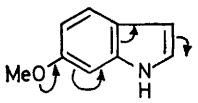
Electrophilic Substitution in Indoles. Part 10.[1] The Mechanism of Substitution in 4,6- and 5,6-Dimethoxyindoles

By **Juana S. L. Ibaceta-Lizana, Ramachandran Iyer, Anthony H. Jackson,* and Patrick V. R. Shannon,**
Department of Chemistry, University College, Cardiff CF1 1XL

Deuterium-labelling experiments show that the boron trifluoride-catalysed cyclisation (at 80 °C) of 4-(4,6-dimethoxyindol-3-yl)butanol (3c) to 5,7-dimethoxytetrahydrocarbazole (9c) occurs by two simultaneous pathways. The main route (61.5%) involves initial cyclisation at the 3-position of (3c) to give an intermediate spirocyclic indole which then rearranges to the tetrahydrocarbazole; the minor pathway (38.5%) involves direct attack at the 2-position. The cyclisation of 4-(5,6-dimethoxyindol-3-yl)butanol (3d) to 6,7-dimethoxytetrahydrocarbazole (9d) also occurs by two routes, but in this case a much lower proportion (13.5%) arises by direct attack at the 2-position. Kinetic studies of the overall rates of cyclisation of the indolylbutanols (3) to tetrahydrocarbazoles (9) were facilitated by the use of high-pressure liquid chromatography, and showed that the relative rates were as follows: 4-indol-3-ylbutanol (3a) > 4-(6-methoxyindol-3-yl)butanol (3b) > 4-(4,6-dimethoxyindol-3-yl)-butanol (3c) > 4-(5,6-dimethoxyindol-3-yl)butanol (3d). The differences in rates were tentatively attributed to the effects of the methoxy-groups on the rates of rearrangement of the protonated spirocyclic indole intermediates (5) formed by direct attack at the indole 3-position.

In previous papers [2,3] we have demonstrated that the initial electrophilic substitution in indoles and their simple alkyl derivatives invariably occurs in the 3-position, even when the latter is substituted by an alkyl group. However a methoxy-group in the 6-position of the indole nucleus activates the 2-position as shown in structure (1) and electrophilic attack occurs at both the 3- and the 2-positions, although the former is still the major pathway;[4] a 4-methoxy-group might also be



(1)

expected to activate the indole nucleus at the 2-position in a similar fashion. It thus seemed possible that a 4,6-dimethoxyindole might even undergo exclusive attack at the 2- rather than at the 3-position.

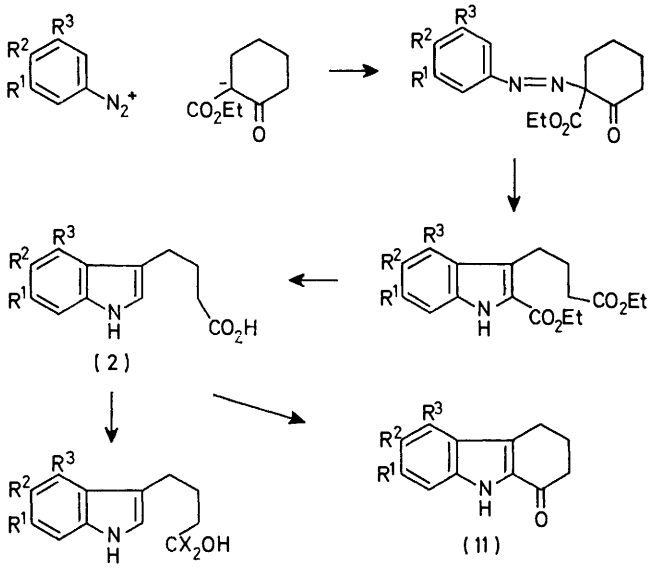
To study this possibility we adopted a similar approach to that used in our earlier work,[2,4] and decided to investigate the boron trifluoride-catalysed cyclisation of 4-(4,6-dimethoxyindol-3-yl)butanol (3c) to the corresponding tetrahydrocarbazole (9c).

The dimethoxyindolylbutanol (3c) was prepared by the same route (see Scheme 1) as that used previously for the 6-methoxy-analogue (3b). Cyclisation of this alcohol (3c) with boron trifluoride–diethyl ether at reflux temperatures (126 °C) afforded the tetrahydrocarbazole (9c) in good yield; the latter gave signals in its n.m.r. spectrum at τ 7.40 and 7.13 corresponding to the protons at the C-1 and C-4 positions respectively, whereas in the case of the monomethoxy-compound (9b) the protons at the C-1 and C-4 positions resonated together at τ 7.37. Assignments of the C-1 and C-4 proton resonances in the spectrum of the dimethoxytetrahydrocarbazole (9c) were confirmed by an examination of the n.m.r. spectrum of the 1,1-dideuteriated analogue (12c); the latter was prepared by lithium aluminium deuteride reduction of the corresponding 1-oxotetrahydrocarbazole (11c) obtained by cyclisation of the indolylbutyric acid (2c).

Our original experiments in the monomethoxy-series had shown that if cyclisation of the monomethoxyindolylbutanol (3b) was carried out at temperatures over 100 °C

[1] Part 9, R. Iyer, A. H. Jackson, and P. V. R. Shannon, *J.C.S. Perkin II*, 1973, 878.
[2] A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.
[3] A. H. Jackson, and B. Naidoo, *Tetrahedron*, 1969, **25**, 4843.
[4] R. Iyer, A. H. Jackson, P. V. R. Shannon, and B. Naidoo, *J.C.S. Perkin II*, 1973, 872.

the tetrahydrocarbazole (9b) formed underwent an acid-catalysed rearrangement reaction of type (9b) ⇌ (5b) resulting in scrambling of the methylene groups at

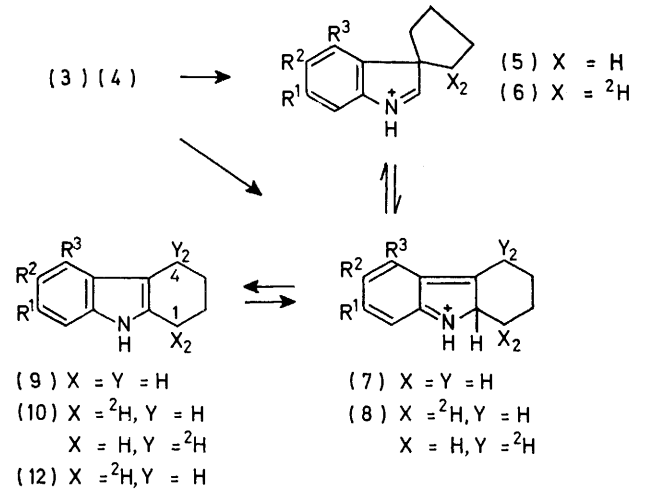


(3) X = H
(4) X = ^{2}H

(a) $R^1 = R^2 = R^3 = H$
(b) R^1 = OMe, $R^2 = R^3 = H$
(c) $R^1 = R^3$ = OMe, $R^2 = H$
(d) $R^1 = R^2$ = OMe, $R^3 = H$

SCHEME 1

the 1- and 4-positions.[4] It was to be expected that the tetrahydrocarbazole (9c) and its deuteriated analogue (12c) would behave in a similar fashion, and that because of the increased activation due to the second methoxy-group, this rearrangement process might well take place at a lower temperature. Samples of the 1,1-dideuteriated tetrahydrocarbazole (12c) were, therefore, subjected to the same general conditions as those used for the



(9) X = Y = H
(10) X = ^{2}H, Y = H
X = H, Y = ^{2}H
(12) X = ^{2}H, Y = H

(7) X = Y = H
(8) X = ^{2}H, Y = H
X = H, Y = ^{2}H

SCHEME 2

cyclisation of the alcohol (3c) but at a series of temperatures in the range 80—126 °C. In each instance the tetrahydrocarbazoles (10c) were recovered, recrystallised, and examined by n.m.r. spectroscopy. The results of these experiments (see Figure 1) showed that rearrangement of the tetrahydrocarbazole was insignificant below 90 °C, although at the reflux temperature almost complete scrambling occurred within 1 h. It appeared from these experiments that the effect of the additional methoxy-group was to activate the 2-position of the indole nucleus towards electrophilic attack slightly more than in the mono-methoxy-series,[4] the temperature at which significant scrambling occurred being lowered by *ca.* 10 °C.

The dideuterioindolylbutanol (4c) prepared by lithium aluminium deuteride reduction of the indolylbutyric acid (2c) was, therefore, cyclised at 80 °C, and the mixture of tetrahydrocarbazoles (10c) formed was analysed by n.m.r. spectroscopy. Calculations based on the ratio of hydrogen and deuterium at the 1- and 4-positions of the tetrahydrocarbazole mixture (10c) led to the conclusion that *ca.* 35% of the alcohol had cyclised by direct attack at the indole 2-position. A second crop of the tetrahydrocarbazole obtained from the cyclisation studies gave identical results and this eliminated the

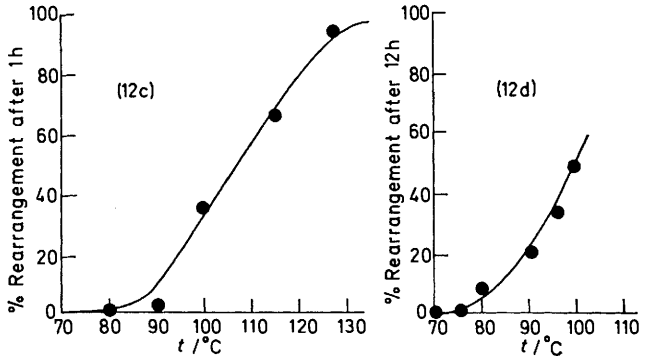


FIGURE 1 Effects of temperature on the boron trifluoride–catalysed rearrangement of the deuteriated tetrahydrocarbazoles (12c) and (12d)

possibility that selective crystallisation of one or other of the two deuteriotetrahydrocarbazoles (10c) had occurred. If a correction is applied for the isotope effect ($K_H/K_D = 1.13$) determined in the rearrangement of the cyclopentanospirocyclic indole (6a) to tetrahydrocarbazoles (10a) [1] the revised value for direct attack at the indole 2-position may be calculated as 38.5%.

These results showed that although an additional methoxy-group does increase the activation of the 2-position of the indole nucleus towards electrophilic attack, the effect is less than twice that of a single methoxy-group at the 6-position. We, therefore, decided to study the effects of methoxy-groups at the 5- and 6-positions of the indole nucleus on the activity of the 2-position towards electrophilic attack. The 5,6-dimethoxyindolylbutanol (3d) was synthesised by the same route as that used for the 6-methoxy- and 4,6-dimethoxy-analogues (3b) and (3c) (see Scheme 1);

the cyclisation of the 5,6-dimethoxyindolylbutanol (3d) was much slower than that of either the 6-methoxy- or the 4,6-dimethoxy-indolylbutanol. For reasons which will become apparent it was necessary to investigate these differences in rate in more detail before studying the cyclisation of the deuteriated analogue.

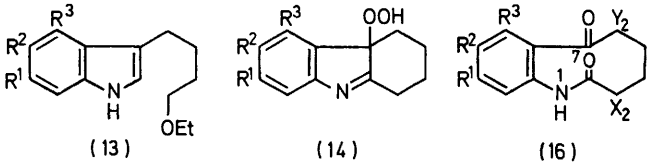
Hitherto, we had made no attempt to study quantitatively the rates of the cyclisation reactions of these indolylbutanols (3) because of the difficulties involved in following the reactions effectively. Fortunately, high-pressure liquid chromatography (h.p.l.c.) became available at this point in our work; the alcohols (3) and tetrahydrocarbazoles (9) were readily separated by h.p.l.c. on silica using mixtures of ethyl acetate and hexane (or light petroleum) as eluants. Quantification was achieved using a u.v. detector set at 270 nm, and full details are given in the Experimental section. Ideally, it would have been desirable to use an internal standard for the rate studies, but although some 20 compounds were tested for this purpose, we were unable to find a suitable compound, *i.e.* one which would absorb at 270 nm, remain unchanged under the reaction conditions, and have a retention time intermediate between the alcohols (3) and the tetrahydrocarbazoles (9). Kinetic experiments were, therefore, carried out without an internal standard, each alcohol being heated with boron trifluoride ether at 80 °C; aliquots were withdrawn at various intervals of time, quenched by addition of water and the products analysed by h.p.l.c.

Each of the alcohols (3) cyclised to the tetrahydrocarbazoles (9) by essentially first-order kinetics. The relative rates of formation of the four tetrahydrocarbazoles (see Table) show that methoxy-substituents

Relative rates of cyclisation of 4-indol-3-ylbutanols (3a—d) in boron trifluoride–diethyl ether at 80 °C to the tetrahydrocarbazoles (9a—d)

Compound (3)	K_1/min^{-1}	Relative rate
a	13.9×10^{-3}	100
b	4.58×10^{-3}	33
c	3.60×10^{-3}	26
d	1.18×10^{-3}	8.5

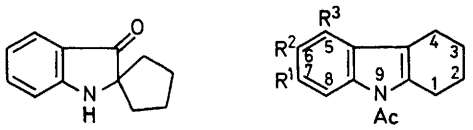
decrease the overall rate, whereas the reverse effect might have been anticipated. However, the overall rate in each case will depend on three, or four, consecutive processes as shown in Scheme 2; initial cyclisation occurs at the indole 3-position in the unsubstituted indolylbutanol (3a) and at both the 3- and the 2-positions in the methoxy-substituted compounds (3b—d). Other kinetic studies [5,6] of the acid-catalysed rearrangement of the unsubstituted spiroindole (5a) to the tetrahydrocarbazole (9a) suggest that the rate of this reaction is closely comparable with the overall rate of formation of the tetrahydrocarbazole (9a) from the indolylbutanol (3a) (see Table), so that the rearrangement (5a) ⇌ (7a) is likely to be the rate-determining step of the reaction. The methoxy-groups in the 4- and 6-positions of the benzene ring of the indolylbutanols (3) would facilitate substitution at the 2-positions by mesomeric electron release. On the other hand rearrangement of the indole salt (5d) may be retarded by electron release from the



(13) (14) (16)

X = H, Y = ^{2}H

X = ^{2}H, Y = H



(15) (17)

(a) $R^1 = R^2 = R^3 = H$

(b) R^1 = OMe, $R^2 = R^3 = H$

(c) $R^1 = R^3$ = OMe, $R^2 = H$

(d) $R^1 = R^2$ = OMe, $R^3 = H$

5-methoxy-substituent. We conclude that the effective rate-determining step in the formation of the tetrahydrocarbazoles (9b—d) is probably the rearrangement of the spirocyclic indole salts (5b—d). The final step in all these reactions, whether initial cyclisation occurs at the 3- or at the 2-position, is loss of a proton [(7) ⟶ (9) see Scheme 2] but this seems unlikely to have a very significant effect on the overall rate. [Studies of the rate of formation of tetrahydrocarbazole (9a) from the 2-deuterioindolyl analogue of the indolylbutanol (3a) indicate that the isotope effect is quite small [6] (K_H/K_D 1.14)].

In each of these cyclisation reactions [of (3) ⟶ (9)] two minor side products were also observed on h.p.l.c. with retention times intermediate between the alcohol and tetrahydrocarbazole. In a preparative scale experiment these by-products were obtained in *ca.* 10% yield each as well as tetrahydrocarbazole, (9a) (60%) and unchanged alcohol (3a) (5%). The less-polar material was isolated by column chromatography as an oil and had molecular weight 217 (field desorption mass spectrometry); its u.v. spectrum was typically indolic and its n.m.r. spectrum was very similar to that of the starting alcohol except that it showed an additional triplet at τ 8.75. On the basis of this spectroscopic evidence the ether structure (13a) was tentatively assigned to this product. The other by-product which ran more slowly on h.p.l.c., or t.l.c., crystallised after column chromatography and the u.v. spectrum ($\lambda_{max.}$ 254 nm) indicated that it was not indolic; however, on addition of dilute hydrochloric acid it was irreversibly converted into a material having $\lambda_{max.}$ 280 and 290 nm. The field desorption mass spectrum of the original product indicated a molecular weight of 203 and we concluded, therefore, that the product was the hydroperoxide (14a)

[5] A. H. Jackson and P. P. Lynch, unpublished results.

[6] J. S. L. Ibaceta-Lizana, A. H. Jackson, and P. V. R. Shannon, unpublished results.

of tetrahydrocarbazole; this was confirmed by comparison with an authentic sample [7] and by conversion of (14a) into the known spirocyclic indole (15).[7]

The rate of cyclisation of the ether (13a) would be expected to be approximately the same as that of the alcohol (3a) and thus its formation should not appreciably affect the rate of formation of the tetrahydrocarbazole (9a). On the other hand the hydroperoxide formation, which presumably occurred as a result of aerial oxidation during sampling or work-up, would have had a small effect on the overall kinetics, and the observed rate constants (see Table) are probably slightly lower than the true values. However, bearing in mind the other possible sources of error in the rate measurements and the fact that the autoxidation process occurred to approximately the same extent in each of the four compounds, the actual rates of cyclisation are in the same relative order as shown in the Table.

The relatively slow rate at which the tetrahydrocarbazole (9d) was formed in the boron trifluoride-catalysed cyclisation of the 5,6-dimethoxyindolylbutanol (3d) gave rise to some difficulties in the next stage of the work.

First, reaction periods of up to 12 h were necessary, rather than the 1 h used in the case of the 6-methoxy- and 4,6-dimethoxy-analogues; moreover, the reactions had to be carried out under strictly anaerobic conditions with carefully purified reagents and solvents, *etc.*, in order to minimise the formation of bluish green by-products which presumably arose as a result of demethylation and oxidation. Secondly, in view of the earlier results with the 4,6-dimethoxy-series it was necessary to ensure that the cyclisations were carried out below the temperature at which the tetrahydrocarbazole (9d) underwent the rearrangement (9d) $\rightleftharpoons$ (5d).

The 1,1-dideuteriotetrahydrocarbazole (12d) was prepared by cyclisation of the acid (2d) to the 1-oxotetrahydrocarbazole (11d); this was also synthesised by Fischer cyclisation of the mono-3,4-dimethoxyphenylhydrazone of cyclohexane-1,2-dione. The 1-oxotetrahydrocarbazole (11d) on reduction with lithium aluminium deuteride afforded the deuteriated tetrahydrocarbazole (12d). The latter was heated with boron trifluoride–ether for 12 h at a series of temperatures in the range 70—100 °C. Unlike the 5,7-dimethoxytetrahydrocarbazole (9c), but like tetrahydrocarbazole (9a) itself and the 7-methoxytetrahydrocarbazole (9b), the resonances of the 1- and 4-methylene groups in (9d) overlapped each other so that n.m.r. spectroscopy could not be used directly to establish the extent of deuteriation at the 1- and 4-positions. In consequence, the procedure adopted in the 7-methoxy-series was used initially and the tetrahydrocarbazoles (10d) were oxidised to the keto-amides (16d) with sodium metaperiodate in methanol. The n.m.r. spectrum of the keto-amides showed resonances at τ 7.46 and 6.90 corresponding to the methylene groups at C-1 and C-4 in the original 6,7-dimethoxytetrahydrocarbazoles (10d). By measuring the relative areas of these two peaks the percentage of rearrangement to spirocyclic indole (6d) could be calculated (see Figure 1b); these experiments showed that the back-rearrangement was negligible at temperatures below *ca.* 75 °C. The cyclisation of the 5,6-dimethoxyindolylbutanol (4d) was, therefore, carried out at 70 °C. Unfortunately, however, the reaction was so slow at this temperature (as measured by h.p.l.c.) that only 10% conversion to tetrahydrocarbazole occurred after 12 h. As relatively large quantities of the tetrahydrocarbazole would have been needed to prepare sufficient of the keto-amide for the same type of n.m.r. studies as those described above, other approaches to the determination of the extent of deuteriation were investigated.

The best method involved acetylation of the indolic nitrogen followed by direct determination of the n.m.r. spectrum in the presence of small amounts of the lanthanide shift reagent, Eu([$^2H_9$]-fod)$_3$. Under these conditions the resonance of the 1-methylene group in the *N*-acetyltetrahydrocarbazole (17d) could be clearly distinguished from that of the 4-methylene group and hence the relative amounts of deuterium at the two-positions could readily be estimated. In a separate experiment it was established that acetylation of the 1,1-dideuteriotetrahydrocarbazole (12d) did not result in rearrangement reactions leading to scrambling of the 1- and 4-methylene groups. A complication in the lanthanide shift experiments was that the europium complexed more strongly with the vicinal methoxy-groups of the *N*-acetyltetrahydrocarbazole (17d) than with the *N*-acetyl group, presumably owing to formation of a bidentate chelate. Similar types of chelates had been observed previously with porphyrins bearing vicinal ester side-chains,[8] and several examples were reported by Wright and Tang-Wei in methoxylated benzene derivatives.[9] N.m.r. spectral titrations on all four tetrahydrocarbazole *N*-acetyl derivatives (17a—d) are recorded in Figure 2.

Following the success of the preliminary lanthanide shift experiments with the *N*-acetyltetrahydrocarbazoles (17) the dimethoxyindolylbutanol (4d) was cyclised at 70 °C for 12 h under nitrogen in boron trifluoride–ether. The crude reaction product was chromatographed on silica under nitrogen and the tetrahydrocarbazoles (10d) were obtained in 6% yield. Later fractions contained unchanged alcohol (40%) whose n.m.r. spectrum showed 100% deuterium retention in the hydroxymethylene group. A polar blue material was retained at the top of the chromatography column and, as mentioned above, this probably arose by cleavage of the methoxy-groups and oxidation of the resulting phenols. The deuteriated 6,7-dimethoxytetrahydrocarbazoles (10d) were immediately acetylated with acetic anhydride at reflux point and the 9-acetyl derivative (17d) after purification by

[7] R. J. S. Beer, L. McGrath, and A. Robertson, *J. Chem. Soc.*, 1950 3283.

[8] M. S. Stoll, G. H. Elder, D. E. Games, P. O'Hanlon, D. S. Millington, and A. H. Jackson, *Biochem. J.*, 1973, **131**, 429.

[9] G. E. Wright and T. Y. Tang-Wei, *Tetrahedron*, 1973, **29**, 3775.

chromatography and crystallisation was investigated by n.m.r. spectroscopy in the presence of europium shift reagent. The ratio of the peak areas corresponding to the proton resonances at positions 1 and 4 was found to be 0.85; this corresponds to 11% direct attack at position 2 and 89% of indirect attack *via* the spirocyclic indole (5d). These values may be corrected to 13.5 and 86.5, respectively, if account is taken of the secondary isotope effect discussed above.

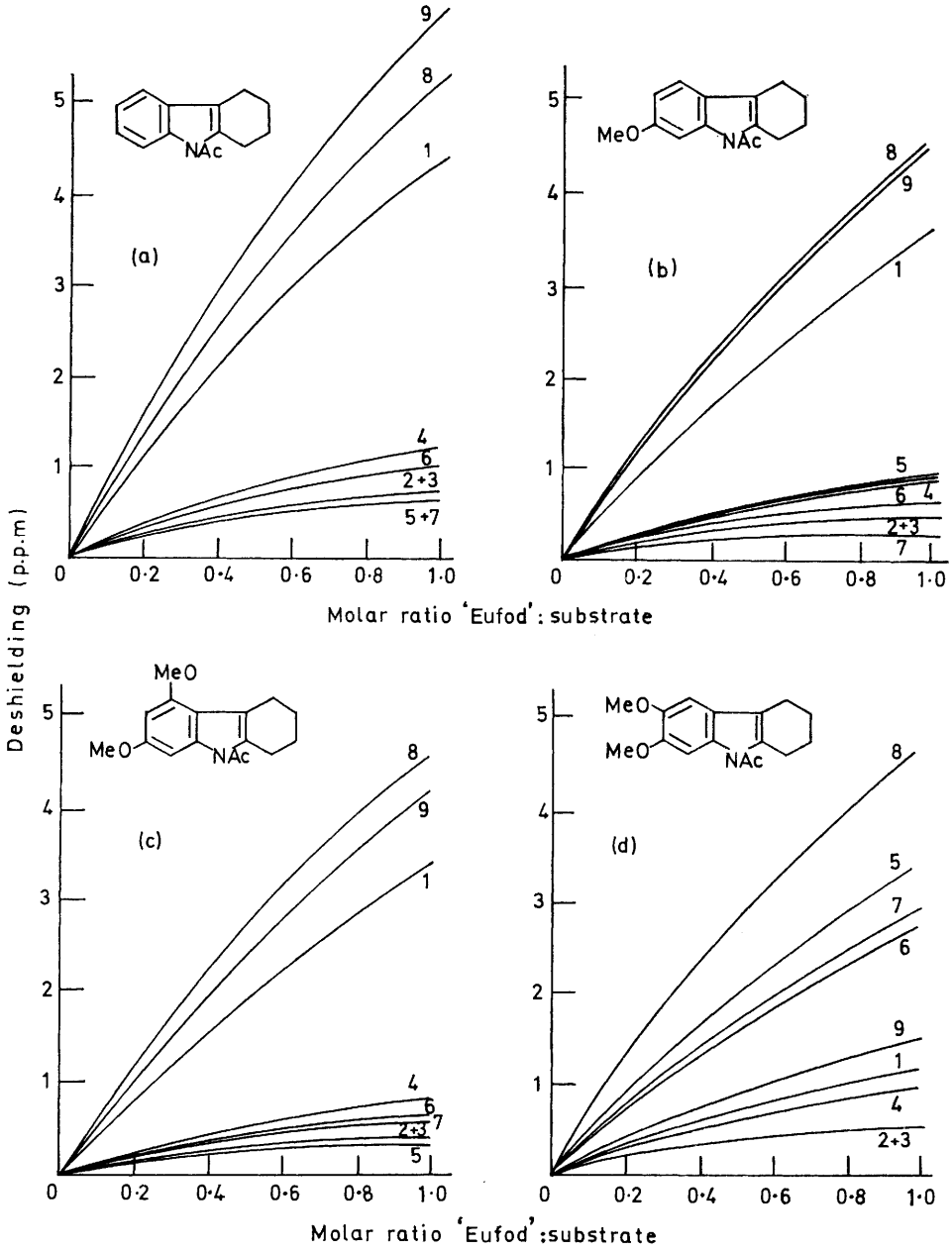


FIGURE 2 Deshielding effects of europium shift reagent Eu([$^2H_9$]fod)$_3$ on the proton magnetic resonance spectra of *N*-acetyltetrahydrocarbazoles (17)

EXPERIMENTAL

M.p.s were determined on a hot stage, and are corrected. Mass spectra were obtained with a Varian CH 5-D instrument (*a*) by electron impact-direct insertion probe at 70 eV and 50 μA, or (*b*) by field desorption at wire currents 15—20 μA. I.r. spectra were measured on a Unicam SP 200 Grating Spectrophotometer; u.v. spectra were determined in spectroscopic ethanol on Unicam SP 800 or Cary 17 instruments. N.m.r. spectra were determined on Perkin-Elmer R-14 (100 MHz) or R-32 (90 MHz) spectrometers in $CDCl_3$ solution unless otherwise stated. Thin-layer chromatography was carried out on Kieselgel HF 254 (Merck).

Deposition of Spectral Data.—Spectral results for compounds marked with an asterisk have been treated as a Supplementary Publication (SUP No. 22274, 21 pp.); see Notice to Authors No. 7, *J.C.S. Perkin I*, 1977, Index issue,

for retrieval of this material. All the spectral data so treated was in accord with the structural assignments.

2,4-Dimethoxybenzenediazonium Tetrafluoroborate.—2,4-Dimethoxyaniline (7 g) was stirred at 0—5 °C in concentrated hydrochloric acid (75 ml) and water (75 ml). A white precipitate (dimethoxyaniline hydrochloride) separated out. Sodium nitrite (4.3 g) in water (15 ml) was added dropwise, with stirring, to the mixture the temperature being maintained at 0—5 °C, to give a clear red solution. On addition of sodium borofluoride (5.5 g) in water (15 ml) to this a yellow solid immediately separated. The mixture was kept at 20 °C for 10 min after which the solid was filtered off and washed with water (3 × 25 ml), methanol (2 × 25 ml), and ether (4 × 25 ml) before being dried (0.5 mmHg/1 h) to give the fluoroborate salt as a buff coloured solid (9.9 g, 87%).

Ethyl 4-(2-Ethoxycarbonyl-4,6-dimethoxyindol-3-yl)butyrate.—To a suspension of sodium hydride (3.3 g of 50% dispersion in oil) in dry tetrahydrofuran (THF) (60 ml) under nitrogen was added slowly a solution of 2-ethoxycarbonylcyclohexanone (6.7 g) in dry tetrahydrofuran (60 ml). The mixture was heated under reflux for 30 min and the resulting clear yellow solution of the anion was cooled to −5 °C, and treated portionwise whilst being stirred with the foregoing dry diazonium fluoroborate salt (10 g). The solution turned red and a yellow deposit of sodium fluoroborate appeared. The mixture was then stirred for 1 h at 20 °C, poured into water (200 ml), and then extracted with ether (3 × 100 ml). The combined ether extracts were washed with water (100 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure at 25 °C afforded the azo-derivative as a red oil (12.2 g, 91%).*

The crude product was immediately taken up in ethanol (100 ml) and saturated with HCl gas. The mixture was heated at reflux point for 15 min after which it was cooled to 20 °C, diluted with water (200 ml), and extracted with chloroform (2 × 100 ml). The chloroform extract was washed with water (100 ml) and dried ($MgSO_4$); removal of the solvent from it under reduced pressure gave the crude diester as a yellow syrup. Crystallisation from light petroleum (b.p. 60—80 °C) gave *ethyl 4-(2-ethoxycarbonyl-4,6-dimethoxyindolyl-3-yl)butyrate* (11.8 g, 81%), m.p. 89—90 °C (Found: C, 62.6; H, 7.1; N, 4.05. $C_{19}H_{25}NO_6$ requires C, 62.8; H, 6.9; N, 3.9%).*

4-(2-Carboxy-4,6-dimethoxyindol-3-yl)butanoic Acid.—The foregoing diester (10 g) in ethanol (200 ml) containing sodium hydroxide (5 g) was heated under reflux for 30 min. The sodium salt of the diacid separated out from the reaction mixture as a pale yellow solid. The reaction mixture was cooled to 20 °C and the sodium salt filtered off at the pump. The solid was dissolved in water (100 ml) and sulphur dioxide gas was bubbled through the aqueous solution when the *diacid* (7.2 g, 85%) precipitated out as a cream solid, m.p. 227—228 °C (decomp) (Found: C, 58.5; H, 5.8; N, 4.7. $C_{15}H_{17}NO_6$ requires C, 58.7; H, 5.5; N, 4.6%).*

4-(4,6-Dimethoxyindol-3-yl)butanoic Acid (2c).—The above diacid (5 g) was divided into 1 g portions and these were cautiously heated in conical flasks until effervescence ceased. The combined residues were crystallised twice from benzene to give the required acid (3.9 g, 90%) as crystals, m.p. 128—129 °C (Found: *M* 263.115 9. $C_{14}H_{17}NO_4$ requires *M* 263.115 7). A completely satisfactory elemental analysis could not be obtained but the compound was shown to be homogenous by t.l.c. and n.m.r. spectroscopy.*

4-(4,6-Dimethoxyindol-3-yl)butanol (3c).—Lithium aluminium hydride (1 g) was suspended in dry THF (100 ml) and a solution of the foregoing mono-acid (2.5 g) and dry THF (100 ml) was added dropwise. After completion of the addition, the mixture was heated under reflux for 15 min, when t.l.c. of the reaction mixture showed the reaction to be complete. The mixture was cooled to 20 °C and the complex decomposed with saturated Rochelle salt solution. The mixture was poured into water (400 ml) and extracted with ether (3 × 125 ml). The ether extract was washed with water (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The solid residue crystallised from benzene to give the *alcohol* (3c) as a cream solid (1.9 g, 80%), m.p. 109—110 °C (Found: C, 67.1; H, 7.5; N, 5.8. $C_{14}H_{19}NO_3$ requires C, 67.5; H, 7.6; N, 5.6%).*

5,7-Dimethoxy-1,2,3,4-tetrahydrocarbazole (9c).—(i) 4-(4,6-Dimethoxyindol-3-yl)butan-1-ol (1.5 g) was heated under reflux for 30 min with boron trifluoride–diethyl ether (freshly distilled, 55 ml). T.l.c. then indicated that the reaction was complete. The reaction mixture was cooled and poured into water (150 ml) and extracted with chloroform (2 × 100 ml). The chloroform extract was washed with water (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a pale green solid. Two crystallisations from ethanol gave the pure tetrahydrocarbazole (9c) (0.35 g, 25%), m.p. 150—151 °C (lit.,[10] m.p. 142—143 °C).*

(ii) 5,7-Dimethoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (see below) (200 mg) in warm ether (10 ml) was added dropwise to a suspension of lithium aluminium hydride (100 mg) in ether (5 ml) and the mixture heated under reflux for 1.5 h (*i.e.* until t.l.c. indicated that reaction was complete). The mixture was cooled to 20 °C and the excess of hydride decomposed by addition of saturated Rochelle salt solution. The mixture was diluted with water (20 ml) and extracted with ether (3 × 15 ml). The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to dryness to form the 5,7-dimethoxytetrahydrocarbazole (90 mg) (48%), m.p. and mixed m.p. with the previous sample 146—147 °C.

6,7-Dimethoxy-1,2,3,4-tetrahydrocarbazole (9d).—This compound was prepared in essentially the same manner as that described above for the analogous 5,7-dimethoxytetrahydrocarbazole, but from 3,4-dimethoxyaniline. The yields, m.p.s, and analytical data for the various intermediates and final product are indicated below.

(a) 3,4-Dimethoxybenzenediazonium tetrafluoroborate (100%).

(b) 2-(3,4-Dimethoxyphenylazo)-2-ethoxycarbonylcyclohexanone (red oil, 72%).*

(c) *Ethyl 4-(2-ethoxycarbonyl-5,6-dimethoxyindol-3-yl)-butyrate* (44%), needles, m.p. 93—94 °C, from light petroleum (b.p. 60—80 °C) (Found: C, 62.7; H, 6.9; N, 4.3. $C_{19}H_{25}NO_6$ requires C, 62.8; H, 6.9; N, 3.9%).*

(d) *4-(2-Carboxy-5,6-dimethoxyindol-3-yl)butanoic acid* (85%), m.p. 187—188 °C (decomp.).*

(e) *4-(5,6-Dimethoxyindol-3-yl)butanoic acid* (2d) (62%), m.p. 191—192 °C (Found: C, 63.4; H, 6.6; N, 5.5. $C_{14}H_{17}NO_4$ requires C, 63.8; H, 6.5; N, 5.3%).*

(f) *4-(5,6-Dimethoxyindol-3-yl)butan-1-ol* (3d) (85%), pale green, m.p. 109—110 °C; after crystallisation from benzene (charcoal) it had m.p. 110—110.5 °C (Found: C, 67.6; H, 7.7; N, 5.7. $C_{14}H_{19}NO_3$ requires C, 67.5; H, 7.6; N, 5.6%).*

(g) *6,7-Dimethoxy-1,2,3,4-tetrahydrocarbazole* (9d). (i)

* See preamble to Experimental section on the deposition of spectral results.

[10] B. Naidoo, Ph.D. Thesis, Liverpool, 1969.

The foregoing alcohol (1 g) and boron trifluoride–diethyl ether (redistilled, 35 ml) were heated under nitrogen at 100 °C for 12 h. The mixture was then cooled, poured into water (200 ml), and extracted with chloroform (4 × 100 ml); the extracts were then washed with water (3 × 100 ml) and dried ($MgSO_4$). The chloroform was evaporated to give a blue gum which was chromatographed on Mallinkrodt silicic acid (60 g) under nitrogen using light petroleum–diethyl ether mixtures of increasing ether content. The main fraction afforded the tetrahydrocarbazole (300 mg) (32%), m.p. 108—110 °C, after recrystallisation from ethanol (lit.,[11] m.p. 105—106 °C).*

(ii) Lithium aluminium hydroxide reduction of the 5,6-dimethoxy-1-oxotetrahydrocarbazole (see below) also afforded the tetrahydrocarbazole (60%) as needles, m.p. 108—111 °C, from ethanol. This material was identical by mixed m.p. and spectra with the foregoing sample.

(iii) 2-Bromocyclohexanone [10] (1.2 g) was added to an intimate mixture of 4-aminoveratrole (1.0 g) and anhydrous sodium acetate (0.7 g) and the reaction mixture was heated in a silicone oil bath at 170—180 °C for 15 min. After the mixture had been cooled to 20 °C a brown residue crystallised out, and this was extracted with diethyl ether (2 × 100 ml, 2 × 50 ml). The ethereal extract was washed with water (4 × 50 ml), dilute hydrochloric acid (4 × 30 ml), water (2 × 50 ml), dilute sodium hydrogen carbonate solution (2 × 50 ml), and water (1 × 50 ml), and was then dried (K_2CO_3) and evaporated to dryness to give a pale brown residue (0.65 g). The latter was dissolved in chloroform (2 ml) and chromatographed over silicic acid (15 g) under nitrogen, and eluted with ether to give the desired 6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole, as white needles (0.35 g, 23%), m.p. 108—110 °C.

5,7-*Dimethoxy*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (11c).—(i) A solution of boron trifluoride–diethyl ether (freshly distilled, 1 ml) in dry ether (15 ml) was added to 4,6-dimethoxyindol-3-ylbutyric acid (1 g) in acetic acid (5 ml) and acetic anhydride (0.8 ml). After 15 min the reaction mixture was submitted to t.l.c. which showed the reaction to be complete. The reaction mixture was poured carefully in portions into a saturated solution of sodium hydrogen carbonate (300 ml). After being stirred for 30 min the mixture was transferred into a separating funnel and extracted with ether (4 × 100 ml). The combined ether extract was washed with saturated sodium hydrogen carbonate solution (2 × 100 ml), and water (2 × 100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a semisolid (0.85 g). Crystallisation from acetone gave the 1-*oxotetrahydrocarbazole* (11c) (0.6 g, 65%) as a pale yellow solid, m.p. 205—206 °C (Found: C, 68.2; H, 6.4; N, 6.0. $C_{14}H_{15}NO_3$ requires C, 68.5; H, 6.1; N, 5.7%).*

6,7-*Dimethoxy*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (11d).—(i) A solution of boron trifluoride–diethyl ether (0.8 ml) in dry ether (12 ml) was added dropwise to a stirred solution of 5,6-dimethoxyindol-3-ylbutanoic acid (3.5 ml) and acetic anhydride (0.6 ml). The reaction mixture was stirred for a further 1.5 h at 20 °C, when t.l.c. examination (using ether as solvent) showed the reaction to be complete. The mixture was poured in portions into a saturated solution of sodium hydrogen carbonate (200 ml), which after being stirred for 30 min was extracted with ether (3 × 200 ml). The combined ether extracts were washed with saturated sodium hydrogen carbonate solution (200 ml) and water (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure to give a pale green solid (0.26 g, 40%). Chromatography on Woelm silica (Activity Grade I, 15 g/100 mg of crude product) packed in light petroleum (b.p. 40—60 °C) and elution with diethyl ether–ethyl acetate mixtures followed by recrystallisation from acetone afforded 6,7-*dimethoxy*-1-*oxo*-1,2,3,4-*tetrahydrocarbazole* (11d) as needles, m.p. 197—197.5 °C (Found: C, 68.2; H, 6.4; N, 5.75. $C_{14}H_{15}NO_3$ requires C, 68.5; H, 6.2; N, 5.7%).*

(ii) *By cyclisation of cyclohexane*-1,2-*dione mono*-(3,4-*dimethoxyphenylhydrazone*). Piperidinocyclohex-1-ene was prepared in 82% yield by a literature method,[12] b.p. 71—73 °C (0.9 mmHg) [lit.,[12] b.p. 108.5 (12 mmHg)].*

A mixture of piperidinocyclohex-1-ene (8.8 g), ice (38 g), and concentrated hydrochloric acid (15 ml) was added during 5 min at −3 to 0 °C, with continuous stirring to a solution of 3,4-dimethoxybenzenediazonium chloride [obtained from 4-aminoveratrole (7.7 g), concentrated hydrochloric acid (15 ml), and sodium nitrite (3.8 g) with ice (100 g)]. The reaction mixture was then rapidly neutralised (to pH 5—6) with a cold saturated solution of sodium acetate, the temperature during the addition being maintained at 0 °C. The resulting suspension was kept at 0 °C for 4 h. The solid was then filtered off, washed with cold water, and dried *in vacuo* to afford the desired *phenylhydrazone* (7.1 g, 71%), m.p. 119—120 °C (Found: C, 63.8; H, 6.9; N, 11.2. $C_{14}H_{18}N_2O_3$ requires C, 64.1; H, 6.9; N, 10.9%).*

The above hydrazone (6.8 g) was heated under reflux with formic acid (98%) (94 ml) for 1 h, when t.l.c. examination (ether) of the mixture showed the reaction to be complete. The mixture was poured onto ice (425 g) and left at 20 °C for 4 h and then extracted with ether (3 × 200 ml); the extract was washed with water (1 × 200 ml) and saturated sodium hydrogen carbonate solution (1 × 200 ml) and then with water until neutral, after which it was dried ($MgSO_4$). The solvent was removed under reduced pressure and the yellow residue crystallised from acetone to give 6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydrocarbazole (11d) (1.4 g, 25%), m.p. 193—195 °C. After two recrystallisations from acetone, the m.p. (195—197 °C) was undepressed upon admixture with material prepared by cyclisation of the indolylbutanoic acid.

Oxidation of 5,7-*Dimethoxy*-1,2,3,4-*tetrahydrocarbazole* (9c) *with Sodium Metaperiodate*.—The 5,7-dimethoxytetrahydrocarbazole (9c) (0.5 g) in methanol (30 ml) was added dropwise with stirring to a solution of sodium metaperiodate (2.0 g) in water (3 ml) and methanol (6 ml) under nitrogen. After 15 min a white precipitate separated out from the reaction mixture. The mixture was stirred for 16 h at 20 °C when t.l.c. showed the reaction to be complete. The mixture was diluted with water (150 ml) and extracted with chloroform (3 × 100 ml). The chloroform extract was washed with 0.1N-sodium thiosulphate (100 ml) and water (100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residual yellow oil was chromatographed on Woelm silica (70 g) and eluted with ether to afford the crystalline (oxo-amide) (16c; X = Y = ^{1}H) * (0.106 g, 17%), m.p. 185—190 °C (decomp.) (Found: C, 63.5; H, 6.2; N, 5.3. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%).*

6,8-*Dimethoxy*-2,3-*dihydrocyclopenta*[b]*quinolin*-9-*one*.*—

* See footnote on p. 738.

[11] R. J. S. Beer, L. McGrath, A. Robertson, and A. B. Woodier, *J. Chem. Soc.*, 1949, 2061.

[12] G. Opitz, H. Hellmann, and H. W. Schubert, *Annalen*, 1959, **623**, 112.

The above oxo-amide (0.06 g) was heated on an oil-bath at 190 °C for 20 min, the resulting solid being sublimed under reduced pressure (0.05 mmHg) to give the *quinolone* * (0.031 g, 55%), m.p. 250—251 °C (Found: *M*, 245.104 5. $C_{14}H_{15}NO_3$ requires *M*, 245.105 2). A completely satisfactory elemental analysis could not be obtained but the compound was shown to be homogeneous by t.l.c. and n.m.r. spectroscopy.*

Oxidation of 6,7-*Dimethoxy* 1,2,3,4-*tetrahydrocarbazole* (9d) *with Sodium Metaperiodate.*—To a solution of sodium metaperiodate (0.5 g) in water (5.6 ml) and methanol (2.8 ml), at 35—40 °C, was added dropwise a solution of 6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole (0.14 g) in methanol (28 ml), under dry nitrogen. Water (10 ml) was added during the reaction to keep the reaction mixture in solution. The reaction mixture was stirred for 5 h at 35—40 °C, when t.l.c. showed the reaction to be complete.

The reaction mixture was cooled to 20 °C, poured into water (80 ml), and extracted with chloroform (2 × 80 ml; 1 × 40 ml). The organic extracts were combined and washed with sodium thiosulphate solution (2 × 40 ml) and water (2 × 40 ml). After the solution had been dried ($MgSO_4$) solvent was removed under reduced pressure to give a brownish solid (0.15 g) which was chromatographed over Woelm silica (activity Grade I) (20 g), and eluted with light petroleum–diethyl ether and ethyl acetate to give the *oxo-amide* (16d; X = Y = ^{1}H) (0.084 g) (53%), m.p. 155—156 °C (Found: C, 63.8; H, 6.4; N, 5.9. $C_{14}H_{17}NO_4$ requires C, 63.9; H, 6.5; N, 5.3%).*

5,7-*Dimethoxy*-1,2,3,4-*tetrahydro*[1,1-$^2H_2$]*carbazole* (12c) was prepared from the corresponding 1-oxotetrahydrocarbazole (2 g) and lithium aluminium deuteride (1 g) in the same manner as the undeuteriated analogue (9c) above. The product (1.3 g, 68%) crystallised from ethanol as feathery needles, m.p. 146—148 °C. The n.m.r. spectrum was identical with that of the undeuteriated analogue except for the absence of the resonance at τ 7.4 (Found: M^+, 233.138 2. $C_{14}H_{15}D_2NO_2$ requires 233.138 5).*

6,7-*Dimethoxy*-1,2,3,4-*tetrahydro*[1,1-$^2H_2$]*carbazole* (12d) was prepared from the 6,7-dimethoxy-1-oxotetrahydrocarbazole (0.6 g) by reduction with lithium deuteride (2.0 g) in dry refluxing tetrahydrofuran (150 ml) until t.l.c. examination showed that reduction was complete (17 h). The product was worked up in the same manner as the undeuteriated analogue (9d) and gave the *dideuteriotetrahydrocarbazole* (12d) (0.3 g, 50%) as needles from ethanol, m.p. 109—110 °C. The n.m.r. spectrum was identical to that of the undeuteriated analogue except that the resonance at τ 7.33 (4-CH_2) integrated for only half that at τ 8.22, (2,3-CH_2CH_2), indicating complete deuteriation at the 1-position.

Treatment of 5,7-*Dimethoxy*-1,2,3,4-*tetrahydro*[1,1-$^2H_2$]-*carbazole* (12c) *with Boron Trifluoride–Diethyl Ether at a Series of Temperatures.*—Five experiments were carried out at different temperatures according to the general procedure described below for the experiment at 80 °C. The tetrahydro[1,1-$^2H_2$]carbazole (0.25 g) was treated with boron trifluoride–diethyl ether (redistilled) (10 ml) for 1 h at 80 °C. The mixture was cooled and poured into water (100 ml). The mixture was extracted with ether (2 × 50 ml) and the extract washed with water (50 ml) and dried ($MgSO_4$); removal of solvent gave the crude solid product (0.11 g). Crystallisation from ethanol gave feathery needles (0.07 g, 28%) the n.m.r. spectrum of which was identical with the starting material. For the experiments at higher temperatures the ratio of the proton signal of the 1 and 4 positions was measured accurately by weighing several repeat scans; the results of experiments at 80, 90, 100, 115, and 126 °C are given in Figure 1; the percentage (x) of rearrangement of the tetrahydrocarbazole *via* the spirocyclic indolenine was calculated from the expression ($y = x/(200-x)$ where y is the ratio of the proton signals of the 1-methylene group (at τ 7.40) relative to those of the 4-methylene group (at τ 7.13).

Rearrangement of 6,7-*Dimethoxy*-1,2,3,4-*tetrahydro*[1,1-$^2H_2$]*carbazole* (12d) *with Boron Trifluoride–Diethyl Ether.*—The dideuteriotetrahydrocarbazole (12d) (0.3 g) and boron trifluoride–diethyl ether (distilled twice) (12 ml) were heated for 12 h under dry nitrogen at 100 °C. The reaction mixture was cooled to 20 °C, poured into water (100 ml), and then extracted with diethyl ether (2 × 100 ml, 1 × 50 ml); the combined extracts were washed with water (2 × 60 ml), dried ($MgSO_4$), and evaporated to give a green gum (0.3 g), which was dissolved in chloroform (5 ml) and chromatographed under nitrogen on silicic acid (20 g). Elution with light petroleum (b.p. 60—80 °C) gave the rearranged deuteriotetrahydrocarbazoles (8d) (0.18 g), m.p. 105—108 °C. The n.m.r. spectrum of this product (50 mg) was identical with that of the starting material and the area of the signal at τ 8.22 was 2.0 ± 0.1 times that at τ 7.33 indicating no loss of deuterium during the reaction.

To a solution of sodium metaperiodate (0.63 g) in water (7.2 ml) and methanol (3.6 ml), warmed to 35—40 °C, was added dropwise a solution of the rearranged dideuteriotetrahydrocarbazoles (0.18 g) in methanol (36 ml), under dry nitrogen. Water (15 ml) was added during the reaction to keep the reactants in solution. The reaction mixture was stirred for 5 h at 35—40 °C, when t.l.c. showed the reaction to be complete. The reaction mixture was cooled to 20 °C, poured into water (100 ml), and extracted with chloroform (2 × 100 ml) (1 × 50 ml). The organic extracts were combined and washed with sodium thiosulphate solution (2 × 80 ml) and water (2 × 80 ml). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a brownish solid (0.18 g), which was recrystallised from ethyl acetate to give the mixed ketoamides (15d) (85 mg, 41%), m.p. 153—156 °C. The n.m.r. spectrum in trifluoracetic acid solution showed that the ratio of the peak at τ 7.46 to that at τ 6.90 was 0.355 ± 0.015.

This ratio is equal to $x/(200 - x)$ where x is the percentage of rearrangement of the tetrahydrocarbazole (9d) *via* the spirocyclic indole (5d). Hence the percentage rearrangement which occurred on heating at 100 °C for 12 h. was 52.5%.

The experiment was repeated at a series of temperatures (70, 75, 80, 90, and 95 °C) and the results are shown in Figure 2.

4-(4,6-*Dimethoxy*[1,1-$^2H_2$]*indol*-3-*ylbutan*-1-*ol* (4c).—4-(4,-6-Dimethoxyindol-3-yl)butyric acid (2.5 g) in warm dry diethyl ether (80 ml) was added dropwise to a suspension of lithium aluminium deuteride (LAD) (1 g) in dry ether (50 ml). When the addition was complete the mixture was heated under reflux for 30 min until t.l.c. showed the reaction to be complete. After work-up in the usual way, as described for the undeuteriated analogue above, the *alcohol* (4c) (2.0 g, 83%) was obtained as a pale yellow solid, m.p. 108—109°; after two crystallisations from ether the n.m.r. spectrum of the compound was identical to that for the non-deuteriated compound except that the resonance at

* See footnote on p. 738.

τ 6.38 (corresponding to CH_2O) was entirely absent; this indicated complete deuteriation (Found: *M*, 251.149 2. $C_{14}H_{17}D_2NO_3$ requires *M*, 251.149 0).*

4-(5,6-*Dimethoxy*[1,1-$^2H_2$]*indol*-3-*yl*)*butan*-1-*ol* (4d).—4-(5,6-Dimethoxyindol-3-yl)butyric acid (1.9 g) in dry THF (140 ml) was added dropwise to a suspension of lithium aluminium deuteride (LAD) (1.1 g) in THF (100 ml). When the addition was complete the mixture was boiled under reflux for 30 min when t.l.c. (1 : 1 $CHCl_3$–EtOAc) showed the reaction to be complete. The reaction mixture was worked up in the usual manner and afforded the *deuteriated alcohol* (4d) (1.6 g) which was recrystallised from benzene to give light green crystals (1.3 g) (68%), m.p. 109—110 °C. The n.m.r. spectrum was identical to the non-deuteriated compound except that the signal at τ 6.38 was entirely absent thus indicating complete deuteriation.

Cyclisation of 4-(4,6-*Dimethoxy*[1,1-$^2H_2$]*indol*-3-*yl*)*butan*-1-*ol* (4c) *to the Deuteriated* 5,7-*Dimethoxytetrahydrocarbazoles* (10c).—The deuterio-alcohol (4c) (2.0 g) was heated at 80 °C with boron trifluoride–diethyl ether (freshly distilled, 55 ml) for 1 h, these conditions being chosen (Figure 1) to avoid subsequent rearrangement of the tetrahydrocarbazole once formed. The product was worked up as described for the non-deuteriated analogue and after chromatography on silicic acid the mixture of deuteriated tetrahydrocarbazoles (0.46 g, 25%) crystallised from ethanol as feathery needles, m.p. 146—147 °C. The n.m.r. spectrum was very similar to that of the non-deuteriated analogue except for the relative areas of the signals due to the 1- and 4-methylene protons; this ratio was found to be 0.477. A second crop (0.1 g, 6%) of crystals obtained from the mother liquors also had m.p. 146—147 °C and the ratio of the 1- and 4-methylene resonances was found to be 0.483. In another experiment carried out under identical conditions the ratio was found to be 0.487. Substituting the average value (0.482) of this ratio (y) in the expression (derived previously for the cyclisation of the corresponding 6-methoxyindolylbutanols) $y = (100 - x)/(100 + x)$, gives the percentage direct cyclisation (x) at the 2-position as 35%. If a correction is applied for the secondary isotope effect (1.13) observed in experiments on the rearrangement of deuteriated spirocyclopentanoindolenine, the revised value for cyclisation at the 2-position is 38.5%.

Preliminary studies of the sodium metaperiodate oxidation of the deuteriated tetrahydrocarbazoles to the ring opened oxo-amides (15c) gave rather low yields (15%) of materials, m.p. 185—190 °C, which did not give sufficiently good n.m.r. spectra to make accurate area measurement, and this approach (only needed as a check) was abandoned.

Cyclisation of 4-(5,6-*Dimethoxy*[1,1-$^2H_2$]*indol*-3-*yl*)*butan*-1-*ol* (4d) *at* 70°.—The deuteriated alcohol (4d) (1.5 g) was dissolved in boron trifluoride–diethyl ether (55 ml, redistilled) which had been previously heated to 70 °C, and kept at this temperature in a thermostat for 12 h, under dry nitrogen. The reaction mixture was cooled to 20 °C, poured into water (150 ml), and extracted with diethyl ether (3 × 150 ml). The combined ethereal extracts were washed with water (150 ml), sodium hydrogen carbonate solution (3 × 150 ml), and water (100 ml), and were then dried (K_2CO_3) and evaporated under reduced pressure to give a dark blue gum (1.0 g) which was chromatographed on silicic acid (70 g) using diethyl ether–light petroleum (b.p. 60—80°) mixtures of increasing ether content as eluant. Two main fractions were recovered: (*a*) colourless crystals (0.080 g, 6%), m.p. 107—109 °C of the required tetrahydrocarbazoles (10d) and (b) the starting alcohol, contaminated with blue material, which was recrystallised twice from benzene (0.60 g, 40%), m.p. 109—110 °C. The n.m.r. spectrum of the recovered alcohol was identical with that of the starting alcohol (4d), indicating 100% deuterium retention at the 1-methylene group.

The above tetrahydrocarbazoles (10d) (0.080 g) were boiled under reflux with acetic anhydride (1.0 ml) for 17 h before being cooled to 20 °C and poured into water (10 ml). The solid which separated was filtered off and chromatographed in silica plates using diethyl ether–light petroleum (b.p. 60—80 °C) as eluant. The main band was extracted from the silica with dry ether; the ether was evaporated under reduced pressure to approximately 5 ml and an equal volume of light petroleum (b.p. 30—40 °C) was added; evaporation under reduced pressure was continued until crystallisation commenced. After being cooled in ice the mixture of deuteriated 9-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydrocarbazoles (30 mg, 35%) was collected; it had m.p. 128—130 °C. The n.m.r. spectrum of this mixture was examined in the presence of Eu([$^2H_9$]fod)$_3$ (1.2 molar equiv.) and the areas of the resonances corresponding to the 1- and 4-methylene resonances were measured. The ratio of these areas (1-CH_2/4-CH_2) was 0.85 and, using the same expression as that derived previously (used also for the related deuteriated 5,7-dimethoxytetrahydrocarbazoles above), the percentage direct cyclisation at the 2-position of the indole nucleus is 13.5%, allowing for the secondary isotope effect as before.

9-*Acetyl*-1,2,3,4-*tetrahydrocarbazoles* (17).—Acetylation was carried out essentially as above for the undeuteriated carbazoles (9a—d). In the case of the 5,7- and 6,7-dimethoxy-derivatives, purification by column or thick layer chromatography on silicic acid (under nitrogen) and elution with diethyl ether–light petroleum (b.p. 60—80 °C) was required before crystallisation.

9-Acetyl-1,2,3,4-tetrahydrocarbazole (17a) was obtained in 8% yield, m.p. 75—75.5 °C (lit.,[13] m.p. 77 °C).

9-*Acetyl*-7-*methoxy*-1,2,3,4-*tetrahydrocarbazole* (17b) was obtained in 50% yield, and had m.p. 119—120.5 °C (Found: C, 73.9; H, 7.2; N, 5.9. $C_{16}H_{19}NO_3$ requires C, 74.05; H, 7.0; N, 5.8%).

9-*Acetyl*-5,7-*dimethoxy*-1,2,3,4-*tetrahydrocarbazole* (17c) was obtained in 39% yield, m.p. 138.5—139.5 °C (Found: C, 70.25; H, 7.25; N, 5.3. $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1%).

9-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole (9d) was obtained in 43% yield, m.p. 132—133 °C (lit.,[14] m.p. 136 °C).

9-*Acetyl*-6,7-*dimethoxy*-1,2,3,4-*tetrahydro*[$^2H_2$]*carbazole*.—1,1-Dideuterio-6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole was prepared by reduction of dimethoxy-1-oxotetrahydrocarbazole with LAD in THF as described above (the n.m.r. spectrum was identical with that of the non-deuteriated compound except that the signal at τ 7.33 was half that of the signal at τ 8.22 indicating complete deuteriation). This material (0.15 g) and acetic anhydride (1.5 ml) were heated under reflux for 17 h. The reaction mixture was cooled to 20 °C and poured into water (10 ml) and the solid which precipitated (0.17 g) was filtered off and dried *in vacuo*.

* See footnote on p. 738.

[13] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 1921, 1825.

[14] F. Lions and M. J. Spurson, *J. Proc. Roy. Soc. N.S. Wales*, 1932, **66**, 171.

Column chromatography on silicic acid (10 g) under nitrogen and elution with ether–light petrol (b.p. 60—80 °C) mixtures afforded the required 9-*acetyl* derivative (0.67 mg, 38%) as needles, m.p. 132—133 °C.* The signal at 7.08 (1-CH_2) present in the non-deuteriated analogue was completely absent, showing complete deuteriation at this position, and that no rearrangement had occurred during the acetylation. This was confirmed by running the n.m.r. spectrum after addition of Eu([$^2H_9$]fod)$_3$ (1 molar equiv.): τ 7.07 (4 H, m, 2- and 3-CH_2), 5.35 (2 H, m, 4-CH_2), 4.18 (3 H, s, N–CO–CH_3), 0.58 (3 H, s, Ar-OCH_3), 0.11 (3 H, s, ArOCH_3), −3.32 (1 H, s, ind 5-H), and −7.32 (1 H, s, ind 8-H). No signal was observed at *ca.* τ 4.5 corresponding to that of the 1-CH_2 in the non-deuteriated analogue thus confirming that complete deuteriation had occurred.

Kinetic Studies of the Cyclisation of 4-(*Indol*-3-*yl*)*butan*-1-*ols* (3) *to the Corresponding* 1,2,3,4-*Tetrahydrocarbazoles* (9).—The indolylbutanol (80 mg) was weighed into a 5 ml volumetric flask and suspended in a thermostat bath at 80 °C. Preheated boron trifluoride–diethyl ether was added up to the mark and the flask shaken and timing started. Aliquots (0.3 ml) were withdrawn at fixed periods of time and quenched by addition of water (1 ml). The quenched samples were extracted with spectroscopic grade chloroform (3 × 2 ml) and these then washed with water (1 × 2 ml) and 5% sodium hydrogen carbonate solution (1 × 2 ml); they were then evaporated to dryness. The residues were dissolved in $CHCl_3$ (0.5 ml) and analysed by h.p.l.c., using two 3 ft × $\frac{1}{8}$ in steel columns packed with Waters Associates Corasil II. The solvent used was 35% ethyl acetate in light petroleum (b.p. 60—80 °C) at a flow rate of 1 ml min^{-1} and with the Cecil UV detector set at 270 nm. The peak area of the tetrahydrocarbazole formed was traced and weighed in each case, and the rate constants calculated in the usual manner. The results are shown in the Table.

Preparative-scale Cyclisation of 4-(*Indol*-3-*yl*)*butan*-1-*ol with Boron Trifluoride–Diethyl Ether at* 80 °C.—The conditions for this experiment were the same as those in the kinetic h.p.l.c. experiments. 4-Indol-3-ylbutan-1-ol (1.0 g) (prepared from LAH reduction of commercial 4-indol-3-ylbutanoic acid) and boron trifluoride–diethyl ether were heated at 80 °C for 2 h. The reaction mixture was cooled to 20 °C, poured into water (100 ml), and extracted with chloroform (3 × 150 ml). The chloroform extracts were combined and washed with water (2 × 100 ml), 5% sodium hydrogen carbonate solution (2 × 100 ml), and water (100 ml) and then dried (K_2CO_3); the solvent was then evaporated under reduced pressure. T.l.c. examination revealed a mixture of four compounds and base line material, the main product being 1,2,3,4-tetrahydrocarbazole (R_F 0.8). Chromatography on silicic acid (20 g), using light petroleum–diethyl ether mixtures of increasing ether content, afforded four main fractions: (i) 1,2,3,4-tetrahydrocarbazole (0.52 g, 58%), m.p. 117—118 °C, which was identified by mixed m.p. with authentic material, i.r. spectroscopy and t.l.c.; (ii) ethyl 4-(indol-3-yl)butyl ether (13a) as an oil (0.15 g, 10%), τ 8.75 (t, *J* 8 Hz, OCH_2CH_3), 8.50—8.20 (4 H, m, $CH_2CH_2CH_2CH_2OCH_2CH_3$), 7.40—7.15 (m, ind-$CH_2$), 6.45—6.25 (m, $CH_2OCH_2CH_3$), 3.15 (1 H, bs, ind 2-H), 3.00—2.82 (2 H, m, ind 5- and 6-H), 2.79 (1 H, m, ind 7-H), and 2.50 (2 H, m, ind 4- and 1-H); *m/e* (field desorption) 217 (100%), $\lambda_{max.}$ 291, 284, and 227 nm; $\nu_{max.}$ (liquid film) 3 470 cm^{-1} (ind NH); (iii) 1,2,3,4-tetrahydrocarbazole hydroperoxide (0.11 g, 10%), tablets, m.p. 110—120 °C (decomp.) (lit.,[7] m.p. 124—129 °C decomp.). Recrystallisation from ethyl acetate–light petroleum afforded a pure sample, in poor yield, m.p. 121—122 °C (decomp); *m/e* 203 (M^+, 100%) (field desorption), $\lambda_{max.}$ 280 sh and 290 nm. This compound was identical with the hydroperoxide prepared by Beer *et al.*[7] Treatment of the hydroperoxide (50 mg) with alkali according to the published [7] procedure afforded a small sample (5 mg) of the spirocyclic indole (15) identical in m.p., u.v., and t.l.c. with an authentic sample.[7]

* See footnote on p. 738.

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