Electrophilic Substitution in Indoles. Part IX.[1] Rearrangements and Isotope Effects in Some Reactions of Tetrahydrocarbazoles

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7-Methoxytetrahydrocarbazole undergoes acid catalysed equilibration with the isomeric indolenine-3-spirocyclopentane at temperatures over 100°. The synthesis of specifically deuteriated compounds enabled deuterium isotope effects in these reactions to be studied, the secondary isotope effect K_H/K_D was found to be 1·13. This result made possible a refinement in the calculation of the relative importance of the two mechanisms of electrophilic substitution in 6-methoxyindole.

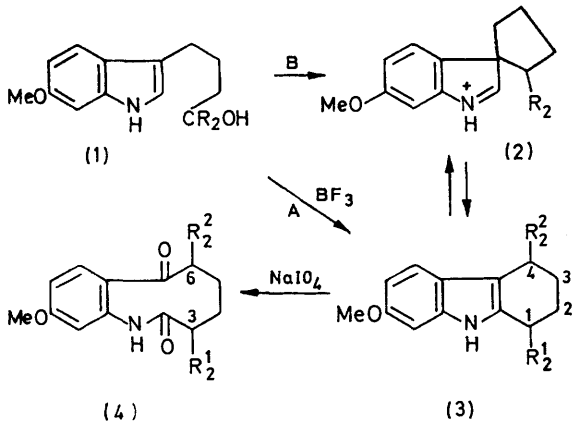
In the preceding paper we demonstrated that the boron trifluoride-catalysed cyclisation of 4-(6-methoxyindol-3-yl)butanol (1; R = H) occurred by two simultaneous pathways (see Scheme). Our preliminary results, using the tritiated alcohol (1; R = ^{3}H) had shown that the apparent percentage substitution at the 2-position (path A, Scheme) was lower (a) the higher the temperature of cyclisation and (b) the longer the reaction time. These facts pointed strongly to a rearrangement of the tetrahydrocarbazole product (3; $R^1 = R^2 = H$) to the spirocyclic indolenine salt intermediate (2; R = H) a process which, of course, would randomise any specific label in the 1-position of the tetrahydrocarbazole (3; $R^1 = R^2 = H$). (The analogous reaction in the demethoxy-series had been shown not to occur below the reflux temperature of boron trifluoride–ether.[2]) Using [1,1-^{2}H]-4-(6-methoxyindol-3-yl)butanol (1; R = ^{2}H) we showed that a similar effect was evident as with tritium. Thus cyclisation of this deuteriated alcohol at 80° afforded a deuteriated tetrahydrocarbazole mixture (3; $R^1 = R^2 = H$ or ^{2}H) which on oxidation [1] gave the deuteriated oxo-amides (4) in which the distribution of deuterium between the 2- and 5-positions, measured by n.m.r., indicated a ratio of substitution by paths A and B (Scheme) of 27 and 73% respectively. At 126°, however, the apparent ratio was 13% (path A) and 87% (path B). We were able to check this deuterium ratio in the oxo-amides (4) by n.m.r. analysis of the thermally derived deuteriated quinolones (5; R = H or ^{2}H) in which the partially

[1] Part VIII, R. Iyer, A. H. Jackson, P. V. R. Shannon, and B. Naidoo, preceding paper.

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

deuteriated *C*-methylene group of (4; R = H or ^{2}H) is specifically removed during the ring closure (4) ⟶ (5).[1]

We decided to investigate the rearrangement of the tetrahydrocarbazole (3; $R^1 = R^2 = H$) to the indolenine (2; R = H) by measuring the extent of randomisation of the deuterium atoms in [1,1-^{2}H]-7-methoxy-1,2,3,4-tetrahydrocarbazole (3, $R^1 = {}^2H$, $R^2 = H$) when submitted to the same conditions used in the cyclisation of the alcohol (1; R = ^{2}H).



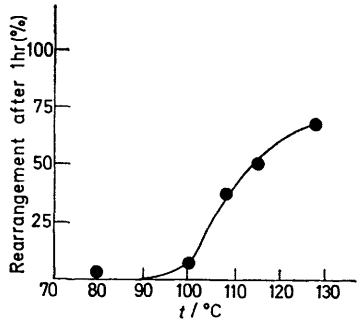
SCHEME

Treatment of the methoxyindolylbutyric acid (6) [1] with boron trifluoride–ether and acetic anhydride gave 7-methoxy-3,4-dihydrocarbazole-1(2*H*)-one (7) as the major product together with its *N*-acetyl derivative. A very minor product (*ca.* 1%) was also isolated whose spectroscopic properties were consistent only with the 5-methoxy-derivative (8) and whose structure was confirmed by its conversion with with diborane to the known 5-methoxy-1,2,3,4-tetrahydrocarbazole.[3] It seems certain that compound (8) was derived from the corresponding 4-methoxyindol-3-ylbutyric acid and its synthetic precursors which were formed from a very small proportion of products of the alternative cyclisation in the primary Japp–Klingemann synthesis [1] from *m*-methoxybenzenediazonium fluoroborate and ethyl 2-oxocyclohexanecarboxylate. It seemed possible that the desired 1-oxo-compound (7) might be obtained more simply from 7-methoxytetrahydrocarbazole (3; $R^1 = R^2 = H$) by oxidation (*cf.* ref. 4) especially as we had noted that this compound was unstable in air and light and apparently decomposed to one main compound (t.l.c.). However, after isolation, the n.m.r. and mass spectra of this product suggested that it was the spirocyclic indolinone (9) (*cf.* ref. 5). This was confirmed by its reconversion to the tetrahydrocarbazole by reduction with lithium aluminium hydride and subsequent rearrangement.[6]

The 1-oxo-compound (7) was reduced by lithium deuteride in good yield to the required 1,1-dideuteriotetrahydrocarbazole (3; $R^1 = {}^2H$, $R^2 = H$), the n.m.r. and mass spectra of which indicated virtually complete deuteriation. Oxidation to the oxo-amide (4; $R^1 = {}^2H$, $R^2 = H$) and n.m.r. analysis of the 3- and 6-methylene resonances confirmed that the label was confined completely to C-3 in this compound.

The crystalline dideuteriotetrahydrocarbazole (3; $R^1 = {}^2H$, $R^2 = H$) was then submitted to the general conditions used for the cyclisation of the alcohol (1; R = ^{2}H) by heating in boron trifluoride–ether for 1 h at a series of temperatures from 80° to reflux at 126°. In each instance the tetrahydrocarbazole was recovered, recrystallised and then, after checking for total deuterium content by n.m.r. analysis, oxidised to the oxo-amides (4; $R^1 = R^2 = H$ or ^{2}H), the deuterium distribution in which was measured as described above. The results of these experiments (see Figure) showed that rearrangement of the tetrahydrocarbazole was insignificant below 100° but that it became very marked at temperatures above this.

The contrast between the 7-methoxytetrahydrocarbazole and the demethoxy-analogue in their tendency to rearrange in acid is to be expected in view of the enhanced nucleophilic activity of the 6-methoxyindolyl group at the 2-position of indole as shown in (10).



Effect of temperature on the boron trifluoride-catalysed rearrangement of deuteriated tetrahydrocarbazole (3; $R^1 = {}^2H$, $R^2 = H$)

This behaviour parallels the difference in their electrophilic substitution mechanisms demonstrated in the preceding paper.

In the latter work, the estimation of the extent of the two simultaneous reaction mechanisms (see Scheme) was based on the final deuterium distribution in the oxo-amides (4; $R^1 = R^2 = H$ or ^{2}H). No account was taken of the possibility of isotope effects which might operate during the rearrangement of the deuteriated indolenine (2; R= ^{2}H) to the tetrahydrocarbazole or in the subsequent oxidation reaction.

One such effect, a secondary isotope effect, would be

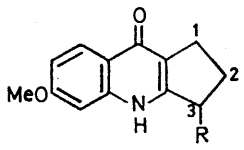
[3] J. R. Chalmers, H. T. Openshaw, and G. F. Smith, *J. Chem. Soc.*, 1957, 1115.

[4] (*a*) E. Leete, *J. Amer. Chem. Soc.*, 1961, **83**, 3645; (*b*) B. Witkop, J. B. Patrick, and M. Rosenblum, *ibid.*, 1951, **73**, 2641; (*c*) W. I. Taylor, *Proc. Chem. Soc.*, 1962, 247.

[5] J. B. Patrick and B. Witkop, *J. Amer. Chem. Soc.*, (*a*), 1950, **72**, 633; (*b*) 1951, **73**, 2188.

[6] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 1953, **75**, 2572.

expected to discriminate between the rates of migration of the two branches of the cyclopentane ring of the deuteriated indolenine (2; R = ^{2}H). To check this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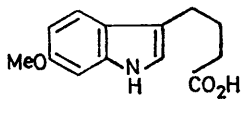
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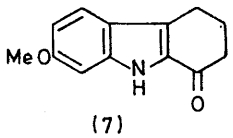
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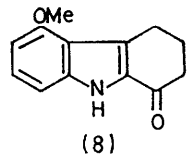
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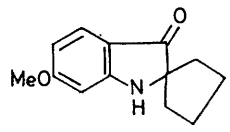
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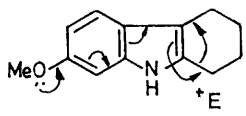
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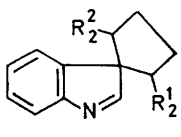
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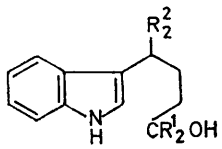
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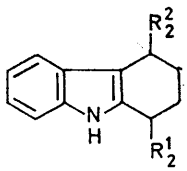
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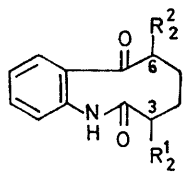
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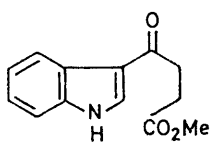
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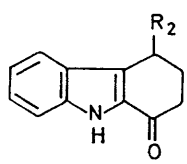
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possibility, we synthesised the model demethoxy-dideuterioindolenine-3-spirocyclopentane (11; $R^1 = {}^2H$, $R^2 = H$). 4-Indol-3-ylbutyric acid was reduced with lithium aluminium deuteride to the completely and specifically deuteriated alcohol (12; $R^1 = {}^2H$, $R^2 = H$) the tosylate of which was converted with potassium t-butoxide to the required indolenine (11; $R^1 = {}^2H$, $R^2 = H$) (*cf.* ref. 7). Rearrangement of the latter at 80° in boron trifluoride–ether [*i.e.* the conditions used to cyclise the alcohol (1; R = ^{2}H)] afforded the mixture of deuteriated tetrahydrocarbazoles (3; $R^1 = R^2 = H$ or ^{2}H) which were crystallised and oxidised as before to the corresponding oxo-amide mixture. N.m.r. estimation of the deuterium distribution in this mixture indicated an effective secondary isotope effect K_H/K_D of 1·13. It seems reasonable that the isotope effect in the demethoxy-compound (11; $R^1 = {}^2H = H$) is a good approximation to that operating in the methoxy-indolenine (2; R = ^{2}H) so that the original figure [1] for the percentage direct substitution at the 2-position (27%) in the cyclisation of the alcohol (1; R = ^{2}H) can be corrected in the light of this factor, leading to a slightly higher figure of 31% direct substitution (path A) and 69% indirect substitution (path B, Scheme).

The final consideration in respect of possible isotope effects concerns the oxidation of the tetrahydrocarbazoles to the oxo-amides. We were able to ascertain that during the oxidation no deuterium originally present in the starting material had exchanged with the solvent or other reagent since the sum of the 3- and 6-H resonances in the mixed deuterio-oxo-amides (4; $R^1 = R^2 = H$ or ^{2}H) was 50% of the total signal of 4- and 5-H. However, this fact did not exclude the possibility of a partially selective oxidation of one or other of the two deuteriotetrahydrocarbazoles (3; $R^1 = H$, $R^2 = {}^2H$) or (3; $R^1 = {}^2H$, $R^2 = H$). This effect, if operating, would be expected to be less marked than a secondary isotope effect, since the bonds broken in (3) are two removed from the carbon–deuterium bond.

The deuterioindolylbutanol (12; $R^1 = {}^2H$, $R^2 = H$) after cyclisation with refluxing boron trifluoride–ether to the mixture of deuteriotetrahydrocarbazoles (13; $R^1 = H$, $R^2 = {}^2H$) and (13; $R^1 = {}^2H$, $R^2 = H$) was oxidised with sodium metaperiodate to the mixture of oxo-amides (14; $R^1 = H$, $R^2 = {}^2H$) and (14; $R^1 = {}^2H$, $R^2 = H$) which showed a slight excess of (14; $R^2 = {}^2H$). When this result is corrected for the secondary isotope effect operating in the indolenine rearrangement the result is an apparent 3% substitution at the 2-position. This figure is in close agreement with that obtained by tritium labelling [2] and is near to that predicted for exclusive initial substitution *via* the 3-position. In order to estimate the importance of any isotope effect in the oxidation of deuteriated forms of (13) to (14) in relation to both this experiment and those in the methoxy-series, we prepared a 1 : 1 mixture of the tetrahydrocarbazole (13; $R^1 = R^2 = {}^2H$) and (13; $R^1 = R^2 = H$). The former was synthesised by reduction of the keto-ester (15) with lithium aluminium deuteride to (12; $R^1 = R^2 = {}^2H$) and repetition of the sequence (12) ⟶ (11) ⟶ (13) described above for the dideuterio-series. Oxidation of the tetrahydrocarbazole mixture gave a mixture of the oxo-amides (14; $R^1 = R^2 = {}^2H$) and (14; $R^1 = R^2 = H$) in which the total of the resonances due to 3- and 6-H was 50 ± 2% of those of 4- and 5-H. Thus the magnitude of any isotope effect in this and other oxidations of deuteriotetrahydrocarbazoles was within the limits of error of our measurements.

[7] A. H. Jackson and B. Naidoo, *Tetrahedron*, 1969, **25**, 4843.

When the oxidation of the original mixture of deuteriotetrahydrocarbazoles, obtained from the cyclisation of the alcohol (12; $R^1 = {}^2H$, $R^2 = H$), was carried out with periodic acid the main product was dihydrocarbazolone.[2] In this case, a primary isotope effect was to be expected and because of incomplete oxidation this was observed; the resulting 1-oxo-compounds comprised a mixture of (16; R = ^{2}H) and (16; R = H) in the ratio 68 : 32.

EXPERIMENTAL

Cyclisation of [1,1-$^2H_2$]-4-(6-*Methoxyindol*-3-*yl*)*butan*-1-*ol* (1; R = ^{2}H) *at* 126° *and Oxidation of the Resultant Tetrahydrocarbazoles with Sodium Metaperiodate.*—The alcohol (2 g) was cyclised exactly as described in the preceding paper except that the reaction time was 40 min and the temperature was 126° (refluxing boron trifluoride–ether). Isolation and oxidation of the tetrahydrocarbazoles (3; R^1, R^2 = H or ^{2}H) (0·35 g) as previously described gave a mixture of crystalline oxo-amides (4; R^1, R^2 = H or ^{2}H) (106 mg) for which the n.m.r. spectrum showed that the ratio of methylene signals at C-2 and C-5 was 0·765 ± 0·005.

Conversion to the Quinolones (5; R = H) *and* (5; R = ^{2}H).—The above deuterio-oxo-amides (30 mg) were heated in an oil bath at 190° for 20 min and the resulting solid was sublimed at 0·05 mmHg to give a mixture of the quinolones (5; R = H) and (5; R = ^{2}H) (20 mg). T.l.c. showed the product to be pure. The n.m.r. spectrum, in trifluoroacetic acid, showed that the ratio of the C-3 methylene signals to the difference between those at C-2 and C-3, corresponding to the ratio of signals at C-3 and C-6 in the oxo-amide, was 0·76 ± 0·01.

Cyclisation of the Acid (6) *with Boron Trifluoride–Ether.*—A solution of boron trifluoride–ether (freshly distilled; 1 ml) in dry ether (15 ml) was added to 7-methoxyindol-3-ylbutyric acid (1 g) in acetic acid (5 ml) and acetic anhydride (2·5 ml). T.l.c. showed after 15 min only traces of starting acid. The mixture was poured into water (100 ml), extracted with ether (2 × 100 ml), and then washed carefully with saturated sodium hydrogen carbonate solution (3 × 100 ml) and water (100 ml). Drying ($MgSO_4$) and removal of solvent gave a green solid (0·8 g). T.l.c. indicated this to be a mixture of at least three compounds. Crystallisation from acetone gave 7-*methoxy*-3,4-*dihydrocarbazol*-1(2H)-*one* (7) (0·35 g), m.p. 158—158·5°, τ 7·76(2H, m, 3-CH_2), 7·39 (2H, m, 2-CH_2), 7·08 (2H, m, 4-CH_2), 6·18 (3H, s, OMe), 3·25 (1H, d, *J* 9 Hz, 6-H), 3·17br (1H, s, 8-H), 2·58 (1H, d, *J* 9 Hz, 5-H), and 0·1br (1H, s, NH), $\lambda_{max.}$ (EtOH) 235 (ε 5700), 257 (4500), and 332 (11,900) nm, $\nu_{max.}$ (CCl_4) 1618 (C=O), and 3500 (NH) cm^{-1}, *m/e* (%) 215 (M^+, 100), 214 (8), 200(32), 187(6), 186(8), 173(8), 172(22), 160(9), 159(51), 158(7), 144(8), 117(5), 116(10) 115(8), and 89(11) (Found: C, 72·2; H, 6·1; N, 6·6. $C_{13}H_{13}NO_2$ requires C, 72·6; H, 6·0; N, 6·5%). P.l.c. of the mother liquors from the crystallisation gave three bands of which the first afforded a further crop of carbazolone (50 mg). The second band, after extraction with ether, afforded a gum which was crystallised from ether–light petroleum to give N-*acetyl*-7-*methoxy*-3,4-*dihydrocarbazol*-1(2H)-*one* as pale yellow needles (138 mg) m.p. 94—96°, τ 7·7 (2H, m, 3-CH_2), 7·35 (5H, superimposed *s* and *m*, NCOMe and 2-CH_2), 7·04 (4H, m, 2- and 4-CH_2), 6·10 (3H, s, OMe), 3·07 (1H, dd, *J* 9, 2 Hz, 6-H), 2·54 (1H, d, *J* 9 Hz, 5-H), and 2·22br (1H, s, 8-H), $\lambda_{max.}$ (EtOH) 233 (ε 15,680), 260 (10,410), 270sh (9770), and 333 (29,560 nm), $\nu_{max.}$ (CCl_4) 1615 (=C·CO) and 1665 (N·C=O) cm^{-1}, *m/e* (%) 257 (M^+, 14), 216(13), 215(100), 214(6), 200(18), 187(10), 186(8), 173(7), 172(18), 159(26), 144(7), 129(5), 116(7), 115(6), and 89(5) (Found: C, 69·7; H, 6·0; N, 5·2. $C_{15}H_{15}NO_3$ requires C, 70·0; H, 5·8; N, 5·4%). The third band, after work-up *via* ether, and crystallisation from benzene afforded 5-*methoxy*-3,4-*dihydrocarbazol*-1(2H)-*one* (8) as crystals (11 mg), m.p. 178—178·5°, τ 7·79 (2H, m, 3-CH_2), 7·39 (2H, t, *J* 6 Hz, 2-CH_2), 6·8 (2H, t, *J* 6 Hz, 4-CH_2), 6·1 (3H, s, OMe) 3·61 (1H, d, *J* 8 Hz, 6-H), 2·7—3·1 (2H, m, 7- and 8-H), and 0·55br (1H, s, NH), $\lambda_{max.}$ (EtOH) 243sh (ε 14,190), 248 (14,900), 307 (13,760), and 343 (5450) nm, $\nu_{max.}$ (CCl_4), 1618 (C=O) and 3500 (NH) cm^{-1}, *m/e* (%) 215 (M^+, 100), 214(15), 200(16), 187(12), 186(14), 173(10), 172(36), 160(5), 159(29), 158(8), 146(6), 130(12), 129(8), 116(6), 115(7), 89(8), and 75(22) (Found: C, 72·3; H, 6·1; N, 6·5. $C_{13}H_{13}NO_2$ requires C, 72·5; H, 6·0; N, 6·5%).

Reduction of Dihydrocarbazolone (7) *with Lithium Aluminium Hydride.*—The dihydrocarbazolone (0·5 g) was dissolved by heating under reflux in dry ether (70 ml) and the solution was added dropwise to a suspension of lithium aluminium hydride (0·25 g) in dry ether (30 ml). The mixture was heated under reflux for 3 hr. T.l.c. then showed the reaction to be complete. Normal work-up procedure and isolation *via* ether gave a semi-solid (0·35 g). Crystallisation from ethanol gave 7-methoxy-1,2,3,4-tetrahydrocarbazole (0·31 g), m.p. 146—147° (in dark) unchanged on mixing with authentic material.[3] The t.l.c. and n.m.r. spectrum were identical to those of authentic material.

[1,1-$^2H_2$]-7-*Methoxy*-1,2,3,4-*tetrahydrocarbazole* (3; R^1 = ^{2}H, R^2 = H).—The ketone (7) (0·5 g) in warm dry ether (75 ml) was added dropwise to a suspension of lithium aluminium deuteride (0·25 g) in dry ether (10 ml) and the mixture was heated under reflux for 3 h. At the end of this period t.l.c. indicated only traces of starting material. After cooling, the reaction mixture was decomposed with a saturated solution of Rochelle salt. The mixture was poured into water (200 ml) and extracted with ether (2 × 100 ml). The organic extract was washed with water (100 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give crude product as a white solid. Crystallisation from ethanol gave [1,1-$^2H_2$]-7-methoxy-1,2,3,4-tetrahydrocarbazole (3; R^1 = ^{2}H, R^2 = H) (0·42 g), m.p. 139—143° not raised by further crystallisation. The n.m.r. spectrum was identical to that of the undeuteriated compound [1] except that the CH_2 signal at τ 7·37 was 50·4 ± 0·5% of that at τ 8·18 indicating effectively complete deuteriation, *m/e* (%) 203 (M^+, 100), 202(19), 201(7), 200(6), 189(9), 183(63), 187(7), 176(10), 175(85), 174(5), 173(8), 160(8), 159(6), 158(6), 132(19), 101(8), and 87(11).

Oxidation of [1,1-$^2H_2$]-7-*Methoxy*-1,2,3,4-*tetrahydrocarbazole to the Oxo-amide* (4; R^1 = ^{2}H, R^2 = H).—The 1,1-dideuteriotetrahydrocarbazole (0·3 g) in methanol (25 ml) was added dropwise to a stirred suspension of sodium metaperiodate (1·3 g) in water (2 ml) and methanol (4 ml) under nitrogen. The nitrogen flow was stopped and the mixture was stirred overnight at 20°. After work-up *via* methylene chloride as described in the preceding paper a brown oil (0·33 g) was obtained. Chromatography on Woelm silica (70 g) gave the dideuterio-oxo-amide (4; R^1 = ^{2}H, R^2 = H) (82 mg), m.p. 172—174° (decomp.)

The n.m.r. spectrum was identical to that of the undeuteriated compound except that the signal at τ 7·46 was absent.

Treatment of [1,1-$^2H_2$]-7-*Methoxy*-1,2,3,4-*tetrahydrocarbazole with Boron Trifluoride at Different Temperatures and Oxidation of the Recovered Tetrahydrocarbazole.*—Five experiments were carried out according to the following general procedure, described for the experiment at 80°. The remaining experiments were identical except that temperatures of 100, 107, 115, and 126° were employed and the experiment at 126° involved heating the tetrahydrocarbazole for 40 min.

The 1,1-dideuteriotetrahydrocarbazole (0·3 g) was treated with boron trifluoride–ether (redistilled; 15 ml) for 1 h at 80°. The mixture was cooled and poured into water. After extraction into ether, washing the ether layer with water, drying ($MgSO_4$), and removal of solvent the crude product was obtained as a solid (0·29 g). A sample (*ca.* 50 mg) was crystallised from ethanol to give off-white crystals, m.p. 139—142°, whose n.m.r. spectrum was identical to that of the starting material.

The whole of the above tetrahydrocarbazole was oxidised with sodium metaperiodate exactly as described above. Chromatography of the derived oxo-amide afforded a specimen (78 mg) whose t.l.c. and n.m.r. spectrum indicated purity. The area of the proton signals at τ 7·46 and 6·9 were measured accurately by tracing and weighing. The spectrum was run at scale factor 2 Hz/div. and sensitivity ×4 for this purpose. The ratio of signal areas at C-3 to those at C-6 in the amide was <5%. The results for the series of experiments are in the Table.

Ratio of areas of protons at C-3 to those at C-6 in keto-amide	Temperature of boron trifluoride–ether (°C)
<0·02	80
0·02	100
0·212	107
0·342	115
0·492	126

Reduction of 5-*Methoxy*-3,4-*dihydrocarbazol*-1(2H)-*one* (8) *with Lithium Aluminium Hydride.*—The dihydrocarbazolone (200 mg) in ether (5 ml) was added dropwise to a suspension of lithium aluminium hydride (100 mg) in dry ether (10 ml). The mixture was heated under reflux for 0·5 h and t.l.c. then showed the reaction to be complete. After the usual work-up a solid product was obtained (0·18 g). Crystallisation from ether gave 5-methoxy-1,2,3,4-tetrahydrocarbazole (90 mg), m.p. 128—130° (lit.,[3] 128—129°), τ 8·18 (4H, m, 2- and 3-CH_2), 7·38 (2H, m, 1-CH_2), 7·19 (2H, m, 4-CH_2), 6·16 (3H, s, OMe), 3·6 (1H, dd, *J* 7·5, 1 Hz, 6-H), 3·22 (1H, dd, *J* 7·5, 1 Hz, 8-H) 3·07 (1H, m, 7-H), and 2·53br (1H, s, NH), *m/e* (%) 201 (M^+, 100), 200(22), 187(5), 186(44), 185(12), 184(13), 174(9), (173(8), 172(20), 169(7), 167(6), 158(20), 156(7), 154(7), 144(14)143(7), 142(5), 130(10), 115(9), 101(8), 87(7), 77(10), and 43(18), $\lambda_{max.}$ (EtOH) 227 (ε 21,000), 273 (4910), 282sh (4690), and 294 (4750)nm, $\nu_{max.}$ (Nujol) 3420 cm^{-1} (NH).

[1,1-$^2H_2$]-4-(*Indol*-3-*yl*)*butan*-1-*ol* (12; R^1 = ^2H, R^2 = H).—Indol-3-ylbutyric acid (5 g) in dry ether (200 ml) was added dropwise to a suspension of lithium aluminium deuteride (2 g) in dry ether (100 ml). The mixture was heated under reflux for 2·5 h at the end of which t.l.c. indicated no starting material. The reaction was worked-up (after treatment with Rochelle salt solution) in the usual way and gave the product as a syrup (3·2 g), pure by t.l.c., τ 3·38 (4H, m, $CH_2CH_2CD_2$) 8·25 (1H, s, OH) 7·24 (2H, t, *J* 7 Hz, Ind-CH_2CH_2), 3·15br (1H, s, Ind-2-H), 2·86 (3H, m, Ind-5-, 6-, and 7-H), 2·43 (1H, m, Ind-4-H), and 2·0br (1H, s, NH), *m/e* (%) 191 (M^+, 24), 131(20), 130(100), 103(6), and 77(7). The n.m.r. spectrum showed no signal at τ 6·49 corresponding to the CH_2OH signal in the nondeuteriated compound.[7]

[2′,2′-$^2H_2$]*Indolenine*-3-*spirocyclopentane* (11; R^1 = ^2H, R^2 = H).—Toluene-*p*-sulphonyl chloride (4·5 g) was added in portions to a stirred solution of the above deuterioindolylbutanol in dry pyridine (45 ml). The temperature of the solution was maintained at −5° during the addition, and then the mixture was stirred at 0° for 2 h. T.l.c. at this stage showed the complete absence of starting material. The mixture was poured into water (150 ml) and extracted into ether (3 × 100 ml). After washing the ether extracts with water (3 × 75 ml), drying ($MgSO_4$), and removal of solvent under reduced pressure the crude product was obtained as an oil which after drying at 20° and 0·5 mmHg overnight afforded the deuterio-tosylate as a syrup (4·8 g). T.l.c. indicated that the compound was pure, τ 8·38 (4H, m, $CD_2CH_2CH_2$), 7·65 (3H, s, ArMe), 7·38 (2H m, $IndCH_2$), 3·2 (1H, s, Ind-2-H), 2·65—3·1 (m, Ind-5-, 6-, and 7-H and Tosyl-3-, and 5-H), 2·53 (1H, m, Ind-4-H), and 2·3 (2H, d, *J* 7·5 Hz, Tosyl-2- and 6-H). The spectrum showed no signal at τ 6·0 corresponding to CH_2O in the undeuteriated compound.[7]

Potassium t-butoxide solution [potassium (6·7 g) in t-butanol (145 ml) heated under reflux for 4 h] (6 ml) was added to dry tetrahydrofuran (THF) (20 ml). The suspension was stirred at 20° and treated during 10 min. with a solution of the above deuteriated tosylate (2·4 g) in dry THF (30 ml). The mixture was stirred for 2 h at 20° when t.l.c. showed none of the starting tosylate. The mixture was poured into water (150 ml) and extracted with ether (3 × 100 ml). The ether extract was washed with water (2 × 100 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the product as a pale yellow oil. The products from two experiments were combined and crystallised from acetone to give the *spiro-compound* (11; R^1 = ^2H, R^2 = H) as plates (1·35 g), m.p. 145—147° (unchanged by recrystallisation). The n.m.r. spectrum was identical with that of the nondeuteriated compound[7] except that the multiplet at τ 8·18 was, as expected, of lower intensity, *m/e* (%) 173 (M^+, 60), 172(31), 171(9), 146(12), 145(100), 144(9), 143(13), 131(9), 130(8), 129(9), 117(11), 116(9), and 115(6). The u.v. spectrum of the compound [$\lambda_{max.}$ 255 (ε 9610) and 302 (2880) nm.] showed by comparison with standards that <0·1% of the tetrahydrocarbazole was present in the sample. T.l.c. [ether–light petroleum (9 : 1)] confirmed the absence of tetrahydrocarbazole.

Rearrangement of Spiro-compound (11; R^1 = ^2H, R^2 = H) *to Deuteriated Tetrahydrocarbazoles.*—The above indolenine (1·35 g) was kept in boron trifluoride–ether (40 ml; freshly distilled) at 80° for 1 h. T.l.c. then showed conversion to tetrahydrocarbazole. After cooling, the mixture was poured into water (150 ml) and extracted with ether (2 × 125 ml). After washing with water the ether layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to leave a semi-solid residue. Crystallisation from ethanol gave the deuteriated tetrahydrocarbazoles (0·82 g), m.p. 117—119°. T.l.c. showed a single spot and the n.m.r. spectrum showed that the area of the C-1 and C-4 methylene resonances (τ 7·36) totalled 50% of that of the C-2 and C-3 methylene resonances (τ 8·16).

Oxidation of the Deuteriated Tetrahydrocarbazoles.—The above deuteriated tetrahydrocarbazole mixture (0·75 g) in methanol (50 ml) was added dropwise to a solution of sodium metaperiodate (2·1 g) in water (15 ml). The mixture was stirred at 20° for 2·5 h. The mixture was worked-up as described previously and the product was crystallised from ethyl acetate and after two recrystallisations the resultant deuteriated oxo-amides (325 mg) had m.p. 150—155° (m.p. of non-deuteriated compound from an analogous experiment 156—157°). Two n.m.r. determinations of the relative areas for the C-3 and C-6 methylene protons were made. It was found that the ratio of areas of 3-CH_2 : 6-CH_2 was 1·135 ± 0·005. For an identical series of measurements on the non-deuteriated amide, the experimentally determined ratio was 1·01 ± 0·01. Hence the ratio of the rate of migration of the CH_2R substituent to the rate of migration of the CD_2R substituent in the indolenine is 1·13 ± 0·01.

Synthesis of [2′,2′,5′,5′-$^2H_4$]*Indolenine-3-spirocyclopentane* (11; $R^1 = R^2 = {}^2H$).—(a) 4-(*Indol-3-yl*)*butan-1-ol*. Methyl 4-(indol-3-yl)-4-oxobutanoate (200 mg) in dry ether (5 ml) was added dropwise to a suspension of lithium aluminium hydride (200 mg) in dry ether (5 ml). The mixture was heated under reflux for 2·5 h and then worked up by the normal procedure to give the indolylbutanol as a syrup (60 mg). The material was identical spectroscopically and chromatographically with an authentic specimen.[7]

(b) [1,1,4,4-$^2H_4$]-4-(*Indol-3-yl*)*butan-1-ol* (12; $R^1 = R^2 = {}^2H$). Methyl 4-(indol-3-yl)-4-oxobutanoate (2·5 g) in dry ether (100 ml) was added dropwise to a suspension of lithium aluminium deuteride (2·0 g) in dry ether (100 ml). The mixture was heated under reflux for 2·5 h when t.l.c. indicated the absence of starting material, and only one product. The usual work-up gave the tetradeuterio-alcohol (12; $R^1 = R^2 = {}^2H$) as a gum (1·05 g). The n.m.r. spectrum was identical with that for the non-deuteriated compound [7] except that there were no signals at τ 7·25—7·35 and 6·40—6·49, *m/e* (%) 193 (M^+, 24), 133(19), 132(100), 131(12), 130(7), and 105(5). T.l.c. (R_F 0·6 in ether) showed only one spot.

Conversion to the tosylate. A stirred solution of the deuterio-alcohol (1·0 g) in dry pyridine (15 ml) was treated with toluene-*p*-sulphonyl chloride (1·5 g) in small portions; the temperature of the mixture was maintained at −5° during the addition, after which the mixture was stirred at 0° for 2 h. T.l.c. examination then revealed no starting material. Work-up as for the dideuterio-tosylate gave the tetradeuterio-tosylate as a pale yellow syrup (1·5 g). The n.m.r. spectrum was identical with that of the non-deuteriated compound [7] except that there were no signals at τ 5·95 and 7·30. The material was chromatographically homogenous.

Spiro-compound (11; $R^1 = R^2 = {}^2H$). Potassium t-butoxide solution (3·5 ml) [from potassium (6·7 g) in t-butanol (145 ml) heated under reflux for 4 h] was added to dry THF (20 ml). The suspension was stirred at 20° and treated during 10 min with a solution of the above tetradeuterio-tosylate (1·5 g) in dry THF (20 ml). The mixture was stirred at 20° for 2 h when t.l.c. showed completion of the reaction. Work-up identical with that for the dideuterio-compound gave a pale yellow solid (280 mg) m.p. 137—139°. Recrystallisation from acetone gave the *spiro-compound* (11; $R^1 = R^2 = {}^2H$) (210 mg), m.p. 144—145° unchanged by further recrystallisation. The n.m.r. spectrum showed mainly signals assignable to the monomeric form,[7] τ 8·18 and 8·00 (4H, s, $CD_2CH_2CH_2CD_2$), 2·3—3·1 (4H, complex m, ArH), and 2·0 (1H, s, Ind-2-H). Minor signals at τ 5·0, 5·63, and 5·78 (3 × s) indicated that approximately 25% of the compound was present as the trimer,[7] *m/e* (%) 175 (M^+, 48), 174(17), 173(18), 148(12), 147(100), 146(9), 145(20), 132(6), 131(11), 130(8), 119(7), 118(9), 117(9), 104(7), 79(5), 78(6), and 77(5).

Air Oxidation of 7-Methoxytetrahydrocarbazole (3; $R^1 = R^2 = H$).—The tetrahydrocarbazole (0·5 g) was stirred in dry dioxan (100 ml) and exposed to a 100 W tungsten lamp. After 3·5 h t.l.c. showed only traces of tetrahydrocarbazole. Approximately one half of the dioxan was removed under reduced pressure and the residue was diluted with water (200 ml) and extracted with ether (2 × 100 ml). After washing with water and drying ($MgSO_4$) the ether solution showed one major spot (blue in u.v. light) of lower R_F than the starting material. Removal of the ether afforded a pale yellow oil (0·7 g) which was chromatographed on Woelm silica. Elution with light petroleum–ether gave the crude product and two further chromatographic separations gave *7-methoxyindole-2-spirocyclopentane-3(2H)-one* (9) as a semi-solid (pure by t.l.c.), τ 8·1 (8H, m, $COC[CH_2]_4$), 6·25 (3H, s, OMe) 4·8br (1H, s, NH), 3·85 (1H, d, *J* 2 Hz, 7-H), 3·7 (1H, dd, *J* 9, 2 Hz, 5-H), and 2·58 (1H, d, *J* 9 Hz, 4-H), $\lambda_{max.}$ 364 (ε 3160), 281 (10,100), 250sh, (14,520), and 237 (15,780) nm, *m/e* (%) 217 (M^+, 30), 189(11), 188(36), 176(12), 175(5), 160(5), 123(7), 105(8), 91(5), 87(11), and 63(5) (Found: M^+, 217·1103. $C_{13}H_{15}NO_2$ requires *M*, 217·1103).

Conversion of Compound (9) *to 7-Methoxy-1,2,3,4-tetrahydrocarbazole* (3; $R^1 = R^2 = H$).—The indolone (45 mg), dissolved in dry ether (15 ml), was added dropwise to a suspension of lithium aluminium hydride (20 mg) in ether (5 ml). The mixture was heated under reflux for 0·5 h at the end of which t.l.c. showed no starting material. The mixture was cooled, poured into water (25 ml), extracted with ether (2 × 25 ml), and the extract was washed with water. T.l.c. examination revealed two spots, one of which corresponded to the tetrahydrocarbazole. The extract was shaken with 2N-hydrochloric acid (25 ml) and then washed and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil (42 mg). Two crystallisations from aqueous ethanol and ethanol gave the tetrahydrocarbazole (3; $R^1 = R^2 = H$) as a pale yellow solid (18 mg) m.p. 145—146°, mixed m.p. 145—146° with an authentic specimen [3] of m.p. 146—147° (m.p.s measured in the dark). The t.l.c. and i.r. spectra of the product were identical with those of the authentic specimen.

Cyclisation of [1,1-$^2H_2$]-4-(*Indol-3-yl*)*butan-1-ol* (12; $R^1 = {}^2H$, $R^2 = H$) *with Boron Trifluoride–Ether*.—The deuterio-alcohol (2·5 g) was heated under reflux in boron trifluoride–ether (60 ml; freshly distilled) for 40 min. The cooled mixture was poured into water (200 ml), extracted into chloroform (2 × 100 ml), and the extract, after washing and drying, ($MgSO_4$), was chromatographed over Mallinckrodt silicic acid. Elution with ether gave the crude product which, after crystallisation from ethanol, gave the deuterio-tetrahydrocarbazoles as a yellow solid (0·53 g), m.p. 109—113°. The n.m.r. spectrum was identical with that of the undeuteriated compound [2] except that the area of the CH_2 signal at τ 7·35 was 50·0 ± 1% of that at τ 8·18.

Oxidation of the Tetrahydrocarbazoles (13; $R^1 = H$ *or* ^2H, $R^2 = H$ *or* ^2H) *with Periodic Acid*.—A solution of the

mixture of tetrahydrocarbazoles (0·5 g) in methanol (30 ml) was added dropwise to a stirred solution of periodic acid (1·5 g) in water (2 ml) and methanol (5 ml) at 0°. The mixture was kept at 20° for 30 min. T.l.c. then showed the reaction to be complete. The mixture was poured into water (100 ml) and extracted with ether (3 × 75 ml). After washing the extract with dilute sodium thiosulphate solution (75 ml) and water (75 ml), drying ($MgSO_4$) and removal of solvent under reduced pressure gave the crude ketone which crystallised from aqueous acetone to give a pale yellow solid (210 mg), m.p. 151—155°. Two subsequent crystallisations gave the mixture of deuteriated dihydrocarbazolones as an off-white solid (110 mg), m.p. 158—161° unaltered by further recrystallisation. The n.m.r. spectrum in deuteriochloroform was identical with that of the non-deuterio-compound [2] but the signal area at τ 7·05 was approximately one third of that of the corresponding peak in the non-deuterio compound. The ratio of signals for protons at C-4 and C-2 was 0·320 ± 0·005.

Oxidation of Deuterioetrahydrocarbazoles (13; R^1, R^2 = H *or* ^2H) *with Sodium Metaperiodate.*—The mixture of tetrahydrocarbazoles (0·5 g) in methanol (30 ml) was added dropwise to a solution of sodium metaperiodate in water (9 ml). The mixture was stirred at 20° for 2·5 h when t.l.c. showed the reaction to be complete. The product was isolated *via* methylene chloride and crystallised twice from ethyl acetate to give the oxo-amides (14; R^1, R^2 = H or ^2H) as needles (190 mg), m.p. 152—155°. The n.m.r. spectrum, in trifluoroacetic acid, showed that the ratio of the area of the methylene signals at C-3 and C-6 was 1·06 ± 0·01.

Rearrangement of Spiro-compound (11; $R^1 = R^2 = {}^2H$) *to* [1,1,4,4-$^2H_4$]-1,2,3,4-*Tetrahydrocarbazole* (13; $R^1 = R^2 = {}^2H$).—The indolenine (210 mg) was heated at 80° for 1 h with boron trifluoride–ether (10 ml). The mixture was cooled to 20°, diluted with water (50 ml), and extracted with ether (2 × 50 ml). The ether extract was washed with water (50 ml), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a brown solid (190 mg) which was crystallised from ethanol to give the *tetradeuteriotetrahydrocarbazole* (13; $R^1 = R^2 = {}^2H$) (160 mg), m.p. 116—118°, *m/e* (%), 175 (M^+, 60), 174(11), 173(11), 171(6), 170(5), 148(12), 147(100), 146(10), 145(18), and 118(5) (Found: M^+, 175·1299. $C_{12}H_9ND_4$ requires M, 175·1299).

Oxidation of the Mixed Tetrahydrocarbazoles.—The above tetradeuterio-compound (160 mg) was intimately ground with its non-deuteriated analogue [7] (160 mg), m.p. 118—119°. The n.m.r. spectrum of the mixture showed the signal area of the methylene protons at C-1 and C-4 to be 50 ± 1% of those at C-2 and C-3. The mixture (320 mg) was oxidised as above for 2·5 h and the crude product (90 mg), after two crystallisations from ethyl acetate, gave the oxo-amides (14; $R^1 = R^2$ = H) and (14; $R^1 = R^2 = {}^2H$) as needles (45 mg), m.p. 152—155°. The n.m.r. analysis showed the ratio of C-3 and C-6 methylene proton signals to be 50 ± 2% of those for the C-4 and C-5 methylene protons.

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