Electrophilic Substitution in Indoles. Part 11.† The Mechanism of Substitution in 5-Methoxyindoles

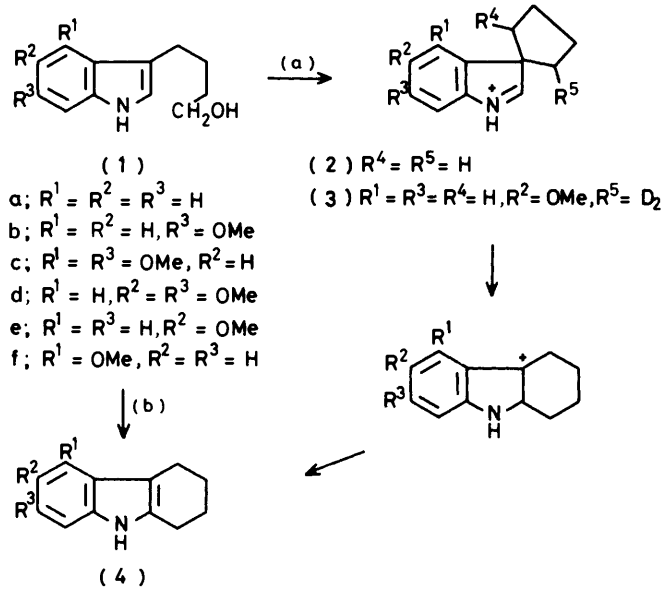
By **Denis W. Clack, Anthony H. Jackson,* Noojaree Prasitpan,** and **Patrick V. R. Shannon,** Chemistry Department, University College, Cardiff CF1 1XL

Deuterium labelling experiments show that the boron trifluoride-catalysed cyclisation at 90 °C of 4-(5-methoxyindol-3-yl)butanol (1e) to 6-methoxytetrahydrocarbazole (11a) occurs by two simultaneous pathways. The main route (83.5%) involves initial cyclisation at the 3-position of (1e) to give an intermediate spirocyclic indolenine which then rearranges to the tetrahydrocarbazole. The minor pathway (16.5%) involves direct attack at the 2-position. A similar duality of mechanism of substitution applies to the 6-methoxy-, 4,6-dimethoxy-, and 5,6-dimethoxy-indole analogues for which the extent of substitution at the 2-position can be correlated with the calculated change in π-electron density at the 2- and 3-positions for a series of methoxy-substituted 3-methylindoles. These calculations do not, however, fit the experimental findings for the 5-methoxy-derivative which appears to be anomalous, showing an unexpectedly high percentage of direct substitution at the 2-position. A possible explanation of this result is advanced.

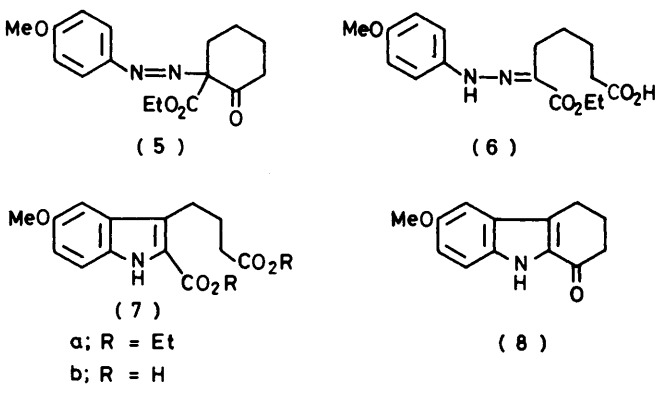
In our earlier work [1] we have demonstrated that initial electrophilic substitution in indoles and their simple alkyl derivatives [2] occurs at the 3-position. By the use of ^{3}H-labelling [2] it was shown that intramolecular electrophilic substitution of 4-indol-3-ylbutanol (1a) to the corresponding tetrahydrocarbazole (4), catalysed by boron trifluoride–diethyl ether, took place virtually exclusively *via* the spirocyclic indolenine salt (2) [path (a), see Scheme 1]. Later investigations of this series showed that a 6-methoxy-group, as in the alcohol (1b), elicits a change in reaction mechanism such that 31% of substitution takes place directly at the 2-position [3,4] [path (b), Scheme 1]. This pathway becomes more important (38.5%) for the 4,6-dimethoxy-analogue (1c) whereas the 5,6-dimethoxy-derivative (1d) shows only 13.5% of attack by direct substitution and 86.5% through the spirocyclic intermediate.[5] In order to try to understand better the effects already observed we decided to examine the analogous cyclisation of the 5-methoxyindolylbutanol (1e).

Japp–Klingemann condensation of *p*-methoxybenzenediazonium fluoroborate and the sodio-derivative of ethyl 2-oxocyclohexanecarboxylate in tetrahydrofuran gave a mixture of the oily azo-intermediate (5) (77%) and the crystalline hydrazone (6) (16%). The mixture was cyclised with ethanolic hydrogen chloride to give the diester (7a) (45%), which on hydrolysis with ethanolic sodium hydroxide afforded the corresponding diacid (7b) (95%). If the diacid (7b) was heated with a free flame, the ketone (8) was obtained in poor yield, but careful pyrolysis at 235 °C for 15 min gave the indolylbutyric acid (9) in 59% yield. Treatment of the acid with boron trifluoride–diethyl ether at 20 °C gave again the ketone (8) in 47% yield.

Reduction of the acid (9) with lithium aluminium hydride in tetrahydrofuran gave a 90% yield of the corresponding alcohol (1e), which on heating to reflux for 1.5 h with boron trifluoride–diethyl ether gave the tetrahydrocarbazole (11a). This was rapidly oxidised in the air on work-up, and on the scale involved it was impossible to obtain in a pure crystalline state. Treatment of the reaction mixture with trifluoroacetic anhydride in pyridine, however, afforded the relatively stable crystalline *N*-trifluoroacetyl derivative (11b) in 20%

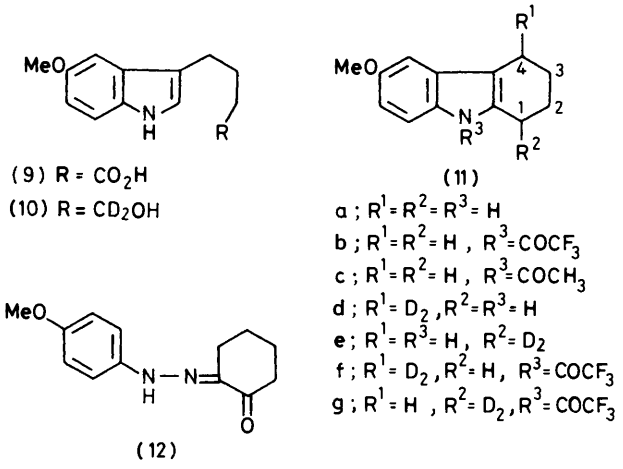


SCHEME 1



† Part 10, see ref. 5.

yield from the alcohol. An alternative synthesis of (11a), on a larger scale, from *p*-methoxyphenylhydrazine and cyclohexanone, gave a crystalline product, m.p. 94—96 °C (lit.,[6] 94—95 °C) which was converted into the *N*-trifluoroacetyl derivative (11b) (44%) identical with that prepared from the cyclisation of the alcohol (1e).



The *N*-acetyl derivative (11c) could also be obtained crystalline but in only very poor yields. For the above reasons, in subsequent experiments on the cyclisation of the deuteriated indolylbutanol (10), it was decided to use the crystalline *N*-trifluoroacetyl derivative (11b) to determine the distribution of deuterium between the 1- and 4-methylene groups, by n.m.r. spectroscopy without attempting to isolate the tetrahydrocarbazole (11a).

Reduction of the acid (9) with lithium aluminium deuteride gave the crystalline alcohol (10) (86%). Treatment of this with boron trifluoride–diethyl ether at 90 °C for 3.5 h under nitrogen gave a crude mixture of the deuteriotetrahydrocarbazoles (11d and e). The products of the reaction were, without prior purification, converted as above into a mixture of the two *N*-trifluoroacetyl derivatives (11f and g). This mixture gave a single peak on h.p.l.c. under nitrogen after which a crystalline sample was obtained. The 90 MHz ^1H n.m.r. spectrum indicated a ratio of proton resonances at C-4 to C-1 of 1.27 : 1. In a repeat experiment, this ratio was 1.25 : 1. For the ratio 1.26 : 1 (11e) : (11d), allowing for a secondary isotope effect [4] in the rearrangement of the spirocyclic indolenine salt (3), the percentage of direct substitution at the 2-position in the indole (1e) is 16.5%.

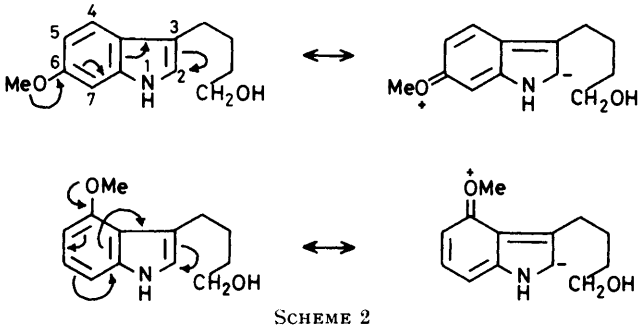
It was necessary to establish that no interconversion of the two products (11d and e) from the cyclisation of the alcohol (1e) had occurred (a) during the cyclisation and (b) during their subsequent conversion into the mixture of trifluoroacetyl derivatives. For this purpose a pure sample of one of the dideuteriotetrahydrocarbazoles was required.

The 1-oxotetrahydrocarbazole (8) was synthesised more expeditiously than through cyclisation of the acid (9), from *p*-methoxybenzenediazonium chloride and cyclohexanone (*cf.* ref. 7). The intermediate hydrazone (12) was cyclised to the ketone (8) in 27% yield, and reduction of (8) with lithium aluminium hydride gave a 43% yield of the crystalline tetrahydrocarbazole (11a), identical with the product obtained from the Borsche cyclisation [6] described above.

The reduction of the ketone with lithium aluminium deuteride proceeded equally well to give the 1,1-dideuteriotetrahydrocarbazole (11e) which was purified by h.p.l.c. under nitrogen. The product was obtained as a solid which rapidly oxidised in air, and so the measurement of its n.m.r. spectrum and subsequent experiments were carried out immediately without further crystallisation. The ^1H n.m.r. spectrum indicated that the compound was pure and completely deuteriated at C-1.

To ensure that no rearrangement between (11d and e) had occurred under the conditions of cyclisation a sample of (11e) was heated with boron trifluoride–diethyl ether under identical conditions to those used for the cyclisation of the alcohol (10). Furthermore, the reaction was repeated in the presence of 1 mol. equiv. of water to simulate the presence of hydrogen fluoride derived from the alcohol. In each instance the tetrahydrocarbazole was rapidly worked up and converted, as before, directly into the *N*-trifluoroacetyl derivative. After h.p.l.c., crystallisation afforded samples whose ^1H n.m.r. spectrum showed the complete absence of a signal for the 1-methylene protons and therefore the absence of any rearrangement between the isomers (11d and e).

The results obtained previously for the increased substitution at the 2-position in the indolylbutanols (1b and c) relative to the unsubstituted analogue (1a) have been rationalised superficially by the electronic shifts shown in Scheme 2. The resulting increase in π-electron

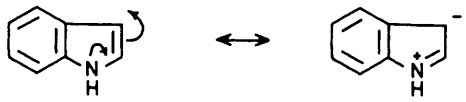


SCHEME 2

density at the indolyl 2-position might be expected to lower the free energy of activation of the transition state leading to the product of direct substitution at the 2-position. This effect would be expected from the 4-methoxy- (1f), 6-methoxy- (1b), and especially from the 4,6-dimethoxy-derivative (1c). The experimental finding for the 5,6-dimethoxy-analogue (1d), namely that the percentage of 2-substitution decreases relative to that for the 6-methoxy-derivative (1b), implied that a 5-methoxy-group (and presumably likewise a 7-methoxy-

group) may exert an effect in opposition to that summarised in Scheme 2.*

In indole itself the propensity for electrophilic substitution at the 3-position [8] can be rationalised as shown in Scheme 3 and this is supported by the calculated π-electron densities at the 2- and 3-positions.[9] It was of



SCHEME 3

interest therefore to calculate the π- and σ-electron densities at the 2- and 3-positions for a series of substituted indoles to investigate a possible correlation with the experimental results described above for the indolylbutanols (1a—e).

Ground-state wave functions were computed using the INDO self-consistent field approximate method.[10] In order to retain simplicity and to allow for the electronic effect of the 4-hydroxybutyl side chain, calculations were based on a series of 3-methylindoles (13a—j). Replacement of the hydroxybutyl side chain by a methyl group would not be expected to alter significantly the ring π-electron or σ-electron distribution relative to the indolylbutanols, and should therefore provide a sensible model approximating to the real molecule.

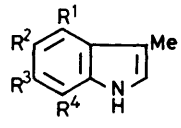
The indole nucleus was taken to have a planar geometry [11] and standard distances and angles were assumed for the various substituents.[12,13] Two calculations were made for the 6-*N*-acyl derivative (13j), both of which employed a planar NCO geometry, but with different dihedral angles (NCO plane–indole plane) of 0 and 30°.

Because of the lack of information on the possible transition state structures, attention was confined solely to the electronic properties of the substrate molecules. In view of the fact that attack by the carbonium ion at positions 2 or 3 might reasonably be expected to depend upon the relative magnitudes of negative charge at these two sites, and in particular perhaps more specifically on their π-electron charge densities, only electronic quantities calculated for these two positions were considered initially.

The Table shows the calculated total charge and total π-electron populations at positions 2 and 3 for all the derivatives (13a—j) examined theoretically. Position 2 always bears a total net positive charge largely as a result of the σ-inductive effect of the adjacent nitrogen atom, whereas position 3 always carries a net negative charge in accord with the preference of this site for electrophilic attack. The difference in total charge at these two positions is smallest for the disubstituted 4,6-dimethoxy-derivative (13c). The π-electron populations show a similar pattern with position 3 having a larger occupation than position 2 in the unsubstituted molecule (13a). This charge distribution for the unsubstituted molecule is similar to that found by other workers.[9] Substitution by methoxy at position 4 and/or position 6 [compounds (13b—d)] leads to a decrease in the position 3 π population and an increase in the π occupancy at position 2, while similar substitution at positions 5 or 7 [compounds (13e and f)] has the opposite effect. In particular only the 5- and 7-methoxy-isomers (13e and f) show a lower ratio of π-electron populations at positions 2 or 3 than for the unsubstituted structure (13a). The 5,6-dimethoxy-derivative (13g) shows a net increase in the π-electron density ratio at positions 2 or 3 relative to (13a). These computed values for π-electron populations support the qualitative predictions based on the electronic shifts of the type shown in Scheme 2 for the indolylbutanols (1a—e). Likewise the experimentally determined extents of substitution at the 2-position, mentioned above, follow the theoretically predicted order of reactivity, *i.e.* (13c) > (13d) > (13g) > (13a). Only the 5-methoxyindolylbutanol (1e) behaves anomalously, with 16.5% direct substitution at position 2.

These calculations therefore provide no explanation for the unusual behaviour of the 5-methoxy-compounds in terms of an electrostatic effect. However, it does appear possible to account for this anomaly by considering the

Total charges and π-electron populations for indoles (13a—j)



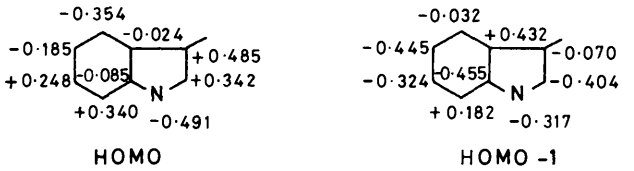
(13)

	Total charge		π-Electron population	
	C-2	C-3	C-2	C-3
(13a) $R^1 = R^2 = R^3 = R^4 = H$	+0.072	−0.044	1.053	1.087
(13b) $R^1 = OMe$, $R^2 = R^3 = R^4 = H$	+0.061	−0.026	1.068	1.076
(13c) $R^1 = R^3 = OMe$, $R^2 = R^4 = H$	+0.055	−0.020	1.079	1.070
(13d) $R^3 = OMe$, $R^1 = R^2 = R^4 = H$	+0.066	−0.038	1.064	1.081
(13e) $R^2 = OMe$, $R^1 = R^3 = R^4 = H$	+0.076	−0.048	1.047	1.094
(13f) $R^4 = OMe$, $R^1 = R^2 = R^3 = H$	+0.075	−0.047	1.048	1.092
(13g) $R^2 = R^3 = OMe$, $R^1 = R^4 = H$	+0.070	−0.042	1.057	1.088
(13h) $R^1 = R^3 = R^3 = OMe$, $R^4 = H$	+0.058	−0.022	1.073	1.074
(13i) $R^3 = NH_2$, $R^1 = R^2 = R^4 = H$	+0.062	−0.038	1.069	1.080
(13j) $R^3 = NHCOCH_3$, $R^1 = R^2 = R^4 = H$	+0.066	−0.038	1.064	1.081

* A referee has suggested that the similarity of the substitution results between the 5-methoxy- and 5,6-dimethoxy-compounds may be due to twisting out of conjugation of the 6-methoxy-group in the latter compound.

second-order contribution to the energy (the frontier orbital term) in frontier orbital theory.[14]

Electrophilic attack at the indole nucleus will involve attack into the π-system, and of prime importance for this purpose will be the highest occupied molecular orbital (HOMO), the coefficients of which are shown in the Figure for the unsubstituted molecule. This orbital is located largely on the nitrogen atom and positions 2 and 3, with a node close to the bridge carbon atoms, effectively isolating the two rings. The computations also showed that both the energy and the form of the HOMO are fairly insensitive to substitution at positions 4—7. Moreover, if the frontier orbital term



Coefficients for the highest occupied (HOMO) and second highest occupied (HOMO — 1) molecular orbitals of 3-methylindole

were dominant, position 3 rather than 2 would be suggested for attack by an electrophile, in harmony with the experimental findings. Substitution with methoxy at the 5-position in both structures (13e and g) is found to decrease the coefficient of position 2 relative to that at position 3 with respect to the unsubstituted molecule.

The second highest occupied molecular orbital (HOMO — 1), shown in the Figure for the unsubstituted molecule, lies only 1.3 eV below the HOMO and consequently might also be expected to contribute to some extent to the frontier orbital term. A number of points emerged from an inspection of this level. The coefficient at position 2 is much larger than that in the HOMO, while that at position 3 is extremely small; thus, any involvement of this orbital will lead to enhanced reactivity at position 2. Secondly, this orbital has a high localisation at position 5 in the benzene nucleus, and consequently substitution by methoxyl at position 5 has the effect of raising the energy of this orbital (HOMO — 1) so that it becomes much closer in energy to that of the HOMO. This indicates that methoxy-substitution at position 5 increases the importance of the (HOMO — 1) orbital in the frontier orbital term. The reason for the destabilising effect on the (HOMO — 1) level when substituted in this way lies in the anti-bonding nature of the $C_{2p\pi}$–$O_{2p\pi}$ (methoxy) coefficients in this particular molecular orbital. Thus, substitution at position 4, which has a negligible coefficient in this orbital (HOMO — 1), hardly alters its energy with respect to the HOMO.

The energy of the HOMO — 1 level in the 5,6-dimethoxy-compound is also affected in a manner similar to that of the 5-methoxy-compound. However, because the coefficient at position 2 in the HOMO — 1 is much smaller for the 5,6-dimethoxy-compound, the effect is likely to be less significant than in the 5-methoxy-compound.

On this basis the anomalous behaviour of the 5-methoxy-derivative might be interpreted in frontier orbital theory as arising not from the HOMO but from the next highest molecular orbital.

EXPERIMENTAL

General.—M.p.s were determined with a Kofler hot-stage apparatus and are corrected. N.m.r. spectra (unless otherwise stated) were measured with a Perkin-Elmer R-32 spectrometer at 90 MHz in deuteriochloroform. I.r. spectra were measured on a Unicam SP 200 grating spectrophotometer. U.v. spectra were determined in absolute ethanol on either a Unicam SP 800 spectrophotometer or on a Cary 17 spectrophotometer. Mass spectra were obtained with a Varian CH5-D instrument by electron impact-direct insertion probe at 70 eV and 50 μA. All solvents were purified according to standard procedures [15] before use. Light petroleum refers to that of boiling range 40—60 °C. Solutions were dried over magnesium sulphate before removal of solvent. T.l.c. was performed using plates coated with Merck silica gel HF 254. Preparative t.l.c. was carried out with 20 × 20 cm plates coated with Merck silica gel PF 254. Merck (Kieselgel 60) silica was used for column chromatography. For qualitative n.m.r. measurements on deuteriated compounds, the proton resonance signal areas were expanded and run at least five times at increased sensitivity and measured by tracing and weighing. The average of these measurements was taken. Ether refers to diethyl ether.

Ethyl 1-(4-*Methoxyphenylazo*)-2-*oxocyclohexanecarboxylate* (5).—To a suspension of sodium hydride (1.40 g, 0.06 mol) in dry tetrahydrofuran (THF) (50 ml) was added dropwise, at 20 °C under nitrogen, a solution of ethyl 2-oxocyclohexanecarboxylate (6.70 g, 0.04 mol) in dry THF (50 ml). The resulting pale yellow solution was heated under reflux for 30 min before cooling to 0 °C. 4-Methoxybenzenediazonium tetrafluoroborate (8.4 g, 0.04 mol) was added portionwise, during the addition the solution turned red, and sodium tetrafluoroborate separated out as a solid. The mixture was heated under reflux for 1 h before cooling to 20 °C. After dilution with water (200 ml) the mixture was extracted into ether (3 × 100 ml). The combined extracts were washed with water (2 × 100 ml) and dried. Removal of the solvent under reduced pressure gave a mixture of the ethyl ester (5) and a yellow solid. Crystallisation from light petroleum afforded the yellow *hydrazone* (6) (1.80 g, 16%), m.p. 96—97 °C (Found: C, 59.7; H, 7.0; N, 8.75. $C_{16}H_{22}N_2O_5$ requires C, 59.6; H, 6.9; N, 8.7%), τ 8.69 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 8.31 [4 H, m, $-N{=}CCH_2(CH_2)_2CH_2$-COOH], 7.59 [4 H, m, $-N{=}C{-}CH_2(CH_2)_2CH_2COOH$], 6.26 (3 H, s, OCH_3), 5.77 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 3.17 (2 H, d, *J* 9 Hz, aromatic protons *ortho* to OCH_3), 2.92 (2 H, d, *J* 9 Hz, aromatic protons *meta* to OCH_3), −0.1br (1 H, s, COOH), and −2.03br (1 H, s, H−N=C−), $\nu_{max.}$ (Nujol) 3 300 (NH), 2 700 (OH acidic), 1 710 (C=O ester), 1 675 (C=O acid), and 1 595 (C=N) cm^{-1}, $\lambda_{max.}$ 215 (ε 6 300), 238 (8 800), 265 (1 100), 314 (7 300), 320 (6 900), and 360 nm (16 700), *m/z* 322 (M^+, 30%), 152 (33), 151 (49), 149 (27), 138 (15), 137 (26), 136 (21), 124 (59), 123 (100), 122 (63), 110 (45), and 108 (45).

The mother liquor was evaporated to dryness to give ethyl 1-(4-methoxyphenylazo)-2-oxocyclohexanecarboxylate (5) as a red oil (8.9 g, 77%), τ 8.77 (3 H, t, *J* 7 Hz, $CO_2CH_2CH_3$), 8.21 [4 H, m, $CH_2(CH_2)_2CH_2CO$], 7.45 [4 H,

m, $CH_2(CH_2)_2CH_2CO$], 6.21 (3 H, s, OCH_3), 5.77 (2 H, q, *J* 7 Hz, $CO_2CH_2CH_3$), 3.1 (2 H, d, *J* 9 Hz, aromatic protons *ortho* to OCH_3), and 2.29 (2 H, d, *J* 9 Hz, aromatic protons *meta* to OCH_3).

Ethyl 4-(2-Ethoxycarbonyl-5-methoxyindol-3-yl)butanoate (7a).—A solution of ethyl 1-(4-methoxyphenylazo)-2-oxocyclohexanecarboxylate (5) and the hydrazone derivative (6) (together 10.5 g) in absolute ethanol (70 ml) was saturated with dry hydrogen chloride gas during which time ammonium chloride separated out as a solid. The mixture was heated to reflux for 15 min before keeping at 20 °C overnight. It was then poured into water (200 ml) and extracted with chloroform (4 × 75 ml). The combined extracts were washed with water (2 × 75 ml) and dried before removal of the solvent under reduced pressure to give a dark brown residue which was crystallised from light petroleum (b.p. 60—80 °C) to give *ethyl 4-(2-ethoxycarbonyl-5-methoxyindol-3-yl)butanoate* (7a) as pale yellow needles (4.40 g, 45%), m.p. 79—80 °C (Found: C, 65.1; H, 7.1; N, 4.2. $C_{18}H_{23}NO_5$ requires C, 64.85; H, 6.9; N, 4.2%), τ 8.8 (3 H, t, *J* 7 Hz, $CH_2COCH_2CH_3$), 8.63 (3 H, t, *J* 7 Hz, indol-$CO_2CH_2CH_3$), 8.0 (2 H, m, $^-CH_2CH_2CO_2CH_2CH_3$), 7.67 (2 H, t, *J* 7 Hz, $CH_2CO_2CH_2CH_3$), 6.9 (2 H, t, *J* 7 Hz, indol-CH_2^-), 6.17 (3 H, s, OCH_3), 5.91 (2 H, q, *J* 7 Hz, $CH_2CO_2CH_2CH_3$), 5.63 (2 H, q, *J* 7 Hz, indol-$CO_2CH_2CH_3$), 3.05 (1 H, dd, *J* 9 and 2 Hz, indol-6-H), 2.99 (1 H, s, indol-4-H), 2.76 (1 H, d, *J* 9 Hz, indol-7-H), and 1.17br (1 H, s, NH), $\nu_{max.}$ (Nujol) 3 350 (NH indolic), 1 730 (C=O saturated, acyclic ester), and 1 680 (C=O aromatic ester) cm^{-1}, $\lambda_{max.}$ 215 (ε 24 800), 227 (28 500), 253 (2 200), 293 (sh, 23 900), 302 (27 400), and 325 (8 400) nm, *m/z* 333 (M^+, 100%), 288 (16), 260 (37), 245 (22), 232 (62), 214 (19), 213 (14), 199 (17), 187 (11), 186 (72), and 158 (16).

4-(2-Carboxy-5-methoxyindol-3-yl)butanoic Acid (7b).—A mixture of sodium hydroxide (1.5 g, 0.04 mol) in absolute ethanol (50 ml) and ethyl 4-(2-ethoxycarbonyl-5-methoxyindol-3-yl)butanoate (7a) (3.40 g, 0.01 mol) was heated under reflux for 30 min, during which time an off-white solid separated. The mixture was allowed to cool to 20 °C before pouring into water (50 ml) when the solid completely dissolved. Ethanol was subsequently removed under reduced pressure and sulphur dioxide was passed through the residual aqueous solution until no more solid separated. The solid was filtered and washed with water until the washings were neutral and then air-dried. Crystallisation from methanol–chloroform afforded *4-(2-carboxy-5-methoxyindol-3-yl)butanoic acid* (7b) as needles (2.70 g, 95%), m.p. 199—200 °C (Found: C, 60.45; H, 5.85; N, 5.35. $C_{14}H_{15}NO_5$ requires C, 60.65; H, 5.45; N, 5.05%), τ($CDCl_3$–[$^2H_6$]DMSO) 8.08 (2 H, m, CH_2CH_2COOH), 7.75 (2 H, t, *J* 7 Hz, CH_2COOH), 6.92 (2 H, t, *J* 7 Hz, indol-CH_2), 6.21 (3 H, s, OCH_3), 3.14 (1 H, dd, *J* 9 and 2 Hz, indol-6-H), 2.96 (1 H, d, *J* 2 Hz, indol-4-H), 2.69 (1 H, d, *J* 9 Hz, indol-7-H), −0.6br (2 H, 2 × COOH), and −0.97br (1 H, s, NH), $\nu_{max.}$ (Nujol) 3 330 (NH indolic), 2 600 (OH acidic), and 1 680 (C=O acid) cm^{-1}, $\lambda_{max.}$ 225 (ε 22 500), 290 (16 100), 299 (18 100), 325 (5 400), and 350 (2 000), *m/z* 277 (M^+, 21%), 233 (9), 215 (55), 204 (34), 200 (34), 186 (100), 172 (28), 160 (50), 159 (38), 158 (41), 145 (22), 144 (22), 116 (28), and 115 (34).

4-(5-Methoxyindol-3-yl)butanoic Acid (9).—4-(2-Carboxy-5-methoxyindol-3-yl)butanoic acid (7b) (2.40 g, 8.70 mmol) was divided into portions (2 × 1.20 g) which were each cautiously heated in a conical flask at 235 °C (silicone oil bath) until u.v. spectroscopy showed the reaction to be complete (*ca.* 15 min). The residues were combined and crystallised from chloroform–light petroleum to give 4-(5-methoxyindol-3-yl)butanoic acid (9) as a solid (1.20 g, 59%), m.p. 138—139 °C (lit.,[16] 135—135.5 °C) (Found: C, 66.9; H, 6.3; N, 6.55. Calc. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.5; N, 6.0%), τ($CDCl_3$–[$^2H_6$]DMSO) 8.04 (2 H, quintet, *J* 7 Hz, CH_2CH_2COOH), 7.67 (2 H, t, *J* 7 Hz, CH_2COOH), 7.25 (2 H, t, *J* 7 Hz, indol-CH_2), 6.19 (3 H, s, OCH_3), 3.25 (1 H, dd, *J* 9 and 2 Hz, indol-6-H), 3.07 (1 H, s, indol-2-H), 3.00 (1 H, d, *J* 2 Hz, indol-4-H), 2.79 (1 H, d, *J* 9 Hz, indol-7-H), and 1.8br (1 H, s, NH), $\nu_{max.}$ (Nujol) 3 320 (NH indolic), 2 650 (OH acidic), and 1 700 (C=O acid) cm^{-1}, $\lambda_{max.}$ 226 (ε 17 200), 250 (2 000), 280 (5 300), 292 (sh, 4 700), 298 (4 600), 305 (sh, 4 000), and 312 (sh, 3 300) nm, *m/z* 234 (M^+ + 1, 16%), 233 (M^+, 97), 161 (17), 160 (100), and 145 (12).

4-(5-Methoxyindol-3-yl)butan-1-ol (1e).—To a suspension of lithium aluminium hydride (0.22 g, 6.00 mmol) in dry THF (20 ml) was added dropwise with vigorous stirring a solution of 4-(5-methoxyindol-3-yl)butanoic acid (9) (0.42 g, 2.00 mmol) in dry THF (10 ml). The mixture was heated under reflux for 30 min before cooling to 20 °C. Excess of lithium aluminium hydride was decomposed by adding dropwise a saturated Rochelle salt solution. The tetrahydrofuran solution was decanted off and the aluminium salts were washed with ether (4 × 50 ml). The ether and the tetrahydrofuran solutions were combined, washed with water (2 × 50 ml), and dried before removal of the solvent under reduced pressure to leave the crude alcohol as an oil (0.36 g, 90%). Crystallisation from ether gave *4-(5-methoxyindol-3-yl)butan-1-ol* (1e) as a solid (0.28 g), m.p. 64—65 °C (Found: C, 71.0; H, 7.65; N, 6.8. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.95%), τ 8.35 (4 H, m, $CH_2CH_2CH_2OH$), 8.18br (1 H, s, OH), 7.3 (2 H, t, *J* 7 Hz, indol-CH_2), 6.39 (2 H, t, *J* 7 Hz, CH_2OH), 6.18 (3 H, s, OCH_3), 3.2 (1 H, dd, *J* 9 and 2 Hz, indol-6-H), 3.14 (1 H, s, indol-2-H), 2.99 (1 H, d, *J* 2 Hz, indol-4-H), 2.85 (1 H, d, *J* 9 Hz, indol-7-H), 2.04br (1 H, s, NH), and 2.04br (1 H, s, NH), $\nu_{max.}$ ($CHCl_3$) 3 540 (NH indolic), 3 400 (OH alcohol), and 1 620 (C=C) cm^{-1}, $\lambda_{max.}$ 226 (ε 21 200), 249 (1 900), 280 (6 600), 298 (sh, 5 300), and 310 (sh, 3 800) nm, *m/z* 220 (M^+ + 1, 21%), 219 (M^+, 76), 161 (58), 160 (100), 148 (11), 145 (55), 130 (13), 117 (33), 90 (11), and 89 (12).

6-Methoxy-1,2,3,4-tetrahydrocarbazole (11a).—A solution of *p*-anisidine (2.46 g, 0.02 mol) in concentrated hydrochloric acid (40 ml) was cooled to 0 °C (ice–salt bath) and a pre-chilled solution of sodium nitrite (1.60 g, 0.02 mol) in water (10 ml) was added dropwise with stirring and efficient cooling over 10 min. Stirring was continued at 10 °C for 10 min before cooling to 0 °C. To the resulting mixture a solution of tin(II) chloride (18.0 g, 0.08 mol) in concentrated hydrochloric acid (16 ml) was added dropwise. A red solid, which soon turned white, separated during the addition. The mixture was kept at 0 °C for 2 h for complete precipitation. The solid was filtered and dissolved in water (200 ml) and subsequently basified with a 2N-NaOH solution. Extraction into chloroform (3 × 100 ml), washing with water (2 × 100 ml), and drying was followed by removal of the solvent under reduced pressure to give 4-methoxyphenylhydrazine as a yellow solid (1.49 g, 54%), m.p. 64—67 °C (lit.,[17] 65 °C) which was used immediately in the next stage, τ 6.3 (3 H, s, OCH_3), 6.24br (1 H, s, NH), 6.16br (2 H, NH_2), and 3.24 (4 H, s, aromatic protons).

A mixture of 4-methoxyphenylhydrazine (1.49 g, 0.01 mol), cyclohexanone (1.0 g, 0.01 mol), and glacial acetic acid (10 ml) were heated at 80 °C for 1 h. The mixture was

cooled to 20 °C and kept in the refrigerator overnight during which time an off-white solid separated out. Filtration was followed by crystallisation of the solid from ethanol affording 6-methoxy-1,2,3-4-tetrahydrocarbazole (11a) as needles (0.85 g, 42%), m.p. 94—96 °C (lit.,[6] 94—95 °C), τ 8.15 (4 H, m, 2-H and 3-H), 7.39 (4 H, m, 1- and 4-H), 6.2 (3 H, s, OCH_3), 3.27 (1 H, dd, *J* 9 and 2 Hz, 7-H), 3.1 (1 H, d, *J* 2 Hz, 5-H), 2.96 (1 H, d, *J* 9 Hz, 8-H), and 2.58br (1 H, s, NH), $\nu_{max.}$ ($CHCl_3$) 3 520 (NH) and 1 635 (C=C) cm^{-1}, $\lambda_{max.}$ 228 (ε 24 500), 254 (2 500), 285 (8 300), and 297 (sh, 7 800) nm.

9-Acetyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (11c).—6-Methoxy-1,2,3,4-tetrahydrocarbazole (11a) (0.25 g, 0.01 mol) in acetic anhydride (1.7 ml) was heated under reflux for 17 h before cooling to 20 °C. The resulting dark brown solution was poured into water (10 ml) when a dark oil separated out. Extraction into ether (3 × 20 ml), washing with water (2 × 10 ml), and drying was followed by removal of the solvent under reduced pressure to leave a crude oil (0.2 g) which was chromatographed over silica gel (50 g) using light petroleum–ether as eluant to give the crude *N*-acetyl derivative as a pale yellow solid (0.07 g, 23%). Crystallisation from ether gave *9-acetyl-6-methoxy-1,2,3,4-tetrahydrocarbazole* (11c) as crystals (0.05 g), m.p. 100—101 °C (Found: C, 73.85; H, 7.05; N, 6.05. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.05; N, 5.75%), τ 8.18 (4 H, m, 2- and 3-H), 7.43 (5 H, m, $COCH_3$ and 4-H), 7.08 (2 H, m, 1-H), 6.18 (3 H, s, OCH_3), 3.2 (1 H, dd, *J* 10 and 2 Hz, 7-H), 3.18 (1 H, d, *J* 2 Hz, 5-H), and 2.02 (1 H, d, *J* 10 Hz, 8-H), $\nu_{max.}$ ($CHCl_3$) 1 680 (C=O) cm^{-1}, $\lambda_{max.}$ 228 (ε 6 500), 256 (22 400), 300 (8 700), and 309 (sh, 7 800), *m/z* 244 ($M^+ + 1$, 13%), 243 (M^+, 76), 202 (15), 201 (100), 200 (17), 173 (72), and 158 (20).

9-Trifluoroacetyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (11b).—A mixture of 6-methoxy-1,2,3,4-tetrahydrocarbazole (11a) (0.23 g, 1.10 mmol) in dry pyridine (2 ml) and trifluoroacetic anhydride (0.5 ml) was stirred at 20 °C for 2 h after which pyridine and some remaining trifluoroacetic anhydride were removed under reduced pressure to leave a solid residue which was taken up in dry ether (50 ml). The undissolved solid was filtered off and the filtrate was evaporated under reduced pressure to give the crude product (0.3 g). This was chromatographed over silica gel (50 g) under nitrogen (light petroleum–ether as eluant) to obtain the required trifluoroacetyl derivative as a pale yellow solid (0.15 g, 44%). Crystallisation from light petroleum gave *9-trifluoroacetyl-6-methoxy-1,2,3,4-tetrahydrocarbazole* (11b) as crystals (0.1 g), m.p. 81—82 °C (Found: C, 60.85; H, 4.8; N, 4.9. $C_{15}H_{14}F_3NO_2$ requires C, 60.6; H, 4.7; N, 4.7%), τ 8.17 (4 H, m, 2- and 3-H), 7.42 (2 H, m, 4-H), 7.09 (2 H, m, 1-H), 6.17 (3 H, s, OCH_3), 3.19 (1 H, d, *J* 2 Hz, 5-H), 3.17 (1 H, dd, *J* 10 and 2 Hz, 7-H), 2.11 (1 H, d, *J* 10 Hz, 8-H), $\nu_{max.}$ ($CHCl_3$) 1 700 (C=O) cm^{-1}, $\lambda_{max.}$ 230sh (ε 11 500), 245 (6 900), 268 (13 000), and 300sh (6 300), *m/z* 298 ($M^+ + 1$, 15%), 297 (M^+, 100), 269 (24), 200 (11), 173 (10), and 172 (32).

Another compound (0.1 g) which crystallised from the mother liquors later was proved to be starting material, presumably formed by hydrolysis of the product during purification.

Cyclisation of 4-(5-Methoxyindol-3-yl)butan-1-ol (1e) *with Boron Trifluoride–Ether.*—A solution of 4-(5-methoxyindol-3-yl)butan-1-ol (1e) (0.36 g, 2.0 mmol) in freshly distilled boron trifluoride–ether (8 ml) was heated under reflux for 1.5 h before cooling to 20 °C. The mixture was poured into water (10 ml) and extracted into ether (3 × 75 ml). The combined extracts were washed with water (2 × 50 ml) and dried before removal of the solvent under reduced pressure to give a dark green gum (0.3 g) which was immediately treated with trifluoroacetic anhydride (0.5 ml) and dry pyridine (2 ml). The mixture was stirred at 20 °C for 2 h after which pyridine and some remaining trifluoroacetic anhydride were removed under reduced pressure to leave a residue which was taken up in dry ether (50 ml). The undissolved solid was filtered off and the filtrate was evaporated to dryness under reduced pressure to give a dark green solid (0.35 g) which was chromatographed over silica gel (50 g) under nitrogen (light petroleum–ether eluant) to yield an off-white solid (0.19 g). Two crystallisations from light petroleum gave pure 9-trifluoroacetyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (11b) obtained as crystals (0.12 g, 20% from starting alcohol), m.p. 81—82 °C, mixed m.p. 80.5—82 °C with an authentic sample prepared as above. The t.l.c., u.v., and n.m.r. spectra of this compound were identical with those of the authentic specimen.

6-Methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (8).—(a) *From thermolysis of 4-(2-carboxy-5-methoxyindol-3-yl)butanoic acid* (7b). 4-(2-Carboxy-5-methoxyindol-3-yl)butanoic acid (7b) (1.0 g, 3.6 mmol) was cautiously heated in a conical flask in a free flame until the evolution of gas ceased (*ca.* 10 min). After cooling to 20 °C the solid residue was crystallised from chloroform–light petroleum and then acetone to give *6-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole* (8) as pale yellow crystals (0.2 g, 26%), m.p. 220—221 °C (Found: C, 72.25; H, 6.1; N, 6.4. $C_{13}H_{13}NO_2$ requires C, 72.55; H, 6.1; N, 6.5%), τ($CDCl_3$–[$^2H_6$]DMSO) 7.83 (2 H, m, 3-H), 7.44 (2 H, t, *J* 6 Hz, 2-H), 7.08 (2 H, t, *J* 6 Hz, 4-H), 6.22 (3 H, s, OCH_3), 3.09 (1 H, dd, *J* 10 and 3 Hz, 7-H), 3.04 (1 H, d, *J* 3 Hz, 5-H), 2.69 (1 H, d, *J* 10 Hz, 8-H), and −0.97br (1 H, s, NH), τ([$^2H_6$]acetone) 7.77 (2 H, m, 3-H), 7.48 (2 H, t, *J* 6 Hz, 2-H), 7.05 (2 H, t, *J* 6 Hz, 4-H), 6.2 (3 H, s, OCH_3), 3.04 (1 H, dd, *J* 10 and 3 Hz, 7-H), 2.91 (1 H, d, *J* 3 Hz, 5-H), 2.6 (1 H, d, *J* 10 Hz, 8-H), and −0.3br (1 H, s, NH), $\nu_{max.}$ (Nujol) 3 300 (NH) and 1 645 (C=O) cm^{-1}, $\lambda_{max.}$ 223 (ε 13 300), 232 (15 000), 264 (600), 314 (23 800), and 256sh (4 200) nm, *m/z* (f.d.) 216 ($M^+ + 1$, 13%) and 215 (M^+, 100), (e.i.) 216 ($M^+ + 1$, 14), 215 (M^+, 100), 200 (31), 186 (10), 172 (13), and 159 (26).

(b) *From boron trifluoride catalysed cyclisation of 4-(5-methoxyindol-3-yl)butanoic acid* (9). A solution of boron trifluoride–ether (freshly distilled, 5 ml) in dry ether (35 ml) was added dropwise to a stirred solution of 4-(5-methoxyindol-3-yl)butanoic acid (9) (2.3 g, 0.01 mol) in acetic anhydride (2.4 ml) and glacial acetic acid (12 ml). Stirring at 20 °C was continued until t.l.c. showed that all the starting material had been consumed (*ca.* 2 h). The solution was then carefully poured into a saturated sodium hydrogencarbonate solution (500 ml) and stirring was continued for a further 30 min. The mixture was extracted with ether (10 × 75 ml), the combined extracts were washed with a saturated sodium hydrogencarbonate solution (300 ml) and water (3 × 200 ml), and dried. Removal of the solvent under reduced pressure left a pale green solid which after two crystallisations from acetone gave pure 6-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (8) as off-white needles (1.0 g, 47%), m.p. 218—219 °C, mixed m.p. 218—220 °C with an authentic sample prepared as above.

The compound had n.m.r., i.r., and u.v. spectra which were identical with those of the specimen from thermolysis of 4-(2-carboxyindol-3-yl)butanoic acid (9).

(c) *From the Fischer indole synthesis.* (1) 1-Piperidinocyclohexene. Cyclohexanone (9.8 g, 0.1 mol) was added dropwise to a stirred, boiling solution of piperidine (8.5 g, 0.1 mol) in dry benzene (55 ml). After complete addition, the solution was heated under reflux using a Dean–Stark apparatus. The mixture was refluxed until the theoretical amount of water was collected in the trap (*ca.* 12 h) before cooling to 20 °C and benzene was removed under reduced pressure to leave an oil which was distilled to give 1-piperidinocyclohexene as an oil (8.2 g, 50%), b.p. 110—115 °C at 13 mmHg (lit.,[18] 108.5 °C at 12 mmHg), τ 8.5 (10 H, m, N–C=CHCH$_2$CH_2CH_2 and N–CH$_2$CH_2CH_2CH_2), 7.95 (4 H, m, CH_2CH=CCH$_2$), 7.24 (4 H, m, CH$_2$NCH$_2$), and 5.32 (1 H, t, *J* 3 Hz, C=C*H*), $\nu_{max.}$ (neat) 1 640 (NC=C) cm^{-1}.

(2) Cyclohexane-1,2-dione mono-4-methoxyphenylhydrazone (12). A solution of *p*-anisidine (6.0 g, 0.05 mol) in concentrated hydrochloric acid (15 ml) was cooled to 0 °C and a mixture of sodium nitrite (3.4 g, 0.05 mol) in crushed ice (100 g) was added with stirring and efficient cooling over 10 min. Stirring was continued at 0 °C and a mixture of 1-piperidinocyclohexene (8.2 g, 0.05 mol), crushed ice (34 g), and concentrated hydrochloric acid (15 ml) was added over 5 min. The mixture was rapidly neutralised (to pH 5—6) with a pre-chilled saturated sodium acetate solution, during the addition the temperature being maintained at 0 °C, and a solid separated out. The resultant suspension was kept at 0 °C for 4 h after which the solid was filtered off, washed several times with cold water until the washings were neutral, and air dried. Crystallisation from ethanol afforded cyclohexane-1,2-dione mono-4-methoxyphenylhydrazone (12) as orange crystals (6.5 g, 57%), m.p. 181—182 °C (lit.,[19] 233—235 °C) (Found: C, 67.35; H, 6.7; N, 11.9. Calc. for $C_{13}H_{16}N_2O_2$: C, 67.2; H, 6.95; N, 12.05%), τ 8.19 [4 H, m, COCH$_2$(CH_2)$_2$CH$_2$C=N]) 7.56 (2 H, m, CH$_2$C=N), 7.36 (2 H, m, COCH$_2$), 6.27 (3 H, s, OCH$_3$), 3.18 (2 H, d, *J* 9 Hz, aromatic protons *ortho* to OCH$_3$), 2.82 (2 H, d, *J* 9 Hz, aromatic protons *meta* to OCH$_3$), and 3.95br (1 H, s, NH), $\nu_{max.}$ (Nujol) 3 250 (NH) and 1 650 (C=O) cm^{-1}, $\lambda_{max.}$ 217 (ε 7 200), 238 (11 600), 280 (2 000), 305 (sh, 4 800), 314 (4 800), 323 (4 000), and 384 (19 200) nm, *m/z* 233 (M^+ + 1, 20%), 232 (M^+, 87), 123 (85), 122 (100), 121 (32), 108 (45), 95 (39), 82 (35), 80 (11), 77 (12), 65 (11), 55 (44), 54 (12), 53 (12), 52 (16), and 41 (30).

(3) Cyclisation of cyclohexane-1,2-dione mono-4-methoxyphenylhydrazone (12) with formic acid. Cyclohexane-1,2-dione mono-4-methoxyphenylhydrazone (5.2 g, 0.02 mol) in formic acid (70 ml) was heated under reflux for 2 h; t.l.c. of a small sample of the mixture (work-up as described below) showed the reaction to be complete. The mixture was then poured onto ice (400 g) and left at 20 °C for 4 h. The resulting mixture was extracted with ether (3 × 200 ml, 2 × 100 ml), the combined extracts were washed with water (2 × 100 ml), saturated sodium hydrogencarbonate solution (150 ml) and water (100 ml), and dried. Removal of the solvent under reduced pressure left a yellow solid which after two crystallisations from acetone gave 6-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (8) as pale yellow needles (1.3 g, 27%), m.p. 220—221 °C. This was identical (m.p., mixed m.p., i.r., u.v., m.s., and ^{1}H n.m.r. spectra) with the product from thermolysis of 4-(2-carboxy-5-methoxyindol-3-yl)butanoic acid (7b).

Reduction of 6-*Methoxy*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (8) *to* 6-*Methoxy*-1,2,3,4-*tetrahydrocarbazole* (11a).—To a stirred suspension of lithium aluminium hydride (0.07 g, 1.8 mmol) in dry THF (10 ml) 6-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (8) (0.2 g, 0.9 mmol) was added portionwise. The mixture was heated under reflux until t.l.c. showed the starting material to be consumed (*ca.* 1 h) after which the temperature was lowered to 20 °C. Excess of lithium aluminium hydride was decomposed by adding dropwise a saturated Rochelle salt solution. The tetrahydrofuran solution was decanted off and the aluminium salts were washed with ether (3 × 70 ml). The ether and the tetrahydrofuran solutions were combined, washed with water (2 × 30 ml), and dried before removal of the solvent under reduced pressure to leave a pale green solid (0.18 g). After crystallisation from ethanol pure 6-methoxy-1,2,3,4-tetrahydrocarbazole (11a) was obtained as crystals (0.08 g, 43%), m.p. 93—94 °C, mixed m.p. 93—96 °C, spectroscopically identical to a sample of 6-methoxy-1,2,3,4-tetrahydrocarbazole prepared from the Fischer indole synthesis.

[1,1-$^2H_2$]-4-(5-*Methoxyindol*-3-*yl*)*butan*-1-*ol* (10).—A solution of 4-(5-methoxyindol-3-yl)butanoic acid (9) (1.09 g, 4.3 mmol) in dry THF (30 ml) was added dropwise with vigorous stirring to a suspension of lithium aluminium deuteride (0.51 g, 12.0 mmol) in dry THF (30 ml). After the addition the mixture was heated to reflux under nitrogen. After 1 h t.l.c. showed the reaction to be complete; the mixture was then cooled to 20 °C. Excess of lithium aluminium deuteride was decomposed by adding dropwise a saturated Rochelle salt solution. The tetrahydrofuran solution was decanted off and the aluminium salts were washed with ether (4 × 100 ml). The ether and the tetrahydrofuran solutions were combined, washed with water (2 × 200 ml), and dried before removal of the solvent under reduced pressure to leave an oil (0.80 g, 86%). Crystallisation from ether gave pure [1,1-$^2H_2$]-4-(5-*methoxyindol*-3-*yl*)*butan*-1-*ol* (10) as a solid (0.75 g), m.p. 63—64 °C.

The ^{1}H n.m.r. spectrum of this compound was identical with that of the non-deuteriated one (1e) except that the signal at τ 6.39 due to the CH_2OH protons was entirely absent indicating complete deuteriation.

Cyclisation of [1,1-$^2H_2$]-4-(5-*Methoxyindol*-3-*yl*)*butan*-1-*ol* (10) *with Boron Trifluoride–Ether.*—[1,1-$^2H_2$]-4-(5-Methoxyindol-3-yl)butan-1-ol (10) (0.21 g, 0.9 mmol) was dissolved in preheated (90 °C) freshly distilled boron trifluoride–ether (7 ml) and the mixture was kept at 90 °C in a thermostatted bath for 3.5 h under nitrogen, these conditions being chosen to avoid subsequent rearrangement of the tetrahydrocarbazole once formed. The mixture was cooled to 20 °C before pouring into water (10 ml) and extracted with ether (3 × 75 ml). The combined extracts were washed with water (2 × 100 ml) and dried before removal of the solvent under reduced pressure to leave a dark green gum (0.19 g) which was purified by h.p.l.c. under nitrogen. The column used was a 250 × 8 mm steel column packed with Lichroprep 5–20, the solvent used was 40% ethyl acetate–light petroleum. The flow rate was 6 ml min^{-1} and the u.v. detector was at 280 nm. After purification by h.p.l.c. the deuteriated isomers of 6-methoxytetrahydrocarbazole were obtained as a solid (0.04 g, 21%) which were treated immediately with trifluoroacetic anhydride (0.25 ml) and dry pyridine (0.12 ml). The mixture was stirred at 20 °C until t.l.c. showed the reaction to be complete (*ca.* 15 min). Removal of pyridine and some remaining trifluoroacetic anhydride under reduced pressure left a residue of the deuteriated isomers of 9-trifluoroacetyl-6-methoxytetrahydrocarbazole (11f and g) which were purified by h.p.l.c. under nitrogen. The column used was

the same as used in the previous stage. The solvent was 5% ethyl acetate–light petroleum, the flow rate was 6 ml min^{-1}, and the u.v. detector was at 280 nm. Removal of the solvent under reduced pressure from the appropriate fraction of eluate (R_F 2 min) provided a mixture of deuteriated 9-trifluoroacetyl-6-methoxytetrahydrocarbazoles (11f and g) which were crystallised from light petroleum to obtain a solid (0.035 g, 59%), m.p. 82—83.5 °C.

The ^1H n.m.r. spectrum of 9-trifluoroacetyl-1,1-dideuterio-6-methoxy-1,2,3,4-tetrahydrocarbazole was examined, the peak areas of the protons at positions 1 and 4 were measured, and the ratio was found to be 1 : 1.25.

Another experiment was carried out under the same conditions, but without purification of the tetrahydrocarbazole formed, which was subjected immediately to trifluoroacetylation. ^1H N.m.r. analysis showed the ratio of the peak areas of the protons at the 1- and 4-positions to be 1 : 1.27.

[1,1-$^2H_2$]-6-*Methoxy*-1,2,3,4-*tetrahydrocarbazole* (11e). To a stirred suspension of lithium aluminium deuteride (0.37 g, 8.8 mmol) in dry THF (10 ml) was added, dropwise, a warm solution of 6-methoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (8) (0.20 g, 0.93 mmol) in dry THF (10 ml). The mixture was refluxed under nitrogen for 1.45 h after which t.l.c. showed the reaction to be complete. The mixture was cooled to 20 °C and excess of lithium aluminium deuteride was decomposed by adding dropwise a saturated Rochelle salt solution. The THF solution was decanted off and the aluminium salts were washed with ether (4 × 75 ml). The ether and the THF solutions were combined, washed with water (2 × 50 ml), and dried before removal of the solvent under reduced pressure to leave a crude green gum (0.15 g) which was purified by h.p.l.c. under nitrogen. (The system used was the same as described for the tetrahydrocarbazole in the previous stage.) Removal of the solvent from the appropriate fraction of eluate (R_F 2.2 min) provided [1,1-$^2H_2$]-6-methoxy-1,2,3,4-tetrahydrocarbazole (11e) as a solid (0.08 g, 42%) which was used immediately in the next stage.

The ^1H n.m.r. spectrum of this compound was identical to that of the non-deuteriated one except that the signal at τ 7.36 due to the methylene protons at the 4-position was exactly half of that at τ 8.15, corresponding to the methylene protons at the 2- and 3-positions indicating complete deuteriation, τ 8.15 (4 H, m, 2- and 3-H), 7.36 (2 H, m, 4-H), 6.2 (3 H, s, OCH_3), 3.27 (1 H, dd, *J* 9 and 2 Hz, 7-H), 3.1 (1 H, d, *J* 2 Hz, 5-H), 2.89 (1 H, d, *J* 9 Hz, 8-H), and 2.49br (1 H, s, NH).

Recovery of [1,1-$^2H_2$]-6-*Methoxy*-1,2,3,4-*tetrahydrocarbazole* (11e) *after Treatment with Boron Trifluoride–Ether and Water at* 90 °C *for* 3.5 h.—[1,1-$^2H_2$]-6-Methoxy-1,2,3,4-tetrahydrocarbazole (11e) (0.045 g, 0.22 mmol) was dissolved in a preheated (90 °C) solution of freshly distilled boron trifluoride–ether (2 ml) and water (4 μl, 0.22 mmol). The mixture was kept at 90 °C in a thermostatted bath for 3.5 h under nitrogen. The mixture was cooled to 20 °C and poured into water (20 ml). Extraction into ether (2 × 50 ml), washing with water (50 ml), and drying were followed by removal of the solvent under reduced pressure to leave a pale green solid (0.04 g). The recovered dideuteriotetrahydrocarbazole was treated immediately with trifluoroacetic anhydride (0.2 ml) and pyridine (0.1 ml) at 20 °C for 15 min. T.l.c. then showed the reaction to be complete. Removal of pyridine and some remaining trifluoroacetic anhydride under reduced pressure left the crude dideuteriated *N*-trifluoroacetyltetrahydrocarbazole which was purified by h.p.l.c. under nitrogen. The system used was the same as used in the previous stage as described for the *N*-trifluoro-derivative. Evaporation of the solvent from the appropriate fraction of eluate gave the desired product as a solid (0.035 g, 59%), m.p. 82—84 °C after crystallisation from light petroleum.

The ^1H n.m.r. spectrum of this compound showed no signal at τ 7.09 due to the methylene protons at the 1-position of the original tetrahydrocarbazole and the signal at τ 7.42 corresponding to the 4-methylene protons was exactly half of the intensity of the signal at τ 8.18 due to the 2- and 3-methylene protons. This result showed that no rearrangement had occurred under these conditions, τ 8.18 (4 H, m, 2- and 3-H), 7.42 (2 H, m, 4-H), 6.17 (3 H, s, OCH_3), 3.16 (1 H, d, *J* 3 Hz, 5-H), 3.15 (1 H, dd, *J* 10 and 3 Hz, 7-H), and 2.09 (1 H, d, *J* 10 Hz, 8-H).

Another experiment, carried out without the addition of water, also gave the same result.

[1/1584 *Received*, 11*th October*, 1981]

REFERENCES

[1] (*a*) A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989; (*b*) A. H. Jackson, P. V. R. Shannon, and A. C. Tinker, *J. Chem. Soc., Chem. Commun.*, 1976, 796.

[2] A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.

[3] R. Iyer, A. H. Jackson, P. V. R. Shannon, and B. Naidoo, *J. Chem. Soc., Perkin Trans. 2*, 1973, 872.

[4] R. Iyer, A. H. Jackson, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 2*, 1973, 878.

[5] J. S. L. Ibaceta-Lizana, R. Iyer, A. H. Jackson, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 2*, 1978, 733.

[6] W. Borsche, *Liebig's Ann. Chem.*, 1908, **359**, 49.

[7] V. I. Shvedov, L. B. Altukhova, and A. N. Grinev, *Zh. Org. Khim.*, 1966, **2**, 1608 (*Chem. Abstr.*, 1967, **66**, 65354a).

[8] R. J. Sundberg, ' The Chemistry of Indoles,' Academic Press, New York, 1970, ch. 1.

[9] J. E. Bloor and D. L. Breen, *J. Am. Chem. Soc.*, 1967, **89**, 6835.

[10] J. A. Pople and D. L. Beveridge, ' Approximate Molecular Orbital Theory,' McGraw-Hill, New York, 1970.

[11] (*a*) T. Sakaki, A. Sogo, A. Wakahara, T. Kanai, T. Fujiwara, and K. Tomita, *Acta Crystallogr.*, 1976, **32B**, 3235; (*b*) M. Inoue, T. Sikaki, T. Fujiwara, and K. Tomita, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1118.

[12] L. E. Sutton, ' Interatomic Distances,' Chemical Society Special Publication, 1958.

[13] M. Haisa, S. Kashino, Y. Matsuzaki, R. Kawai, and K. Kunitomi, *Acta Crystallogr.*, 1977, **33B**, 2449.

[14] I. Fleming, ' Frontier Orbitals and Organic Chemical Reactions,' Wiley, New York, 1976.

[15] A. Weissberger, 'Technique of Organic Chemistry,' Interscience, New York, 1955, vol. VII.

[16] N. N. Suvorov, V. P. Mamaev, and L. B. Shagalov, *Doklady Akad. Nauk. SSSR*, 1955, **101**, 103 (*Chem. Abstr.*, 1956, **50**, 2543d).

[17] T. Altschul, *Ber.*, 1892, **25**, 1849.

[18] G. Opitz, H. Hellmann, and H. W. Schubert, *Liebig's Ann. Chem.*, 1959, **623**, 112.

[19] V. I., Shvedov, L. B. Altukhova, and A. N. Grinev, *Zh. Org. Khim.*, 1965, **1**, 879 (*Chem. Abstr.*, 1965, **63**, 6894a).