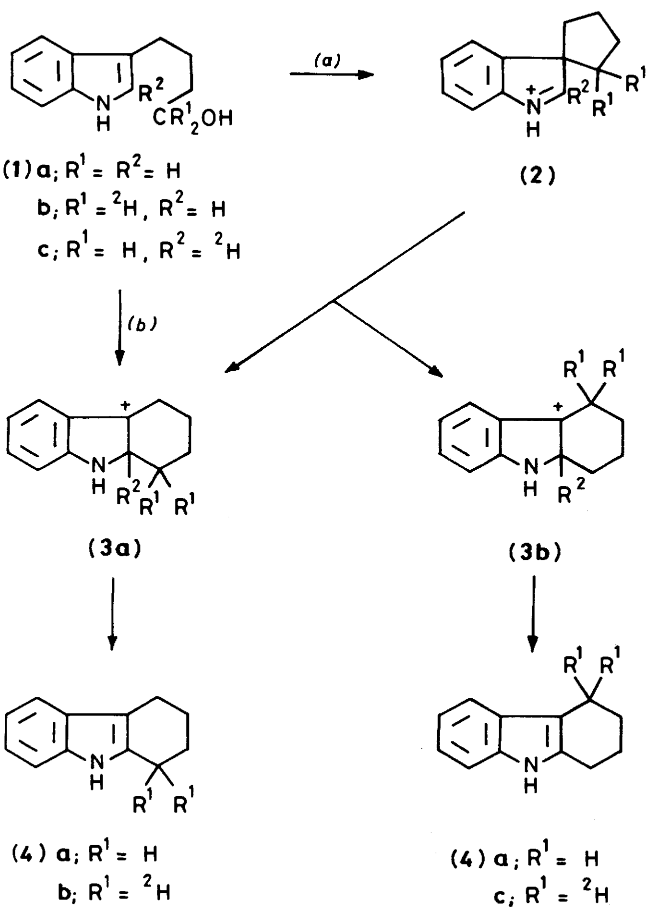
Electrophilic Substitution in Indoles. Part 13.[1] The Synthesis and Rearrangement of 2-Deuteriospiro[cyclopentane-3'-indolenine]

Juana S. L. Ibaceta-Lizana, Anthony H. Jackson,* Noojaree Prasitpan, and Patrick V. R. Shannon
Department of Chemistry, University College, P.O. Box 78, Cardiff CF1 1XL

2-Deuterioindole was prepared from *N*-phenylsulphonylindole by lithiation, quenching with D_2O, and hydrolysis. Treatment of the 2-deuterioindole Grignard reagent with succinic anhydride gave 4-(indol-3-yl)-4-oxobutanoic acid with partial loss of the deuterium from the 2-position. 2,3-Dideuterioindole (prepared by acid-catalysed deuteriation of 2-deuterioindole) when treated in the same way, gave the indolyl oxobutanoic acid, 92% deuteriated at the indolyl 2-position. Reduction to the deuterioindolylbutanol and treatment of its toluene-*p*-sulphonate with potassium t-butoxide give 2-deuterio-spiro[cyclopentane-3'-(3*H*)indole] which was 88% deuteriated at the 2-position. The kinetics of the acid-catalysed rearrangement of the deuterioindolenine and its non-deuteriated analogue were measured and the ratio k_H/k_D of the pseudo-first-order rate constants was found to be 1.08, showing that the isotope effect was very small.

In preceding Parts,[1-5] it has been shown that the intramolecular electrophilic substitution of the indolylbutanol (**1a**) takes place *via* the intermediate spiro[cyclopentane-3'-indolenine] (**2a**) which rearranges to the tetrahydrocarbazole (**4a**) [path (*a*), Scheme 1], and that the introduction of aromatic methoxy substituents in the indolylbutanol (**1**) induces a partial change in reaction mechanism to direct substitution [path (*b*)] the extent depending upon the positions, and number of methoxy groups. The relative contributions of paths (*a*) and (*b*) have been determined generally by estimation of the distribution of deuterium in the 1- and 4-position of the tetrahydrocarbazole obtained when the deuteriated indolylbutanol (**1b**) (and its methoxy-substituted analogues) were used for the cyclisations. This analysis depended upon the assumption (amongst others experimentally verified) that during the cyclisation of the indolylbutanol (**1a**) and its methoxy analogues the conversion of the spirocyclic indolenine salt (**2a**) into the intermediate (**3a**) ($R^1 = R^2 = H$) is not reversible under the reaction conditions used. A small secondary deuterium isotope effect was observed in comparing the rates of the overall transformations of the indolylbutanols (**1a** and **b**) to the tetrahydrocarbazoles (**4b** and **c**). In other investigations of the electrophilic substitution of 3-methylindoles by arenediazonium salts, the products were 2-arylazo-3-methylindoles, and a significant primary isotope effect ($k_H/k_D = 2.7$) was observed when 2-deuterio-3-methylindole was compared with 3-methylindole.[6] For this reason we also decided to investigate the cyclisation of the 4-(2-deuterioindol-3-yl)butanol (**1c**); the azo coupling reactions were more complex and will be described in another paper.

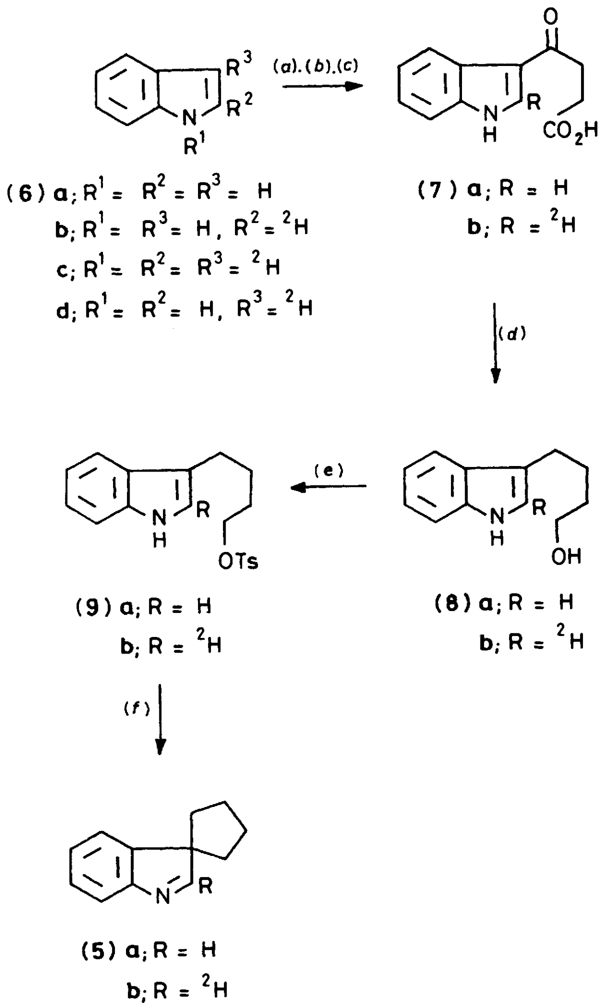


Scheme 1.

The cyclisation of the indolylbutanols (**1**) to spirocyclopentane-3'-indolenine (**2**) is almost certainly irreversible and under the conditions used for the earlier experiments the subsequent rearrangement to the intermediates (**3**) was also irreversible. Thus, in order to investigate whether or not there was a primary kinetic isotope in the final stage of the reaction *i.e.* (**3**) ⟶ (**4**) we decided to synthesize the 2-deuteriospiro[cyclopentane-3'-indolenine] (**5b**), and compare the rate of acid-catalysed formation of tetrahydrocarbazole (**4a**) with that from the undeuterated analogue (**5a**).

The indolenine (**5a**) was synthesized earlier as shown in Scheme 2 and this procedure followed essentially the same method as that used for the synthesis of analogues deuteriated in the cyclopentane ring.[3,7] It was also known[7] that the indolenine (**5a**) exists as an equilibrium mixture of the monomer and trimer (**10**), but that in the presence of a large excess of acid the equilibrium is very rapidly displaced completely in favour of the protonated monomeric species (**2a**). Moreover, the acid-catalysed rearrangements of a number of indolenines were found[1] to follow good first-order kinetics under these conditions.

The use of the established synthetic route[3,7] (see Scheme 2) for deuterioindolenine (**5b**) required 2-deuterioindole (**6b**) as the starting material. In 1973 Sundberg and Russell[8] described the lithiation of 1-phenylsulphonylindole (**11a**) at the 2-position,



(6) a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^3 = H$, $R^2 = {}^2H$
c; $R^1 = R^2 = R^3 = {}^2H$
d; $R^1 = R^2 = H$, $R^3 = {}^2H$

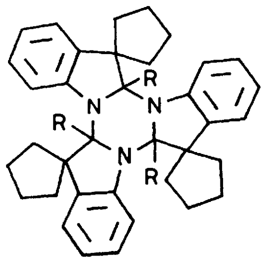
(7) a; R = H
b; R = ^2H

(8) a; R = H
b; R = ^2H

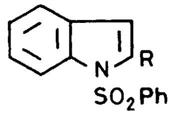
(9) a; R = H
b; R = ^2H

(5) a; R = H
b; R = ^2H

Scheme 2. *Reagents*: (*a*) EtMgI; (*b*) succinic anhydride; (*c*) H^+–H_2O; (*d*) $LiAlH_4$–THF; (*e*) toluene-*p*-sulphonyl chloride, pyridine; (*f*) $KOBu^t$, THF



(10) a; R = H
b; R = ^2H



(11) a; R = H
b; R = ^2H

and after quenching the lithio derivative with D_2O the 2-deuterio-1-phenylsulphonylindole (**11b**) was obtained in good yield. Indole was converted into its *N*-phenylsulphonyl derivative (**11a**) in 70—75% yield by treatment with potassium hydroxide in dry dimethyl sulphoxide (DMSO) followed by benzenesulphonyl chloride at low temperature.[9] The ^1H n.m.r. spectrum at 90 MHz showed a one-proton doublet, J 4 Hz, at δ 6.61 due to 3-H but the remaining aromatic protons, particularly the 2-H, were unresolved. The addition of a 0.3 molar equivalent of $Eu([^2H_9]fod)_3$, however, induced the separation of the 2-H signal at δ 8.07 as a clear doublet, J 4 Hz. As expected the 3-H doublet shifted to slightly lower field (δ 6.78). The 1-phenylsulphonylindole was lithiated with n-butyl-lithium in dry tetrahydrofuran (THF) at −78 °C and, after quenching of the lithio derivative with D_2O, the required 2-deuterio compound (**11b**) was obtained in 85% yield. Its ^1H n.m.r. spectrum in the presence of a 0.3 molar ratio of $Eu([^2H_9]fod)_3$ was identical with that of the non-deuteriated sample except that the signal at δ 8.07 was absent and the doublet formerly at δ 6.78 due to 3-H had collapsed to a sharp singlet. Careful analysis of the expanded spectrum indicated that the deuterium content at the indole 2-position was *ca.* 98%. The mass spectrum (see Experimental section) showed that the predominant species (m/z 259, 77%) corresponded to dideuteriation, but from the ions at m/z 116 (100) and 115 (1.2%) in the spectrum of (**11a**) and 117 (100) and 116 (3.5%) from (**11b**) it was clear that monodeuteriation had occurred in the indole ring to the extent of *ca* 98% in agreement with the ^1H n.m.r. analysis and that the second deuterium had entered the phenylsulphonyl group.

Basic hydrolysis of the *N*-phenylsulphonyl derivative gave 2-deuterioindole (**6b**) in 90% yield. The mass spectrum of the indole relative to that of the undeuteriated compound (**6a**) (see Experimental section) indicated that the deuterium content was 97% of that expected for complete deuteriation at the 2-position. This result was approximately confirmed by reconversion of a sample of (**6b**) into its *N*-phenylsulphonyl derivative and re-examination of its ^1H n.m.r. spectrum in the presence of shift reagent as previously described. This showed that the proton content at the 2-position was of the order of 2% of that at the 3-position. Hence essentially no loss of deuterium had occurred during the hydrolysis.

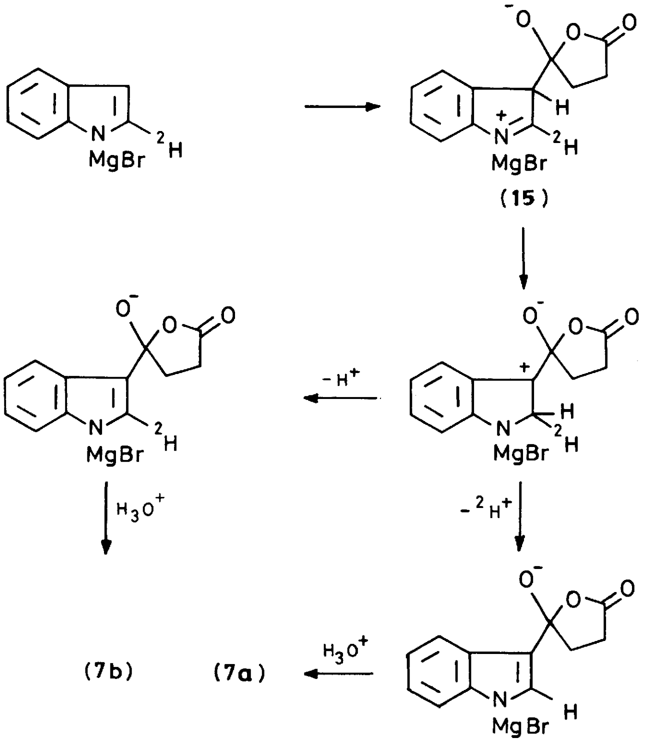
Following the sequence outlined in Scheme 2, the 2-deuterioindole (**6b**) was treated with ethylmagnesium iodide to give the indole Grignard reagent which, on acylation with succinic anhydride, gave the deuterioindolyloxobutanoic acid (**7b**) in 42% yield. The ^1H n.m.r. spectrum of the product was identical with that of the non-deuteriated compound except that the signal at δ 8.4 assigned to the indolyl 2-H was substantially reduced in size. Quantitative analysis showed that the proton content in the 2-position of the indole nucleus had risen to 18% of that at the 3-position, *i.e.* that there had been a significant (*ca.* 16%) loss of deuterium during the acylation. In a second experiment the loss of deuterium was 20% as judged by mass spectrometry and ^1H n.m.r. analysis.

A similar effect has been reported by Smith and Taylor,[10] who observed losses of 4—13% of deuterium from position 2 when 2-deuterioindole was sulphonated with the pyridine–SO_3 complex. This was shown not to be due to protonation of the starting deuterioindole or exchange during the work-up procedure. These effects are formally related to the N.I.H. shift in aromatic hydroxylation in which a very high isotope retention can be observed when the isotope (^2H or ^3H) displaced by the entering group migrates to an adjacent position. For example hydroxylation of [4-^3H]phenylalanine by phenylalanine hydroxylase produces tyrosine having >95% of ^3H in the 3-position.[11] The latter observation has been explained by the assumption of the intermediacy of arene oxides.

Chemical hydroxylation by electrophilic[12] and free-radical[13] reagents however leads to a very much reduced isotope retention. In particular Witkop *et al.*[12] observed a 7.5% retention of deuterium in the hydroxylation of *p*-deuterioacetanilide and rationalised this by an electrophilic mechanism in which the intermediate electrophile may either lose $^2H^+$ directly to give *p*-hydroxyacetanilide or undergo 1,2-anionotropic shift before loss of either $^2H^+$ or H^+, governed by the kinetic isotope effect, to give both undeuteriated and *m*-deuterioacetanilide.

A similar mechanism can be proposed to explain the results which we have described for the acylation of the indole

Grignard reagent, but in this instance the two alternative pathways, direct loss of H^+ or 1,2 migration, originate from an intermediate of type (**12**) (see Scheme 3). The slow exchange of the 2-H of indole itself in [$^2H_2$]sulphuric acid[14] may also be due to migration of ^2H from the [3-$^2H_2$]indolenine formed in the strong acid, rather than by direct substitution at the 2-position.



Scheme 3.

The 2-deuterioindole itself was also subjected to acylation under other, previously established conditions. Thus acetylation by acetic acid and acetic anhydride[15] and chloroacetylation with chloroacetyl chloride[16] gave 1,3-diacetyl-2-deuterioindole and 3-chloroacetyl-2-deuterioindole respectively, but with no significant loss of deuterium from the indole 2-position.

In order to avoid the loss of deuterium in the acetylation of the indole Grignard reagent it was decided to prepare 1,2,3-trideuterioindole (**6c**). It is known that deuterium exchange of indole occurs in acid at the 1- and 3-position[17] and 1,3-dideuterioindole has previously been obtained[7] in reasonable yield by treatment of indole with DCl in D_2O at 60 °C. By a modification of this method using 0.01M-DCl in D_2O at 60 °C for a short time it was possible to convert 2-deuterioindole (see above) (97% deuteriated at C-2) into 1,2,3-trideuterioindole in 88% yield.

The ^1H n.m.r. spectrum showed that the extent of deuteriation at C-3 was 97% whilst conversion of a sample of the *N*-phenylsulphonyl derivative and ^1H n.m.r. examination in the presence of shift reagent as described above indicated a 94% deuteriation at C-2. The slight loss of deuterium from the 2-position may be explained by some migration of hydrogen from the 3- to the 2-position during the exchange process at the 3-position.

Acetylation of the 1,2,3-trideuterioindolyl Grignard derivative as described previously gave again the deuterio-acid (**7b**). N.m.r. analysis of this sample showed that the proportion of hydrogen at the 2-position had slightly increased to 8%. This result was, however, significantly better than that obtained in the acid synthezised from 2-deuterioindole, and supports the proposal for migration of hydrogen from the 3-position outlined in Scheme 3.

The deuterioacid (**7b**) was reduced with a large excess of lithium aluminium hydride to the corresponding alcohol (**1c**) (83%) and n.m.r. analysis then revealed 11% of hydrogen at the indolyl 2-position. Tosylation of the deuteriated alcohol gave the deuteriotoluene-*p*-sulphonate (**9b**) (44%) which was cyclised[2] with potassium t-butoxide in dry THF to the required crystalline 2-deuterioindolenine (**5b**) (47%). The n.m.r. spectrum was identical to that of the non-deuteriated analogue (**5a**),[7] except that the signals at δ 4.23, 4.38, and 5.01, due to the protons in the indolyl 2-position in the trimer (**10a**), were of greatly reduced intensity; the hydrogen content at the indolyl 2-position was *ca.* 12%. The percentage deuteriation was less than that ideally required for investigation of the possible kinetic isotope effect on the rearrangement of the spiroindolenines (**5a** and **b**), but it was considered to be sufficiently high to provide a valid test.

The kinetics of the rearrangement of the indolenines (**5a** and **b**) in a large excess of ethanolic hydrochloric acid were measured at 30 °C; the concentration of the product tetrahydrocarbazole (**4a**) was measured from $\lambda_{max.}$ 230 nm. Under these conditions the reaction exhibits pseudo-first-order kinetics.[1] The results for the pseudo-first-order rate constants for 10 kinetic runs on the spiroindolenine (**5a**) and its deuteriated analogue (**5b**) were as follows:

	k_H for (**5a**)/s^{-1}	$k_{^2H}$ for (**5b**)/s^{-1}
mean	6.42×10^{-4}	5.95×10^{-4}
standard deviation	0.50×10^{-4}	0.27×10^{-4}

The experimental ratio k_H/k_D is 1.08. The loss of proton in the final step of the indolenine rearrangement is therefore not the rate-determining step. Indeed it is conceivable that the very small effect observed could be a secondary isotope effect on the first step (**3**) ⟶ (**4**) in the rearrangement of the spirocyclic indolenines (**2**) to tetrahydrocarbazole. It is concluded that the formation of the intermediate (**3**) (Scheme 1) during the cyclisation of indolylbutanols is followed by the relatively rapid loss of a proton or deuterium to give the tetrahydrocarbazole (**4a**). The rates of cyclisation of all the methoxy-substituted indolylbutanols so far studied are known to be of the same order of magnitude.[1–5] and thus it seems likely that the initial cyclisations are the rate-determining steps also.

Experimental

M.p.s are uncorrected. U.v. spectra were determined with Unican SP 800 or Carey-17 spectrophotometers; kinetic runs were all carried out with the latter instrument. N.m.r. spectra were determined with a Perkin-Elmer R32 90 MHz instrument, and mass spectra with a Varian CH 5D spectrometer by e.i. (at 70 eV and 200 °C) or f.d. (wire current 5—20 μA).

1-*Phenylsulphonylindole* (**11a**).—Crushed potassium hydroxide pellets (22.4 g) were added to DMSO (200 ml) and stirred for 5 min. A solution of indole (13.2 g) in dry ether (50 ml) was added dropwise and the mixture was stirred for 45 min. Benzenesulphonyl chloride (20 g) in dry ether (50 ml) was then added to the solution dropwise and the mixture was stirred at 20 °C for 30 min, after which water (200 ml) was added, and the ether layer separated. The aqueous layer was extracted with ether (3 × 150 ml), and the combined ethereal layers were washed with water (2 × 100 ml) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a yellow oil, which crystallised from hexane–ether (2:1) on cooling in a dry ice–acetone bath. Recrystallisation from methylene dichloride–hexane, using charcoal, gave the title compound (21.7 g, 75%),

Table. Mass spectra of indole (**6a**) and 2-deuterioindole (**6b**)

	Indole (**6a**) *m/z*	Relative abundance (%)	2-Deuterio-indole (**6b**) *m/z*	Relative abundance (%)
$M^+ + 1$	118	8.53	119	9.38
M^+	117	100	118	100
$M^+ - 1$	116	6.97	117	10.29
$M^+ - 2$	115	0.46	116	0.98

m.p. 77.5—79 °C (lit.,[8] m.p. 77.5—79 °C); δ 6.65 (1 H, d, indol 3-H), 7.20—7.65 (6 H, m, 2-, 5-, and 6-H indol and 2′-, 3′-, and 4′-H phenylsulphonyl moiety), and 7.84—8.10 (4 H, m, 4- and 7-H indol and 1′- and 5′-H phenylsulphonyl moiety). In the presence of 0.3M ratio of Eu([$^2H_9$]fod)$_3$ the signals shifted to 6.78 (1 H, d, J = 4 Hz, indol 3-H), 8.07 (1 H, d, J = 4 Hz, indol 2-H), 7.22—7.72 (6 H, m), and 8.33—8.49 (3 H, m); $\lambda_{max.}$(EtOH) 250 (ε 22 300 dm^3 mol^{-1} cm^{-1}), 275sh (6 600), 285sh (5 800), and 292sh nm (5 600); *m/z* 257 (M^+, 90%), 141 (31), 117 (13), 116 (100), 89 (24), 77 (52), and 51 (13).

1-*Phenylsulphonyl*-[2-^{2}H]*indole* (**11b**).—A solution of 1-phenylsulphonylindole (**11a**) (10.0 g, 38.0 mmol) in dry THF (150 ml) was cooled to −78 °C (solid CO$_2$–acetone bath). To this solution n-butyl-lithium (50.0 ml; 1.5M in hexane) was added dropwise with vigorous stirring under nitrogen using a syringe and the temperature was maintained at −78 °C during the addition. The resulting orange solution was allowed to warm to 20 °C and stirred for 2 h before cooling to −78 °C (during which time a solid separated out) and D$_2$O (5 ml, 0.25 mol) was added using a syringe. The mixture was allowed to warm to 20 °C again and dry ether (400 ml) was added with stirring followed by anhydrous potassium carbonate. When the ethereal layer was clear the solid was filtered off and the filtrate was evaporated under reduced pressure to give, after two crystallisations from ether, 1-phenylsulphonyl-[2-^{2}H]indole (8.5 g, 85%) as crystals, m.p. 81.5—82.5 °C.

The n.m.r. spectrum in the presence of 0.3M ratio of Eu([$^2H_{27}$]fod)$_3$ was identical to that of the non-deuteriated sample except that the signal at δ 8.07 was absent indicating deuteriation at C-2 and the doublet at δ 6.78 assigned to the proton at the 3-position had reduced to a sharp singlet. Analysis of the 2- and 3-H signals by tracing and weighing showed that the proton content at the 2-position was ⩽2%, *m/z* 261 (M^+ + 2, 5%), 260 (M^+ + 1, 14), 259 (M^+, 77), 142 (29), 118 (12), 117 (100), 90 (20), 89 (12), 78 (54), 63 (11), and 53 (11). The mass spectrum indicated that polydeuteriation had occurred, but the n.m.r. spectra showed that the additional deuterium was in the phenylsulphonyl group.

[2-^{2}H]*Indole* (**6b**).—A mixture of (**11b**) (17.0 g, 66 mmol) in methanol (250 ml) and 2M-NaOH solution (70 ml) was heated to reflux under nitrogen for 6 h. The mixture was cooled and poured into water (300 ml) and extracted with ether (6 × 100 ml) and dried before evaporation of the solvent under reduced pressure to give a solid (7.5 g). After crystallisation from light petroleum (b.p. 40—60 °C) [2-^{2}H]indole (7.0 g, 90%) was obtained as plates, m.p. 49.5—50.5 °C; δ 6.48 (1 H, d, J 2 Hz. indol 3-H), 7.0—7.25 (3 H, m, indol 5-, 6-, and 7-H), 7.5—7.7 (1 H, m, indol 4-H), and 8.0 (1 H, br s, NH). The n.m.r. spectrum of this compound was identical to that of the non-deuteriated one except that the signal at δ 6.95 due to the proton at the 2-position was absent indicating complete deuteriation at C-2.

[3-^{2}H]*Indole* (**6d**).—A suspension of indole (1.0 g, 8.5 mmol) in 0.01M-DCl in D$_2$O (10 ml) was stirred for 4 h at 60 °C under nitrogen. The mixture was cooled to 20 °C and the indole was recovered by extraction with dry ether (4 × 20 ml) followed by evaporation of the solvent from the combined extracts under reduced pressure. The residue was treated with fresh deuteriating solution and the process repeated twice with 0.01M-DCl in D$_2$O (8 and 6 ml, respectively). After drying (MgSO$_4$) of the final ethereal extracts, the solvent was removed under reduced pressure to leave a residual oil (0.9 g) which was crystallised twice from light petroleum (b.p. 40—60 °C) to give 1,3-dideuterioindole (0.54 g, 54%) as plates, m.p. 48—50 °C.

A mixture of the above indole (0.54 g, 4.5 mmol) in ether (5 ml) and water (10 ml) was stirred at 20 °C for 2 h. The mixture was then extracted with ether (4 × 10 ml), dried, and the solvent was evaporated off under reduced pressure. The residue was crystallised from light petroleum (b.p. 60—80 °C) to obtain [3-^{2}H]indole (0.48 g, 89%) as plates, m.p. 48—49 °C. The n.m.r. spectrum of this compound was identical to that of the non-deuteriated sample except that the signal at δ 6.48 due to the proton at the 3-position was very small. Analysis of the peak area at δ 6.48 in comparison with the peak areas at δ 6.95 due to the proton at the 2-position and δ 7.5—7.7 due to the indole 4-H showed that the proton content at the 3-position was ⩽3%, *m/z* 118 (M^+, 100%), 117 (M^+ − 1, 16), 116 (1), 91 (29), 90 (27), and 89 (8).

[1,2,3-$^2H_3$]*Indole* (**6c**).—A suspension of [2-^{2}H]indole (98% deuterium; 5.0 g, 42 mmol) in 0.01M-DCl in D$_2$O (10 ml) was stirred for 3 h at 60 °C under nitrogen. The mixture was cooled to 20 °C and the indole was recovered by extraction with dry ether (4 × 50 ml) followed by evaporation of the solvent from the combined extracts under reduced pressure. The residue was treated with fresh deuteriating solutions and the process was repeated twice with 0.01M-DCl in D$_2$O (8 ml for 2 h and 6 ml for 1.5, respectively). After drying (MgSO$_4$) of the final ethereal extracts, the solvent was evaporated off under reduced pressure to give a solid (4.8 g) which was crystallised from light petroleum (b.p. 60—80 °C) to afford 1,2,3-trideuterioindole (4.4 g, 88%) as plates, m.p. 49—51 °C. The n.m.r. spectrum of this compound was identical to that of the non-deuteriated sample except that the signals at δ 6.48, 6.95, and 8.0 corresponding to protons at the 3-, 2-, and 1-position respectively were reduced greatly in size. Expansion of the region between δ 6.0—8.5 followed by integration of the peak area at δ 6.48 and a comparison with the area of the protons at the 4-, 5-, 6-, and 7-position indicated the hydrogen content at the 3-position was only 3%.

1-*Phenylsulphonyl*-[2-^{2}H]*indole from* [2-^{2}H]*indole*.—In a similar manner to that described for the non-deuteriated compound, using [2-^{2}H]indole (0.17 g, 1.4 mmol) 1-phenylsulphonyl-[2-^{2}H]indole was obtained in 70% yield, m.p. 76—77 °C. The n.m.r. spectrum of this compound in the presence of 0.3M ratio of Eu([$^2H_{27}$]fod)$_3$ was identical to that of the non-deuteriated sample except that the signal at δ 8.07 due to the proton at the 2-position was absent and the doublet at δ 6.78 corresponding to indole 3-H had reduced to a sharp singlet. Analysis of the 2- and 3-H signals by tracing and weighing showed that there was ⩽2% residual hydrogen at the 2-position. This result indicated that no loss of deuterium had occurred during the hydrolysis of 1-phenylsulphonyl-[2-^{2}H]indole with 2M-NaOH solution.

1-*Phenylsulphonyl*-[2,3-^{2}H]*indole*.—In a similar manner to that described for the non-deuteriated compound, using 1,2,3-trideuterioindole (0.17 g, 1.4 mmol) 1-phenylsulphonyl-[2,3-^{2}H]indole (68%) was obtained, m.p. 79—81 °C. The n.m.r. spectrum of this compound in the presence of 0.3M ratio of Eu([$^2H_{27}$]fod)$_3$ was identical to that of the non-deuteriated sample except that the signals at δ 8.07 and 6.78 were reduced greatly in size. Expansion of the region between δ 6.0—8.5 followed by several integrations of the peak areas at δ 8.07 and 6.78 and comparison with the area of the remaining aromatic signals indicated a hydrogen content at C-2 of 6% and at C-3 of 3%. It can be deduced that there was a small loss of deuterium at the 2-position during the exchanging process of [2-^{2}H]indole with 0.01M-DCl in D_2O.

4-(*Indol*-3-*yl*)-4-*oxobutanoic acid* (**7a**).—Ethyl iodide (32.0 g, 0.20 mol) was added dropwise with stirring to Mg turnings (5.0 g, 0.20 mol) in dry anisole (70 ml) and the mixture was warmed gently until the reaction started. When all the magnesium had dissolved the solution was cooled and indole (23.0 g, 0.20 mol) in dry anisole (50 ml) was added dropwise and the temperature was raised to 70 °C for 30 min to complete reaction. After the mixture had been cooled to 20 °C succinic anhydride (20.0 g, 0.20 mol) in anisole (100 ml) was added rapidly with vigorous stirring. The mixture became hot and a bright red complex was formed. After being heated at 100 °C for 1 h the mixture was cooled and poured into glacial acetic acid (30 ml) and water (150 ml). The oxo-acid which precipitated was filtered off and washed (water) until the washings were neutral. The residual solid was dissolved in aqueous 10% NaOH. The oxo-acid was reprecipitated with SO_2, filtered off, washed (water) until the washings were neutral, and dried (air). Two crystallisations from ethanol gave the required acid as off-white needles (19.0 g, 45%), m.p. 241—242 °C (lit.,[2] 240—241 °C) (Found: C, 66.3; H, 5.3; N, 6.1. Calc. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.1; N, 6.45%); δ([$^2H_6$]DMSO) 2.60 (2 H, t, *J* 6 Hz, CH_2CO_2H), 3.15 (2 H, t, *J* 6 Hz indol–CO–CH_2), 7.22 (2 H, m, indol 5-, 6-H), 7.50 (1 H, m, indol 7-H), 8.20 (1 H, m, indol 4-H), 8.40 (1 H, d, *J* 3 Hz, indol 2-H), and 11.87 (1 H, br s, NH); $\lambda_{max.}$ 240 (ε 12 600), 260sh (9 200), 270 (7 000), and 295 nm (12 100); *m/z* 217 (*M*, 24%), 144 (100), 116 (11), and 89 (11).

4(-[2-^{2}H]*Indol*-3-*yl*)-4-*oxobutanoic acid* (**7b**).—(*a*) *From* [2-^{2}H]*indol* (**6c**). In a similar manner to that described for the non-deuteriated compound, using [2-^{2}H]indole (0.33 g, 98% [2-^{2}H]) the oxo-acid was obtained in 42% yield, m.p. 239—240 °C. The n.m.r. spectrum of this compound was identical to that of the non-deuteriated sample except that the signal at δ 8.4 due to the indol 2-H was very small. The area of the proton signals at δ 8.4 and 8.2 (due to the indol 4-H) were measured accurately by tracing and weighing. It was found that the deuterium content in the 2-position had fallen to 82%.

(*b*) *From* [3-^{2}H]*indole* (**6d**). In a similar manner to that described for the non-deuteriated compound, using [3-^{2}H]-indole (0.33 g, 97% [3-^{2}H]) the oxo-acid was obtained in 43% yield, m.p. 236—238 °C. The n.m.r. spectrum of this compound was identical to that of the non-deuteriated sample. Expansion of the signal area at δ 8.4 and comparison with 4-H indolic signal at δ 8.2 showed that the proton content in the 2-position was 97%; *m/z* 218 (M^+, 13%), 217 ($M^+ - 1$, 71), 146 (4), 145 (41), 144 (100), 143 (7), 117 (8), 116 (28), 115 (87), and 89 (24). Comparison of the mass spectrum of this compound with that of the non-deuteriated sample showed that there was no change in the deuterium content at the 2-position; $\lambda_{max.}$ 240 (ε 12 600), 260sh (9 200), 270 (7 000), and 295 nm (12 100); *m/z* 217 (M^+, 24%), 144 (100), 116 (11), and 89 (11).

(*c*) *From* [1,2,3-$^2H_3$]*Indole* (**6c**). In a similar manner to that described for the non-deuteriated compound, using [1,2,3-$^2H_3$]-indole (3.3 g, 95% [1-^{2}H], 94% [2-^{2}H], 97% [3-^{2}H]) the oxo-acid was obtained in 40% yield, m.p. 246 °C. The n.m.r. spectrum of this compound was identical to that of the non-deuteriated analogue except that the signal at δ 8.4 (due to the proton at the 2-position) was greatly reduced in size. The area of the proton signals at δ 8.4 and 8.2 were measured in the usual manner and it was found that the deuterium content in the 2-position had fallen to 92%.

4-(*Indol*-3-*yl*)*butan*-1-*ol* (**8a**).—To a stirred suspension of lithium aluminium hydride (6.0 g, 0.16 mol) in dry THF (100 ml) was added dropwise a pre-heated solution of 4-(indol-3-yl)-4-oxobutanoic acid (**7a**) (5.0 g, 0.023 mol) in dry THF (100 ml). The mixture was heated to reflux for 1 h before cooling to 20 °C. Excess of lithium aluminium hydride was decomposed by adding dropwise a saturated Rochelle salt solution. The THF solution was decanted, and the aluminium salts were washed with ether (3 × 100 ml). The ether and the THF solutions were combined, washed with water (2 × 100 ml), and dried ($MgSO_4$) before removal of the solvent under reduced pressure to leave the crude solid 4-(indol-3-yl)butan-1-ol which crystallised from ether–light petroleum (b.p. 40—60 °C) to give the pure product as a solid (4.0 g, 90%), m.p. 31—33 °C (lit.,[3] 32—33 °C) (Found: C, 76.0; H, 8.25; N, 7.6. Calc. for $C_{12}H_{15}NO$: C, 76.15; H, 8.0; N, 7.4%); δ 1.6 (4 H, m, $CH_2CH_2CH_2OH$), 1.89 (1 H, br s, OH), 2.7 (2 H, t, *J* 7 Hz, indol CH_2), 3.53 (2 H, t, *J* 7 Hz, CH_2OH), 6.78 (1 H, d, *J* 2 Hz, indol 2-H), 7.11 (3 H, m, indol 5-, 6-, and 7-H), 7.55 (1 H, m, indol 4-H), and 8.0 (1 H, br s, NH); $\lambda_{max.}$ 224 (ε 36 000), 275sh (7 700), 283 (8 100), and 291sh nm (7 300); *m/z* 189 (M^+, 27%), 131 (12), and 130 (100).

4-([2-^{2}H]*Indol*-3-*yl*)*butan*-1-*ol* (**8b**). In a similar manner to that described for the non-deuteriated compound, but using 4-([2-^{2}H]-indol-3-yl)-4-oxobutanoic acid (2.5 g, 92% [2-^{2}H]), the required alcohol (**8b**) was obtained in 83% yield, m.p. 32—34 °C. The n.m.r. spectrum of this compound was identical to that of the non-deuteriated analogue except that the signal at δ 6.78 due to the proton at the 2-position was of lower intensity. Analysis of the peak areas at δ 6.78, 7.11, and 7.55 in the usual manner indicated that the deuterium content in the 2-position had fallen to 89%. This result indicated that some deuterium had been lost during the process of reduction.

4-(*Indol*-3-*yl*)*butyl Toluene*-p-*sulphonate* (**9a**).—To a stirred solution of 4-(indol-3-yl)butan-1-ol (2.0 g, 10.8 mmol) in dry pyridine (20 ml) was added toluene-4-sulphonyl chloride (3.0 g, 15.7 mmol) in portions, the temperature of the solution being maintained at −5 °C during the addition. The mixture was allowed to stir at 0 °C for 4 h before pouring into water (100 ml). Extraction into ether (3 × 100 ml), washing with water (3 × 100 ml), and drying (K_2CO_3) was followed by evaporation of the solvent under reduced pressure. The residual oil was dried under vacuum at 20 °C for 24 h. After crystallisation twice from ether–light petroleum (b.p. 40—60 °C) the pure 4-(indol-3-yl)-butyl toluene-*p*-sulphonate (**9a**) was obtained as off-white crystals (1.8 g, 50%), m.p. 65—66 °C (Found: C, 66.2; H, 6.3; N, 3.85. Calc. for $C_{19}H_{21}NO_3S$: C, 66.5; H, 6.2; N, 4.1%); δ 1.66 (4 H, m, $CH_2CH_2CH_2OTs$), 2.36 (3 H, s, Me), 2.66 (2 H, m, indol–CH_2), 4.0 (2 H, m, CH_2OTs), 6.84 (1 H, d, *J* 2 Hz, indol 2-H), 7.0—7.4 (3 H, m, indol 5-, 6-, and 7-H), 7.26 (2 H, d, *J* 9 Hz, aromatic protons *ortho* to Me), 7.5 (1 H, m, indol 4-H), 7.75 (2 H, d, *J* 9 Hz, aromatic protons *meta* to Me), and 7.95 (1 H, br s, NH); $\lambda_{max.}$ 224 (ε 37 500), 227 (35 400), 245 (3 100), 274sh (6 700), 284 (6 700), and 292sh nm (5 800); *m/z* 172 (6%), 171 (50), 170 (15), 144 (10), 143 (100), and 130 (13).

4-([2-^{2}H]*Indol*-3-*yl*)*butyl Toluene*-p-*sulphonate* (**9b**).—In a similar manner to that described for the non-deuteriated compound but using 4-([2-^{2}H]indol-3-yl)butan-1-ol (1.4 g, 89% [2-^{2}H]) the required toluene-*p*-sulphonate was obtained in 44% yield, m.p. 66—67 °C. The n.m.r. spectrum of this compound was identical to that of the non-deuteriated sample except that the signal at δ 6.84 due to the proton at the 2-position was, as expected, of lower intensity. By analysis of the proton signals at δ 6.84 and 7.5 (due to the indol 4-H) in the usual manner it was found that the deuterium content in the 2-position had fallen to 88.5%.

Spiro[cyclopentane-3′-indolenine] (**5a**).—Potassium-t-butoxide solution [potassium (6.7 g, 0.17 mol) in dry t-butyl alcohol (145 ml) heated under reflux for 4 h] (3.5 ml) was added to dry THF (20 ml). The solution was stirred at 20 °C and treated during 10 min with a solution of 4-(indol-3-yl)butyl toluene-*p*-sulphonate (1.50 g, 4.4 mmol) in dry THF (20 ml); during the addition a solid separated out. The mixture was then stirred at 20 °C for 1 h before being poured into water (100 ml). Extraction with ether (3 × 100 ml), washing with water (2 × 100 ml), and drying ($MgSO_4$) was followed by removal of the solvent under reduced pressure to give the title compound as an oil, which was crystallised twice from acetone to give the pure product as crystals (0.6 g, 77%), m.p. 148—150 °C (lit.,[6] 146 °C); (Found: C, 84.2; H, 7.8; N, 7.95. Calc. for $C_{12}H_{13}N$: C, 84.2; H, 7.65; N, 8.2%); δ 1.8 [24 H, m, 3($CH_2CH_2CH_2CH_2$)], 4.23 (1 H, s), 4.38 (1 H, s), 5.01 (1 H, s), 5.77 (1 H, m), 6.13 (1 H, d, *J* 8 Hz), and 6.4—7.25 (10 H, m).

The n.m.r. spectrum of this compound showed almost exclusively signals assignable to the trimeric form; $\lambda_{max.}$ 215 (ε 13 900), 220 (15 200), 255 (20 000), and 302 nm (5 700); *m*/*z* 172 (7%), 171 (56), 149 (19), 144 (11), 143 (100), 129 (15), and 115 (17).

At source temperature 200 °C, the spectrum corresponded to the monomer.

[2′-^{2}H]*Spiro[cyclopentane-3′-indolenine]* (**5b**).—In a similar manner to that described for the non-deuteriated compound, using 4-[2-^{2}H]indol-3-ylbutyl toluene-*p*-sulphonate (0.85 g, 88.5% [2-^{2}H]) the required product was obtained in 70% yield m.p. 148—149 °C. The n.m.r. spectrum of this compound was identical to that for the non-deuteriated one except that the signals at δ 4.23, 4.38, and 5.01 corresponding to the 2-H of the trimer were greatly reduced in size. Analysis of the peak areas at δ 4.23, 4.38, and 5.01, and comparison with the peak area of the remaining aromatic protons indicated that the proton content at the 2-position was ⩽12%.

1,3-Diacetylindole was prepared from indole (2.0 g) by the procedure described by Saxton[15] in 44% yield, m.p. 147—149 °C (lit.,[15] m.p. 150—151 °C); δ([$^2H_6$]acetone) 2.55 (3 H, s, COMe), 2.80 (3 H, s, NCOMe), 7.22—7.32 (2 H, m, indol 5- and 6-H), 8.28—8.48 (2 H, m, indol 7- and 4-H), and 8.60 (1 H, s, indol 2-H); *m*/*z* 202 (M^+ + 1, 4%), 201 (M^+, 35), 160 (3), 159 (28), 145 (11), 144 (100), 143 (2), 117 (5), 116 (12), 115 (5), 89 (10), and 44 (43).

1,3-Diacetyl-[2-^{2}H]indole was prepared from [2-^{2}H]indole (0.4 g, 89% [2-^{2}H]) by the procedure described by Saxton[15] in 41% yield, m.p. 148—150 °C (lit.,[15] m.p. 150—151 °C). The n.m.r. spectrum in [$^2H_6$]acetone was identical with that of the undeuteriated compound except that the signal at δ 8.60 corresponding to the indole 2-H was greatly reduced in size. Expansion of the signal area and comparison with the signal at δ 8.28—8.48 corresponding to the indole 4- and 7-H signals showed 11% H retention. This was confirmed by the mass spectrum, *m*/*z* 202 (M^+, 36%), 201 (4), 160 (30), 159 (4), 146 (11), 145 (100), 144 (14), 118 (5), 117 (13), 116 (5), 115 (2), 90 (9), 89 (6), and 42 (45), from which it can be deduced that no exchange of isotopes has occurred at position 2 during the reaction.

3-Chloroacetylindole was prepared from indole and chloroacetyl chloride catalysed by pyridine according to the procedure described by Bergman.[16] This compound was obtained in 50% yield after recrystallisation from ethanol, m.p. 232—233 °C (lit.,[16] m.p. 230—232 °C); δ([$^2H_6$]acetone) 4.76 (2 H, s, CCH_2Cl), 7.20—7.30 (2 H, m, indol 5- and 6-H), 7.50—7.60 (1 H, m, indol 7-H), 8.42—7.28 (2 H, m, indol 4- and 2-H), and 11.80 (1 H, br s, indol 1-H); *m*/*z* 195 (M^+ ^{37}Cl, 9%), 193 (M^+ ^{35}Cl, 29), 145 (11), 144 (100), 143 (2), 130 (7), 116 (18), and 89 (15).

3-Chloroacetyl-[2-^{2}H]indole was prepared by the above method from [2-^{2}H]indole (96% [2-^{2}H]) in 46% yield, m.p. 232—233 °C (lit.,[16] m.p. 230—232 °C). The n.m.r. spectrum in [$^2H_6$]acetone was identical with that of the undeuteriated compound except that the signal corresponding to indole 2-H could not be distinguished from that of the neighbouring 4-H (δ 8.42 and 7.28). The region from δ 7.4—8.5 was expanded and the area of the higher field signal corresponding to the indole 7-H was found to be *ca.* 1.04 times greater than the lower field multiplet of the combined 2- and 4-H, from which it can be deduced that no exchange of isotopes has occurred at position 2 during the chloroacetylation. This was confirmed by mass spectrometry, *m*/*z* 196 (9%), 194 (28), 193 (1), 146 (11), 145 (100), 144 (6), 117 (18), 116 (4), and 90 (13).

Kinetic Studies of the Rearrangement of the Spirocyclic Indolenines (**5a**) *and* (**5b**) *to Tetrahydrocarbazole* (**4a**).—The kinetics of the rearrangement of the undeuteriated and deuteriated indolenine to 1,2,3,4-tetrahydrocarbazole were measured at 30 °C by the appearance of the tetrahydrocarbazole u.v. absorption at 225 nm, using a Cary 17 spectrophotometer. The indolenine (1.3 mg) was dissolved in absolute ethanol (250 ml); 2 ml of this solution were transferred into a 10 mm u.v. cell and placed in a water-jacketed cell holder in the spectrophotometer, which was maintained at 30 °C by the circulation of water from a thermostat bath. Ethanolic hydrochloric acid [concentrated hydrochloric acid (5 ml) in absolute ethanol (50 ml)] (1 ml) was added to the indolenine solution, mixed well, and the timing started. Typical first-order kinetics were observed.

References

1 Part 12, A. H. Jackson and P. P. Lynch, preceding paper.
2 A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.
3 R. Iyer, A. H. Jackson, B. Naidoo, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 2*, 1973, 872; R. Iyer, A. H. Jackson, and P. V. R. Shannon, *ibid*, p. 878.
4 J. S. L. Ibaceta-Lizana, R. Iyer, A. H. Jackson, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 2*, 1978, 733.
5 D. Clack, A. H. Jackson, N. Prasitpan, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 2*, 1982, 909.
6 A. H. Jackson, P. P. Lynch, and K. A. F. Record, unpublished work.
7 A. H. Jackson and B. Naidoo, *Tetrahedron*, 1969, **25**, 4843.
8 R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, 1973, **38**, 3324.
9 H. Heaney and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1973, 499.
10 G. F. Smith and D. A. Taylor, *Tetrahedron*, 1973, **29**, 669.
11 G. Guroff, C. A. Reifsnyder, and J. W. Daly, *Biochem. Biophys. Res. Commun.*, 1966, **24**, 720.
12 D. Jerina, J. Daly, W. Landis, B. Witkop, and S. Udenfriend, *J. Am. Chem. Soc.*, 1967, **89**, 3347.
13 J. A. Blair and A. J. Pearson, *J. Chem. Soc., Perkin Trans. 2*, 1975, 245.
14 R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, 1962, **84**, 2534.
15 J. E. Saxton, *J. Chem. Soc.*, 1962, 3592.
16 J. Bergman, J.-E. Backvall, and J.-O. Lindström, *Tetrahedron*, 1973, **29**, 971.
17 R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, 1964, **29**, 2437.

Received 11*th July* 1986; *Paper* 6/1384