combined organic layers were washed with water (2 x 50 cm^3), brine (25 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure. The residue was purified by column chromatography to yield the title compound as a pale yellow oil (480 mg, 19%). R_F = 0.45 (pet.ether:ethyl acetate 3:2); ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2250 (C≡N), 1735 (C=O); δ_H ($CDCl_3$) ppm 8.08 (1H, br. s. N-*H*), 7.50 - 6.92 (9H, m, aromatic protons), 5.11 (2H, s, $OCH_2C_6H_5$), 4.20 (2H, q, *J* = 7.1Hz, OCH_2CH_3), 3.78 (1H, dxd, *J* = 6.0Hz, $CH(CN)CO_2Et$), 3.39 (2H, m, $CH_2CH(CN)CO_2Et$), 1.23 (3H, t, *J* = 7.1Hz, OCH_2CH_3); λ_{max}nm(ε) 275(8 100), 250(5 800); *m/z* (70 eV) 348 (M^+, 42%), 257 (74%), 236 (23%), 145 (26%), 91 (100%), 68 (43%), 29 (100%) [Found: 348.1480 $C_{21}H_{20}N_2O_3$ requires: 348.1471].

Method B:

To a stirred solution of 5-benzyloxygramine (7 g, 25 mmol) in dry THF (50 cm^3) and HMPA (5 cm^3), under a nitrogen atmosphere, was slowly added a solution of freshly distilled dimethyl sulphate (3.15g, 2.4

cm^3, 25 mmol) in dry THF (25 cm^3). In a separate flask, a solution of ethyl cyanoacetate (2.6 cm^3, 24.5 mmol) in dry THF (35 cm^3) was slowly added to a cooled, stirred suspension of NaH (0.59 g, 25 mmol) in dry THF (15 cm^3), under nitrogen, in an ice bath. After the addition was complete, the ice bath was removed and the reaction mixture stirred for 30 minutes.

The resultant suspension was then slowly transferred, *via* a cannula, into the main reaction vessel. After the addition, the pale yellow solution was stirred for 2.5h before the solvent was removed and the residue partitioned between 2M HCl (125 cm^3) and ethyl acetate (125 cm^3). The aqueous layer was extracted with ethyl acetate (2 x 50 cm^3) and the combined organic layers washed with water (2 x 75 cm^3), brine (50 cm^3), dried (Na_2SO_4) and evaporated at reduced pressure.

T.l.c. analysis of the residue (pet.ether:ethyl acetate 3:2) indicated the presence of two compounds. These were separated by column chromatography. The first compound eluted (R_F = 0.46, pet.ether:ethyl acetate 3:2) was a pale yellow oil (1.93g, 24%) and was characterised as the title compound. The second compound eluted (R_F = 0.38) was a colourless solid (3.39g, 47%) which crystallised from ethyl acetate/pet.ether, m.p. 93°C. This compound was characterised as *ethyl 2-cyano-2,2-di(5-benzyloxy-3-indolyl)ethanoate*; ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2220 (C≡N), 1720 (C=O); δ_H ($CDCl_3$) ppm 8.14 (2H, br. s, 2 x N-*H*),7.47 - 6.86 (18H, m, aromatic protons), 5.09 (4H, s, 2 x $OCH_2C_6H_5$), 3.80 (2H, q, J = 7.1Hz, OCH_2CH_3), 3.41 (4H, ABq, J = 14.1Hz, 2 x $CH_2(CN)CO_2Et$), 0.74 (3H, t, J = 7.1Hz, OCH_2CH_3); λ_{max} nm (ε) 306 (7500), 295 (10650), 276 (13300), 248 (7800); *m/z* (70 eV) 91 (100%), (C.I.) 349 (76%), 348 (51%), 257 (25%), 236 (46%), 146 (42%), 91 (100%) [Found: C, 75.5; H, 5.7; N, 7.0 $C_{37}H_{33}N_3O_4$ requires: C, 76.1; H, 5.7; N, 7.2%].

N-(3-Chloro-2-oxopropyl)phthalimide (34)

N-(3-Chloro-2-hydroxypropyl)phthalimide[21] (50.0 g, 0.21 mol) was stirred in acetone (1000 cm^3) and cooled with an ice bath. Jones reagent [CrO_3(132 g), H_2O (380 cm^3) and conc. H_2SO_4 (110 cm^3)] was added, dropwise, in such a manner that the temperature did not rise above 30°C. After the addition was completed, the mixture was stirred at ambient temperature for 45 minutes. The solvent was then evaporated at reduced pressure and ice water (3000 cm^3) added to the residue. The green precipitate was filtered and washed with water until most of the green colour had been removed. The solid was then partitioned between ethyl acetate (500 cm^3) and water (250 cm^3). After separation the organic layer was washed with water (250 cm^3) and dried (Na_2SO_4). The solvent was removed to yield the title compound (23.0g, 48%) as colourless crystals, which recrystallised from ethyl acetate/pet.ether, m.p. 124-126°C. R_F = 0.74 (pet.ether:ethyl acetate 3:2); ν_{max} ($CHCl_3$) cm^{-1} 1780 (C=O), 1720 (C=O); δ_H (d^6 DMSO) ppm 7.96 - 7.84 (4H, m, aromatic protons), 4.83 (2H, s, CH_2Cl), 4.77 (2H, s, NCH_2C=O); λ_{max}nm (ε) 294 (2800), 252 (1600); *m/z* (70eV) 160 (100%), (C.I.) 238 [(M+1)$^+$,81%], 160 (100%) [Found: C, 55.6; H, 3.4; N, 6.0 $C_{11}H_8NO_3Cl$ requires: C, 55.6; H, 3.4; N, 5.9%].

Ethyl 2-cyano-4-oxo-5-(N-phthalimidyl)pentanoate (35)

Ethyl cyanoacetate (0.45 cm^3, 4.2 mmol) was added, dropwise, to a stirred, cooled suspension of NaH (100 mg, 4.2 mmol) in dry DMF (10 cm^3), under a nitrogen atmosphere. After the final addition, the ice-bath was removed and the reaction vessel stirred at ambient temperature for 30 minutes. This solution was then slowly injected, *via* a cannula, into a cooled, stirred suspension of the ketone (34) (1.0 g, 4.21 mmol) in dry DMF (10 cm^3), under nitrogen. After the addition, the mixture was allowed to warm slowly

to room temperature. After 4h, the reaction mixture was added to water (120 cm^3) and extracted with ethyl acetate (2 x 75 cm^3). The combined organic extracts were washed with water (4 x 50 cm^3), brine (10 cm^3) and dried (Na_2SO_4). The solvent was evaporated at reduced pressure to yield the title compound as a white solid. This solid was collected, washed well with pet.ether and crystallised from ethyl acetate/pet.ether to yield colourless crystals, (1.09 g, 82%), m.p. 140-142°C; R_F = 0.46 (pet.ether:ethyl acetate 3:2); ν_{max} ($CHCl_3$) cm^{-1} 1730 (C=O), 1720 (C=O); δ_H ($CDCl_3$) ppm 7.89-7.78 (4H, m, aromatic protons), 4.70 (2H, s, NCH_2), 4.31 (1H, t, J = 5.5Hz, $NCCHCO_2Et$), 4.21 (2H, q, J = 7.0Hz, OCH_2CH_3), 3.40 (2H, d, J = 5.4Hz, $O{=}CCH_2CH$), 1.28 (3H, t, J = 7.0Hz, OCH_2CH_3); λ_{max}nm (ϵ) 294 (1900), 250 (1100); *m/z* (70eV) 160 (100%), (C.I.) 315 [$(M+1)^+$, 40%], 238 (62%), 160 (30%), 148 (100%) [Found: C, 60.7; H, 4.3; N, 8.7 $C_{16}H_{14}N_2O_5$ requires: C, 61.1; H, 4.5; N, 8.9%].

5-(5-Benzyloxy-3-indolyl)-4-cyano-4-ethoxycarbonyl-1-(N-phthalimidyl)pentan-2-one (37)

A solution of the ketone (35) (12.8 g, 0.04 mol) and DMAD (5.0 cm^3, 0.04 mol) in dry THF (300 cm^3) was added, dropwise, to a cooled, stirred solution of the gramine (36) (11.47 g, 0.04 mmol) in dry THF (200 cm^3), under a nitrogen atmosphere. After the final addition, the ice bath was removed and the reaction mixture stirred at ambient temperature for 3.5h. The solvent was removed, at reduced pressure, and 2M HCl (25 cm^3) added. This was extracted with ethyl acetate (2 x 25 cm^3) and the combined organic layers were washed with water (2 x 40 cm^3), brine (10 cm^3) and dried (Na_2SO_4). The solvent was removed, at reduced pressure, to yield an orange foam. Crystallisation of this foam (ethyl acetate/pet.ether) produced a pale yellow solid (18.0 g, 80%), which crystallised from ethyl acetate/pet.ether. m.p. 165-170°C; R_f = 0.26 (pet.ether:ethyl acetate 3:2); ν_{max} ($CHCl_3$) cm^{-1} 3460 (N-H), 2200 (w, C≡N), 1720 (C=O); δ_H (d^6 DMSO) ppm 10.28 (1H, br. s, N-*H*), 7.84-7.75 (4H, m, phthalimidyl protons), 7.48-6.80 (9H, m, other aromatic protons), 5.08 (2H, s, $OCH_2C_6H_5$), 4.59 (2H, d, J = 2.6Hz, CH_2phth.), 4.02 (2H, q, J = 7.2Hz, OCH_2CH_3), 3.55-3.34 (4H, m, 2 x CH_2), 1.05 (3H, t, J = 7.2Hz, OCH_2CH_3); λ_{max} nm (ϵ) 294 (6000), 277 (6500), 253 (4000); *m/z* (70eV) 160 (100%), 43 (70%), (C.I.) 315 (100%), 204 (22%), 160 (85%), 148 (56%) [Found: C, 69.7; H, 4.9; N, 7.5 $C_{32}H_{27}N_3O_6$ requires: C, 69.9; H, 5.0; N, 7.7%].

6-Benzyloxy-4-cyano-4-ethoxycarbonyl-1H-2,3-dihydro-1-(N-phthalimidyl methylene)carbazole (38)

A mixture of the indole (37) (500 mg, 0.9 mmol) and 4-toluene sulphonic acid (15 mg) was heated in refluxing toluene (60 cm^3), employing Dean-Stark apparatus. The dark green solution was allowed to cool after 30 minutes. The mixture was washed with saturated $NaHCO_3$ solution (3 x 20 cm^3), water (30 cm^3) and brine (20 cm^3). The dried (Na_2SO_4) organic phase was then evaporated at reduced pressure. The residue was purified by column chromatography (pet.ether/ethyl acetate) to yield a yellow oil (464 mg, 96%). ^1H N.m.r. analysis indicated that this product was a mixture of the exo-cyclic and endo-cyclic double bond compounds, (38) and (42) respectively. $\delta_H(CDCl_3)$ppm; 8.99 (0.88H, s, N-*H*), 8.56 (0.12H, s, N-*H*), 7.85 - 7.71 (4H, m, phthalimidyl protons), 7.49 - 6.87 (8H, m, other aromatic protons), 6.63 (0.88H, s, endocyclic olefinic proton), 6.10 (0.12H, s, exocyclic olefinic proton), 5.05 (2H, s, 2 x $OCH_2C_6H_5$), 4.35 (0.24H, q, J = 7.2 Hz, OCH_2CH_3), 4.23 (1.76H, q, J = 7.14 Hz, OCH_2CH_3), 3.22 (1.76H, s, CH_2-phthalimide), 3.18 - 2.96 (2.24H, m, 3 x CH_2), 1.35 (3H, m, 2 x OCH_2CH_3). However, crystallisation from ethyl acetate/pet.ether yielded a pale yellow solid, m.p. 240°C, dec., which was exclusively the exo-cyclic double bond product (38). The mixture was used in subsequent experiments. R_f = 0.64 (pet.ether:ethyl acetate 1:1); ν_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 2210 (w, C≡N), 1720 (C=O), 1600 (C=C); δ_H

(d^6 DMSO) ppm 10.65 (1H, br. s, exchanges with D_2O, N-*H*), 7.94 - 7.86 4H, m, phthalimidyl protons), 7.48 - 6.81 (8H, m, other aromatic protons), 6.18 (1H, s, olefinic proton), 5.10 (2H, s, $OCH_2C_6H_5$), 4.31 (2H, q, J = 7.3Hz, OCH_2CH_3), 3.44 + 3.21 (2 x 2H, 2 x ABq, J = 15.5Hz, 2 x CH_2), 1.29 (3H, t, J = 7.3Hz, OCH_2CH_3); λ_{max} nm (ϵ) 324 (5450), 252 (3600); *m/z* (70 eV) 531 (M^+, 5%), 440 (8%), 155 (92%), 127 (54%), 99 (100%) [Found: C, 71.9; H, 4.7; N, 7.8 $C_{32}H_{25}N_3O_5$ requires: C, 72.3; H, 4.7; N, 7.9%].

6-Benzyloxy-4-cyano-4-ethoxycarbonyl-1,2,3,4-tetrahydro-2-{N-[2-(methox ycarbonyl)-benzoyl]amino methylene}carbazole (41, R=OMe)

A solution of the indole (42) (120 mg, 0.23 mmol) and 4-toluenesulphonic acid (10 mg) in dry methanol (5 cm^3) was stirred, under a nitrogen atmosphere, for 24h. The solvent was evaporated at reduced pressure and the residue purified by column chromatography (ethyl acetate/pet. ether) to yield the title compound as a bright yellow solid (74 mg, 93% based on recovered starting material), which crystallised from ethyl acetate/pet. ether; m.p. 145 - 148°C. R_F = 0.73 (pet. ether:ethyl acetate 1:1); υ_{max} (Nujol) cm^{-1} 3350 (N-H), 1720 (C=O), 1645 (C=O); δ_H (d^6 DMSO) ppm; 11.25 (1H, s, indole N-*H*), 10.30 (1H, d, J = 10.3Hz, amide N-*H*), 7.89-6.78 (13H, m, other aromatic protons + olefinic proton), 5.09 (2H, s, $OCH_2C_6H_5$), 4.30 (2H, q, J = 7.0Hz, OCH_2CH_3), 3.81 (3H, s, OCH_3), 3.54-2.88 (4H, m, 2 x CH_2), 1.31 (3H, t, J = 7.0Hz, OCH_2CH_3); λ_{max} nm (ϵ) 337 (32 500), 313 (27 500), 250 (20 000); *m/z* (70 eV), 279 (4%), 149 (30%), 119 (39%), 105 (43%); (C.I.) 391 (5%), 149 (42%), 100 (100%), 91 (78%) [Found : C, 70.1, H, 5.1, N, 7.4 $C_{33}H_{29}N_3O_6$ requires: C, 70.3, H, 5.2, N, 7.5%].

6-Benzyloxy-4-cyano-4-ethoxycarbonyl-1,2,3,4-tetrahydro-1-{N-[2-(hydrazino)-benzoyl]aminomethylene}carbazole (41, R=$NHNH_2$).

A mixture of (42) (320 mg, 0.60 mmol) and 85% aqueous hydrazine hydrate (0.5 cm^3) was heated in refluxing methanol (10 cm^3), under a nitrogen atmosphere, for 15 minutes. The solution was cooled and the yellow precipitate was filtered, washed with water (5 cm^3) and dried over P_2O_5 (*in vacuo*) to yield the title compound as a bright yellow solid (138 mg, 41%), m.p. 150 - 153°C (dec.). ^1H N.m.r. analysis indicated approximately 25% conversion to the corresponding methyl ester. R_F = 0.19 (DCM:methanol:ammonia 200:8:1); υ_{max} ($CHCl_3$) cm^{-1} 3300 (br,m N-H), 1730 (C=O); δ_H (d^6 DMSO) ppm; 11.29 (1H, s, exchanges with D_2O, indole N-*H*). 10.32 (1H, d, exchanges with D_2O, J = 10.3Hz, ArCON*H*C=CH), 9.67 (1H, s, exchanges with D_2O, ArCON*H*NH_2), 7.60-6.79 (13H, m, other aromatic protons + olefinic proton), 5.10 (2H, s, $OCH_2C_6H_5$), 4.45 (2H, br, s, exchanges with D_2O, ArCONHNH_2), 4.39 (2H, q, J = 7.0Hz, OCH_2CH_3), 3.65-2.83 (4H, m, 2 x CH_2), 1.28 (3H, t, J = 7.0Hz, OCH_2CH_3); λ_{max} nm (ϵ) 337 (38 300), 300 (33 800), 247 (34 900); *m/z* (70 eV) 162 (100%), 104 (83%), (C.I.) 163 (100%), 162 (84%), 104 (58%), 76 (24%).

6-Benzyloxy-3-cyano-1-methylcarbazole (44).

A solution of (42) (212 mg, 0.4 mmol) and potassium cyanide (26 mg, 0.4 mmol) in HMPA (5 cm^3) was heated at 125°C, under a nitrogen atmosphere, for 48h. The mixture was allowed to cool and added to water (20 cm^3). This was extracted with ethyl acetate (2 x 20 cm^3) and the combined organic layers were washed with water (3 x 10 cm^3) and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue purified by column chromatography (pet.ether/ethyl aacetate) to yield the title compound as a

colourless oil (15 mg, 12%); R_F = 0.68 (pet. ether:ethyl acetate 7:3); υ_{max} ($CHCl_3$) cm^{-1} 3450 (N-H), 220 (C≡N); δ_H (d^6 DMSO) ppm 11.63 (1H, s, N-*H*), 8.50 (1H, s, C-4*H*), 7.93 (1H, d, *J* = 2.6Hz, C-2*H*), 7.53 - 7.17 (8H, m, other aromatic protons), 5.19 (2H, s, $OCH_2C_6H_5$), 2.56 (3H, s, CH_3); *m/z*(70 eV) 312 (M^+, 38%), 221 (75%), 147 (100%) [Found: 312.1268 $C_{21}H_{16}N_2O$ requires: 312.1261].

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