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Electrophilic Substitution in Indoles. Part 14.[1] Azo-coupling of Indoles with *p*-Nitrobenzenediazonium Fluoroborate

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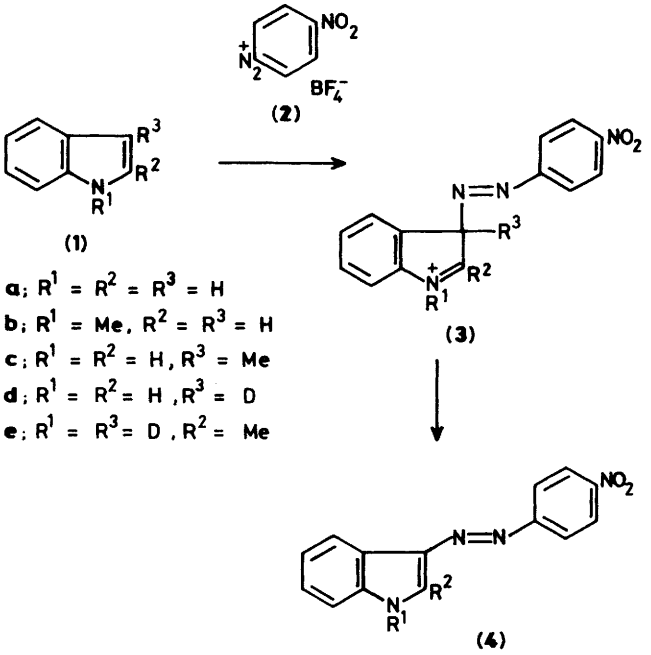
Indole and its 1- and 2-methyl derivatives undergo second-order azo-coupling reactions with *p*-nitrobenzenediazonium tetrafluoroborate to afford the corresponding indole-3-azo-(4′-nitrobenzenes). Kinetic studies with related 3-deuterioindoles showed that there is no isotope effect, thus confirming that the initial attack of the electrophile is the rate-determining step, as in the majority of electrophilic aromatic substitutions.

In contrast, 3-methylindole afforded 3-methylindole-2-azo-(4′-nitrobenzene) and the reaction not only showed a small deuterium isotope effect (*ca.* 2) but was also affected by base catalysis by water added to the acetonitrile. The difference in behaviour of the 3-methylindole from indole and its 1- and 2-methyl derivatives could be accounted for by a mechanism involving primary attack of the diazonium salt at the 3-position followed by rearrangement; further evidence for this mechanism was provided by the straight line plot obtained in comparisons of the rates of reactions for the four indoles with acidity functions (which reflect protonation at the 3-position).

In our earlier studies we have shown that many electrophilic substitution reactions of 3-alkylindoles proceed by attack at the 3-position followed by rearrangement, either of the incoming electrophile, or of the alkyl substituent already present to afford 2,3-disubstituted indoles.[2] Many of our previous investigations were concerned with alkylation reactions, but the same principles apply in other electrophilic substitutions, *e.g.* acylations,[3] reactions with aldehydes and ketones[4] (or the related imines[5]), reactions with α,β-unsaturated ketones,[6] halogenations,[7] and sulphenylations.[8] Most of our earlier work involved studies of intermediates and products; isotropically labelled substrates were also utilised and some kinetic studies were also carried out. In the present paper, we describe the azo-coupling of indoles as this can be readily studied kinetically; in this way the differences between the behaviours of 3-methylindole and 3-unsubstituted indoles have been compared and deductions made about the mechanisms of the reactions involved. The diazonium salt coupling reactions have the considerable advantage that they can be readily followed spectrophotometrically as the products are yellow or orange dyes. Moreover, the reactions have the advantage over some of the classical electrophilic substitution reactions of aromatic compounds, such as nitrations or halogenations, that no pre-equilibria are involved, and under the conditions which we used no buffering is required.

It has long been known[9] that indole (**1a**) itself forms indole-3-azo-(4-nitrobenzenes) (**4**) on coupling with benzenediazonium salts (*cf.* Scheme 1) and we have found that 3-methylindole (**5a**) also reacts with benzenediazonium salts to form the 3-methylindole-2-azo-(4′-nitrobenzenes) (**8**). We now describe our studies of the kinetics of the azo-coupling of 1-, 2-, and 3-methylindoles in comparison with that of indole itself using *p*-nitrobenzenediazonium salts in order to ascertain whether or not the formation of the 3-methylindole-2-azobenzene from the 3-methylindole involes initial substitution at the 3-position followed by rearrangement [path (a)] or direct substitution at the 2-position [path (b)] (*cf.* Scheme 2).



Scheme 1.

Previous kinetic studies of the coupling of indole with *p*-nitrobenzenediazonium chloride have been carried out by Binks and Ridd[10] who concluded that in aqueous solution it is the neutral molecule which is involved in the rate-determining step in the formation of the indole-3-azobenzene (**4a**). They also studied the azo-coupling of 3-deuterioindole (**1d**) and showed that there was no kinetic isotope effect, thus confirming that the coupling reaction was a typical example of an aromatic electrophilic substitution reaction, the formation of the Wheland-type intermediate (**3**) being rate-determining (Scheme 1).

In our initial studies, we also decided to utilise the *p*-nitrobenzenediazonium chloride. However, this was rather slow to react with indole in aqueous solution at neutral pH, whereas the readily prepared tetrafluoroborate salt reacted rapidly with all four indoles (**1a**—**c**) and (**5**) in aqueous ethanolic solution

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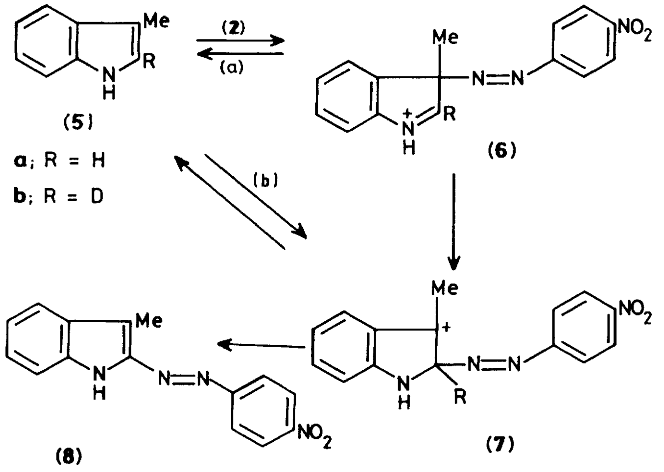

Scheme 2.

to give almost quantitative yields of the corresponding indole-3-azo-(4′-nitrobenzenes) (**4**) or the 3-methylindole-2-azo-(4′-nitrobenzene) (**8**) for the 3-methylindole. Ethanol was not, however, suitable for kinetic studies as the diazonium salt was unstable in dilute solutions in this solvent and the rate of decomposition appeared to be faster than the coupling reactions. Acetonitrile was, therefore, used instead, as it proved to be an excellent solvent for arenediazonium tetrafluoroborates, and moreover enabled the coupling reactions to be studied under essentially neutral conditions.

Preliminary studies showed that the coupling reactions of indole with *p*-nitrobenzenediazonium tetrafluoroborate in acetonitrile were second-order. In the presence of a large excess of either reactant, the azo-coupling reactions became pseudo-first-order and the results are given in Table 1 and the Experimental section. Similar kinetic behaviour was observed with *N*-methylindole (**1b**) and with 2-methylindole (**1c**) and neither 3-deuterioindole (**1d**) nor 1,3-dideuterio-2-methylindole (**1e**) showed a kinetic isotope effect. These results are in accord with Binks and Ridd's earlier observations[10] of the azo-coupling of indole, which were carried out in aqueous buffer solution over the pH range 3.8—6.2. Furthermore, the azo-coupling reactions of indole and 2-methylindole in acetonitrile did not show significant evidence of base catalysis.

The water concentration in the solvent, acetontrile, used for the majority of the kinetic runs was usually less than 0.01M, and increasing this to 2M resulted in increases in the second-order rate constants of the coupling of the diazonium tetrafluoroborate with indole and 2-methylindole by factors of 1.69 and 1.26 respectively. Good first-order behaviour was observed over some four half-lives in each case and it was, therefore, concluded that these small changes in rates could be attributed to a medium effect rather than to base catalysis by water.

Table 1. Azo-coupling of indole and its 1- and 2-methyl derivatives with *p*-nitrobenzenediazonium tetrafluoroborate in acetonitrile at 30 °C *

Indole	Second-order rate constant/dm^3 mol^{-1} s^{-1}
Indole (**1a**)	1.37 ± 0.02
3-Deuterioindole (**1d**)	1.36 ± 0.03
N-Methylindole (**1b**)	6.50 ± 0.13
2-Methylindole (**1c**)	435 ± 10
1,3-Dideuterio-2-methylindole (**1e**)	440 ± 15

* Full details of the azo-coupling reactions are given in the Experimental section.

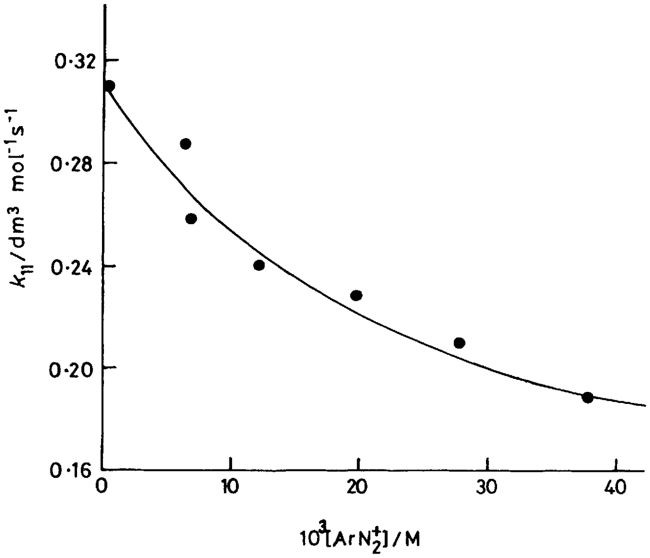

Figure 1. Variation of second-order rate constant with diazonium ion concentration for the coupling of 3-methylindole with *p*-nitrobenzenediazonium tetrafluoroborate in acetonitrile at 30 °C

A shortened version of Scheme 1 is shown in Scheme 3 and adopting the steady-state treatment originally suggested by Bodenstein, and developed by Melander[11] (for aromatic nitrations), the rate of formation of the aryl-2-azobenzene is given by equation (1) assuming that the concentration of the Wheland intermediate **C** is small. However, if the back reaction, k_{-1}, is small compared with k_2 then the equation reduces to (2). When this condition applies no primary isotope, or base catalysis, is expected and the reactions should show typical second-order kinetics. Our results all clearly accord with these predictions, as do those obtained earlier by Binks and Ridd,[10] and they confirm that the azo-couplings of these 3-substituted indoles are typical electrophilic aromatic substitution reactions in which the initial step (1) ⟶ (2) (Scheme 1) is rate-determining.

$$\mathbf{A} + \mathbf{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{C} \xrightarrow[k_2]{\text{base}} \mathbf{P}$$

A = Indole
B = Diazonium salt
C = Wheland intermediate (**6**)
P = Indoleazobenzene (**8**)

Scheme 3.

$$\frac{d[\mathbf{P}]}{dt} = \frac{k_1 k_2[\mathbf{A}][\mathbf{B}][\text{base}]}{k_{-1} + k_2[\text{base}]} \qquad (1)$$

$$\frac{d[\mathbf{P}]}{dt} = k_1[\mathbf{A}][\mathbf{B}] \qquad (2)$$

In contrast to the reactions of indole and its 1- and 2-methyl derivatives, the azo-coupling of 3-methylindole (**5a**) proved to be subject to base catalysis, the rate constants varied with the diazonium salt concentration, and 2-deuterio-3-methylindole (**5b**) showed a small kinetic isotope effect. Initial studies, carried out in acetonitrile containing <0.01M water, showed that 3-methylindole behaved in a pseudo-first-order fashion when treated with an excess of diazonium salt. However, when the water concentration was increased to 2M, or 6M, the 'first-order' plots showed appreciable deviations from straight lines, but crude estimates based on initial rate measurements indicated that the second-order rate constants increased by factors of 28

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Table 2. Azo-coupling of 3-methylindole and 2-deuterio-3-methylindole with *p*-nitrobenzenediazonium tetrafluoroborate in acetonitrile at 30 °C

3-Methylindole*				2-Deuterio-3-methylindole*				
10^3 [Indole] /M	10^3 [ArN_2^+] /M	10^2 k_1/s^{-1}	10^2 k_{11}/dm^3 mol^{-1} s^{-1}	10^3 [Indole] /M	10^3 [ArN_2^+] /M	10^2 k_1/s^{-1}	10^2 k_{11}/dm^3 mol^{-1} s^{-1}	k_H/k_D
1.37	0.52	1.65	31.7	1.74	0.52	0.97	18.7	1.70
1.37	18.7	4.10	21.9	1.74	18.7	1.81	9.66	2.27
1.37	34.6	7.44	21.5	1.74	34.6	2.61	7.52	2.86

* Duplicate or triplicate runs were carried out in each case and the results did not differ by more than ±2%. (Water concentration <0.01M).

and 37 respectively; somewhat lower estimates (20 and 24 respectively) were obtained from calculations based on the time to reach the first half-life. These estimates are rather imprecise but clearly show that base catalysis is taking place in the presence of water. Furthermore, the second-order rate constants of the azo-coupling reactions of 3-methylindole decreased with increasing diazonium salt concentrations as shown in Figure 1, whereas the second-order rate constants of the coupling reactions with indole and with 1- and 2-methylindole were independent of diazonium concentration (see Experimental section).

In contrast to the 3-unsubstituted indoles, it is the 2-proton of the indole which is eliminated in the coupling reactions of 3-methylindole. 2-Deuterio-3-methylindole (**5b**) was, therefore, prepared and coupled with the diazonium tetrafluoroborate. A small primary isotope effect (*ca.* 2—3) was observed and which increased with increasing diazonium salt ion concentration (Table 2).

It is difficult to account for these observations with 3-methylindole by a simple mechanism involving direct substitution at the 2-position followed by loss of the 2-H [path (b) in Scheme 2] in an analogous manner to substitution at the 3-position in the 3-unsubstituted indoles (**1**). The alternative possibility, of course, is that the reaction involves initial substitution at the 3-position followed by rearrangement of the azobenzene entity, and loss of the 2-H as shown by path (a) in Scheme 2. In principle, a similar kinetic treatment can be applied to this process, as that given in equation (1), but with the k_2 term referring to a composite rate for the two, essentially irreversible, steps of rearrangement (**6**) ⟶ (**7**), and proton loss (**7**) ⟶ (**8**).

An explanation for the deuterium isotope effect and base catalysis observed in the 3-methylindole coupling reactions is that steric effects in the initial intermediate (**6**) (Scheme 3) will lead to an increase in the back reaction k_{-1}, relative to k_2; the final step involving k_2[base] [*cf.* equation (1)] must also be at least partially rate-determining. It is interesting to note that in the azo-coupling of 8-substituted 2-naphthols kinetic isotope effects and base catalysis were also observed;[12] these reactions are not, of course, directly analogous as *ipso*-substitution is not involved but Zollinger[12] attributed the isotope effect and base catalysis to steric hindrance in the bond-making process so that k_{-1} became relatively large (compared with the situation in 8-unsubstituted 2-naphthols).

If the intermediates (**6**) or (**7**) (*cf.* Scheme 2) do not build up because k_{-1} is also large compared with k_2[base] then equation (1) reduces to equation (3) and the observed second-order rate constant is determined by equation (4). However, this is clearly not the case as the observed rate depends on the diazonium salt concentration (Figure 1), and is not directly proportional to the base concentration.

$$\frac{d[P]}{dt} = \frac{k_1k_2}{k_{-1}}[A][B][base] \qquad (3)$$

$$k_{11} = \frac{k_1k_2}{k_{-1}}[base] \qquad (4)$$

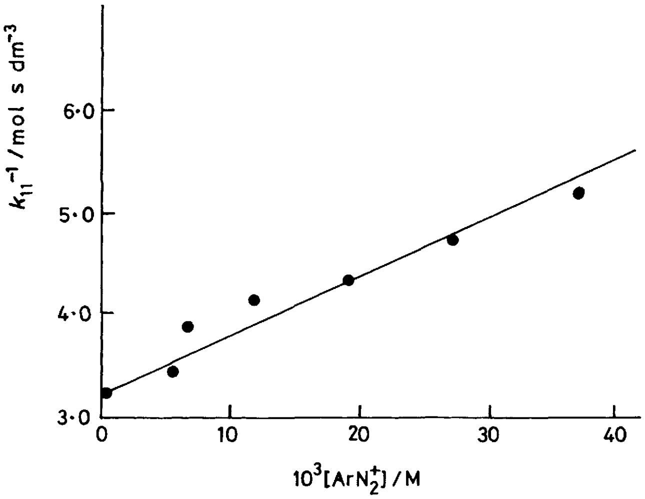

Figure 2. Variation of the reciprocal of the second-order rate constant with diazonium ion concentration for the coupling of 3-methylindole with *p*-nitrobenzenediazonium tetrafluoroborate in acetonitrile at 30 °C

An alternative possibility is that the intermediate (**6**) builds up somewhat and the rate expression can then be represented by equation (5), in the presence of a large excess of diazonium salt [**B**], and where the indole concentration is [A′] = [A] − [C]. Assuming a steady-state condition in which the 3-methylindole, the diazonium salt, and the intermediate (**6**) are in equilibrium, then equation (3) may be rewritten as equation (6). Combining equations (5) and (6), leads to expression (7). However, at a steady-state condition, **A′**, **B**, and **C** are related by the expression (8).

Combining this with equation (7) affords the new equation (9) relating the observed second-order rate constants k_{11} to the diazonium salt and base concentrations. This may be rewritten as in equation (10a) or (10b) and hence the reciprocal of the

$$\frac{d[P]}{dt} = k_{11}([A'] + [C])\,[B] \qquad (5)$$

$$\frac{d[P]}{dt} = \frac{k_1k_2[A'][B][base]}{k_{-1}} \qquad (6)$$

$$k_{11}([A'] + [C])\,[B] = \frac{k_1k_2[A'][B][base]}{k_{-1}} \qquad (7)$$

$$\frac{k_1}{k_{-1}} = \frac{[C]}{[A'][B]} \qquad (8)$$

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$$k_{11}([\mathrm{A}'] + \frac{k_1}{k_{-1}}[\mathrm{A}'][\mathbf{B}])[\mathbf{B}] = \frac{k_1k_2}{k_{-1}}[\mathrm{A}'][\mathbf{B}][\mathrm{base}] \quad (9)$$

$$\frac{1}{k_{11}} = \frac{k_{-1}}{k_1k_2[\mathrm{base}]} + \frac{[\mathbf{B}]}{k_2[\mathrm{base}]} \quad (10a)$$

or

$$\frac{1}{k_{11}} = \frac{1}{Kk_2[\mathrm{base}]} + \frac{[\mathbf{B}]}{k_2[\mathrm{base}]} \quad (10b)$$

where K, the equilibrium constant $= k_1/k_{-1}$

observed second-order rate constant ($1/k_{11}$) if plotted against the diazonium ion concentration [**B**] should give a straight-line relationship of slope $1/k_2$[base] and intercept k_{-1}/k_1k_2[base]. The validity of this kinetic analysis is highly dependent on the relative values of k_{-1} and k_2[base], and on the other assumptions made. However, a plot of $1/k_{11}$ against diazonium salt concentration is essentially a straight line, as shown in Figure 2 and leads to values for k_2 (3.9 ± 0.1 dm^3 mol^{-1} s^{-1}) and k_{-1}/k_1 for the first step ($5.4 \pm 0.4 \times 10^{-2}$) (although it is unfortunately not possible to derive the actual values k_{-1} and k_1). Other workers[13] have derived similar expressions to equation (10b) for reactions involving a preliminary equilibrium stage, followed by a first-order breakdown of the intermediate to give the final product. For example, Kuntz and Rouse[13b] in studying the reaction of aniline with 2,4-dinitrochlorobenzene used a somewhat different method to derive equation (11)

$$\frac{1}{k_{\mathrm{obs}}} = \frac{1}{Kk_2} + \frac{[\mathbf{B}]}{k_2} \quad (11)$$

relating the reciprocal of the observed second-order rate constant to the concentration of one of the components; they were considering a very similar overall scheme to that shown in Scheme 3, but where no base was involved in the final step leading to products.

The experimental results described above provide good evidence for the mechanism shown in path (a) Scheme 2, and for the validity of the kinetic analysis. More importantly, perhaps, this analysis, and the data shown in Figure 2, enable us to obtain an extrapolated value for the second-order rate constants k_{11} at zero diazonium salt concentration for use in comparisons of the relative rates of coupling of the four indoles. These vary in the order 2-methylindole > 1-methylindole > indole > 3-methylindole, *i.e.* much as one would expect from known basicities. A plot of the log of the second-order rate constants against either the pK_as,[14] or Hinman and Lang's[15] acidity constants (log H_0) of the indoles is shown in Figure 3. With 3-methylindole, the log k_{11} value was that obtained by extrapolation to zero diazonium salt concentration (*qv.* Figure 2) whereas in the other cases the log k_{11} values were obtained from simple determinations. Excellent correlations were obtained using either the pK_a values, or acidity constants, and this clearly suggests that the primary step in the reactions of 3-methylindole is the same as those of indole and the 1- and 2-methylindoles, *i.e.* initial *ipso*-substitution at the 3-position. This conclusion is strongly supported by other work carried out in Cardiff on the reactions of 3,3'-di-indolylmethanes which shows that a labile 3-alkyl residue can be displaced by a *p*-nitrobenzenediazonium salt to form the indole-3-azobenzene.[16]

Experimental

M.p.s are uncorrected. U.v. spectra were determined with either Unicam SP500 or SP800 spectrophotometers with 1 mm or 10 mm cells. N.m.r. spectra were determined with Varian A-60 or HA-100 instruments with Me$_4$Si as internal reference.

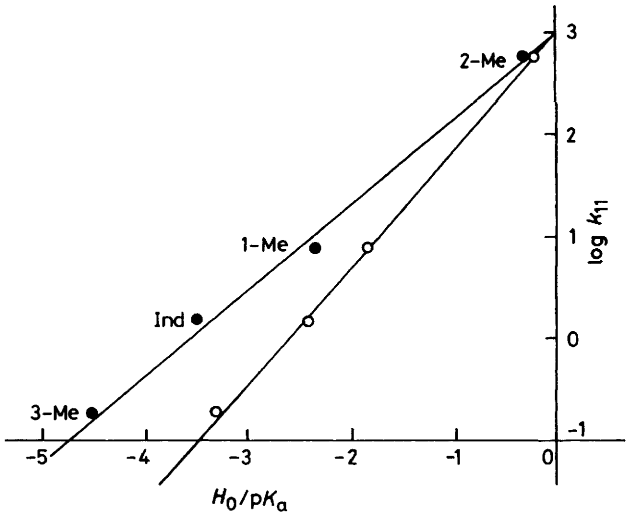

Figure 3. Coupling of *p*-nitrobenzenediazonium tetrafluoroborate with indole and its 1-, 2-, and 3-methyl derivatives: correlation of the second-order rate constants (k_{11}) with acidity functions [●: acidity constants (H_0), ○: pK_a]

Indoles.—Indole and 2- and 3-methylindole were commercial samples and were recrystallised from light petroleum (b.p. 60—80 °C) before use in the kinetic experiments: indole, m.p. 51—52 °C, 2-methylindole, m.p. 61 °C, and 3-methylindole, m.p. 94—95 °C.

N-*Methylindole* (**1b**). Sodium hydride (2.4 g, 0.1 mol) in dimethyl sulphoxide (DMSO) (50 ml) was added to a solution of indole (11.7 g, 0.1 mol) in DMSO (50 ml) followed by the addition of methyl iodide (16 g, 0.11 mol). After dilution with water (250 ml) the DMSO was acidified by the further addition of concentrated hydrochloric acid (50 ml). The mixture was extracted with ether (2 × 100 ml) and the ethereal extract dried (MgSO$_4$) and evaporated to dryness. The residual pale yellow oil was chromatographed on alumina in benzene and the major fraction was distilled to give *N*-methylindole (8.1 g, 65%), b.p. 55—60 °C/0.5 mmHg, lit.,[17] 70—75 °C/2 mmHg (Found: C, 82.35; H, 6.8; N, 10.7. Calc. for C$_9$H$_9$N: C, 82.4; H, 6.9; N, 10.7%).

3-*Deuterioindole* (**1d**). A suspension of indole (1 g) in D$_2$O (10 ml) and DCl (1 ml; 0.1M) was stirred for 4 h at 60 °C. The indole was recovered by extraction with ether and the process repeated twice with fresh deuteriating solutions. Deuterium was then removed selectively from nitrogen by treatment with aqueous potassium hydrogenphthalate (0.05M; pH 4). After ether extraction and evaporation of the solvent, the crude product was twice sublimed at 100 °C/0.1 mmHg, to give 3-deuterioindole (Found: C, 81.6; H + D, 6.3; N, 11.9. Calc. for C$_8$H$_6$DN: C, 81.4; H + D, 6.8; N, 11.6%); *m/z* 118 (100%) M^+, 117 (22), 92 (12), 91 (68), 90 (71), and 89 (28). The n.m.r. spectrum showed 7% residual hydrogen at the 3-position.

1-*Deuterio*-2-*methylindole*. Treatment of 2-methylindole with D$_2$O–DCl at pH 1 (as in the preceding preparation) for 5 h at 60 °C gave, after ether extraction and sublimation at 110 °C/0.1 mmHg, 1-deuterio-2-methylindole, m.p. 61 °C. The n.m.r. spectrum showed the absence of N–H but little exchange at the 3-position.

1,3-*Dideuterio*-2-*methylindole* (**1e**). Treatment of 2-methylindole with D$_2$O–DCl at pH 2.5 for 15 h at 60 °C gave, after ether extraction and sublimation at 110 °C and 0.1 mmHg, 1,3-dideuterio-2-methylindole. The n.m.r. spectrum showed 93%

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and 95% exchange at the 1- and 3-position respectively (relative to the 7-H).

Treatment with aqueous potassium hydrogen phthalate (0.05M; pH 4) partially exchanged both the 1- and 3-deuterium atoms about equally.

2-*Deuterio*-3-*methylindole* (**5b**). A solution of 3-methyloxindole (0.5 g) in dry tetrahydrofuran (25 ml) was added dropwise to lithium aluminium deuteride (0.5 g) in dry tetrahydrofuran (25 ml). The mixture was heated under reflux for 30 min and after cooling added cautiously to a mixture of crushed ice–water in a 600 ml beaker. The mixture was stirred for 1 h and then extracted with ether (3 × 50 ml). The ether extract was dried ($MgSO_4$), evaporated to dryness, and the crude product (0.24 g) chromatographed on a silica column in benzene. The indolic product obtained was sublimed at 120 °C/0.5 mmHg in a tube in a hot block to give 2-deuterio-3-methylindole (0.25 g), m.p. 93—95 °C (Found: C, 81.4; H + D, 7.5; N, 10.5. Calc. for C_9H_8DN: C, 81.8; H + D, 7.6; N, 10.6%). The n.m.r. spectrum showed that the 2-H (normally at δ 6.70) was absent. The spectrum was expanded, run on increased amplification, and repeat scanning showed that less than 0.5% residual hydrogen remained at the 2-position; m/z 132 (100%) (M^+), 131 (92), 130 (32), and 111 (10).

Indole-azobenzenes.—Indole-3-*azo*-(4′-*nitrobenzene*) (**4a**). (a) *p*-Nitroaniline (3 g) in dilute hydrochloric acid (325 ml; 0.9M) was diazotised at 0 °C with aqueous sodium nitrite (2.5 g) and added slowly to indole (2 g) in dilute potassium hydroxide solution (5 g/800 ml) containing crushed ice (200 g). The crude precipitate (1.4 g) was dried and part dissolved in benzene and chromatographed on alumina in benzene–5% ethanol. The first dark red band was eluted and, after evaporation of the solvent, the residue was recrystallised from aqueous alcohol to give indole-3-azo-(4′-nitrobenzenes). (b) *p*-Nitrobenzenediazonium tetrafluoroborate (4.6 g, 0.02 mol) was dissolved in ethanol (300 ml) and water (200 ml) and added to indole (2.5 g, 0.02 mol) in ethanol (200 ml) with stirring over a period of 20 min. A dark red precipitate formed which was filtered off, washed (water), and dried to give the crude product (5.7 g) which was shown by t.l.c. to consist essentially of one major component. This product was dissolved in hot benzene, filtered, and the solvent removed by evaporation. The red-brown solid obtained was chromatographed on silica on benzene–5% ethanol and the major red band collected and evaporated to dryness. The residue crystallised from aqueous ethanol to give indole-3-azo-(4′-nitrobenzene) as dark red needles, m.p. 196—199 °C (lit.,[10] m.p. 195—197 °C) (Found: C, 63.3; H, 3.8; N, 20.9. Calc. for $C_{14}H_{10}N_4O_2$: C, 63.3; H, 3.8; N, 21.1%); δ([$^2H_6$]DMSO) 12.9 (br s, NH), 8.96 (1 H, d, 4-H), 8.8 (3 H, m, 2-, 3′-, and 5′-H), 8.38 (2 H, d, *J* 8 Hz, 2′- and 6′-H), 7.95 (1 H, m, 7-H), and 7.7 (3 H, m, 2-, 5-, and 6-H); $\lambda_{max.}$(MeCN) 419 (log $\varepsilon_{max.}$ 4.44 $dm^3\ mol^{-1}\ cm^{-1}$) and 287 (4.15) nm.

2-*Methylindole*-3-*azo*-(4′-*nitrobenzene*) (**4c**). In a similar manner and using the same relative molar concentrations of 2-methylindole and *p*-nitrobenzenediazonium tetrafluoroborate, the crude product was obtained as described above and t.l.c. showed this to be essentially a single compound. After benzene extraction and evaporation of solvent as previously described the *title compound* (4.13 g, 69%) was obtained as dark red needles from aqueous alcohol, m.p. 228—230 °C (Found: C, 64.6; H, 4.45; N, 20.0. $C_{15}H_{12}N_4O_2$ requires C, 64.3; H, 4.3; N, 20.0%); δ([$^2H_6$]DMSO) 12.3 (br s, NH), 8.3 (1 H, m, 4-H), 8.28 and 7.90 (2 d, each 2 H, ABq, *J* 8 Hz, $C_6H_4NO_2$), 7.4 (1 H, m, 7-H), 7.2 (2 H, m, 5-, 6-H), and 2.77 (3 H, s, Me); $\lambda_{max.}$(MeCN) 432 (log $\varepsilon_{max.}$ 4.48 $dm^3\ mol^{-1}\ cm^{-1}$) and 259 (4.10) nm.

N-*Methylindole*-3-*azo*-(4′-*nitrobenzene*) (**4b**). This was obtained in a similar manner from *N*-methylindole and *p*-nitrobenzenediazonium tetrafluoroborate. It formed dark red crystals (5.68 g, 95%) from aqueous alcohol, m.p. 188—191 °C (Found: C, 64.15; H, 4.65; N, 20.2. $C_{15}H_{12}N_4O_2$ requires C, 64.3; H, 4.3; N, 20.0%); δ([$^2H_6$]DMSO) 8.52 (1 H, s, 2-H), 8.34 and 7.92 (2 d each 2 H, ABq, *J* 8 Hz, $C_6H_4NO_2$), 7.6 (1 H, m, 4-H), 7.35 (3 H, m, 5-, 6-, 7-H), and 3.92 (3 H, s, Me); $\lambda_{max.}$(MeCN) 421 (log $\varepsilon_{max.}$ 4.41 $dm^3\ mol^{-1}\ cm^{-1}$) and 287 (4.07) nm.

3-*Methylindole*-2-*azo*-(4′-*nitrobenzene*) (**8**). This was obtained in a similar manner from 3-methylindole and *p*-nitrobenzenediazonium tetrafluoroborate as red needles (5.39 g, 90%), m.p. 217—220 °C, from aqueous alcohol (Found: C, 64.45; H, 4.6; N, 20.2. $C_{15}H_{12}N_4O_2$ requires C, 64.3; H, 4.3; N, 20.0%); δ([$^2H_6$]DMSO) 11.52 (s, NH), 8.36 and 8.00 (2 d, each 2 H, ABq, *J* 8 Hz, $C_6H_4NO_2$), 6.69 (1 H, d, 4-H), 7.35 (2 H, m, 4- and 5-H), 7.1 (1 H, m, 6-H), and 2.77 (3 H, s, Me); $\lambda_{max.}$(MeCN) 426 (log $\varepsilon_{max.}$ 4.48 $dm^3\ mol^{-1}\ cm^{-1}$) and 250sh (3.79) nm.

Kinetics of the Azo-coupling of Indoles

Solvent. Acetonitrile was kept for 24 h over phosphorus pentaoxide and then distilled through a short column. The initial distillates were tested for free cyanide ion with silver nitrate solution. When the distillate, b.p. 82 °C, no longer showed the presence of cyanide or cloudiness it was collected. In this way, several litres of 'stock' solvent were obtained free from hydrocyanic acid and acetamide. The water content was considerably reduced and was estimated to be *ca.* 0.01M by titration with Karl Fischer reagent.

Preparation of solutions. (a) *Indoles in acetonitrile.* The indoles were chomatographed and either sublimed, or recrystallised and then dried *in vacuo* for 24 h before used. The standard solutions in acetonitrile was approx. 0.0001M (*ca.* 0.01 g/l). Dilution, usually by one part in fifty, gave an indole concentration such that a complete conversion into azoindole resulted in an optical density of about 0.5—0.7 at $\lambda_{max.}$ for the azoindole.

(b) p-*Nitrobenzenediazonium tetrafluoroborate in acetonitrile.* The tetrafluoroborate salt was prepared and purified as described, dried for 24 h *in vacuo*, and stored in dark bottles, sealed and kept in a desiccator. The tetrafluoroborate was soluble in absolute ethanol but decomposed, or reacted with the solvent fairly rapidly.[18] For this reason acetonitrile was chosen as solvent although, even so, the diazonium tetrafluroborate slowly decomposed over several days. Fresh solutions of the diazonium tetrafluoroborate, usually *ca.* 2×10^{-5}M (*i.e.* 10 × that of the indole solutions used for kinetic studies), were made up daily as required. The observed D_∞ values were compared with the D_∞ values expected for complete conversion of the indole concerned into the corresponding azoindole. The observed D_∞ value was usually greater than 95% of the expected D_∞ value. These results are thus consistent with quantitative conversion of the indoles to their azo-derivatives.

Procedure. The indole solution in acetonitrile (2.0 ml) was pipetted into a quartz or glass cell (1 cm) and the diazonium tetrafluoroborate salt solution (0.5 ml) pipetted into a marsupial tube of suitable capacity. Both the cell and the marsupial tube had ground glass joints as shown in the diagram. The solutions were then thermostatted in the cell holder of the

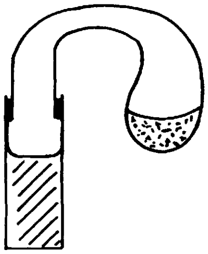

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Table 3. Azo-couplings of indole and its derivatives with *p*-nitrobenzene diazonium tetrafluoroborate in dry acetonitrile[a] at 30 °C

	10^5[Indole] /M	10^3[ArN_2^+] /M	10^3 k_1/s^{-1}	k_{11}/dm^3 mol^{-1} s^{-1}
Indole (**1a**)	1.52	27.6	37.6	1.36
	1.52	22.0	30.3	1.38
	1.52	12.7	17.9	1.40
	1.52	6.54	8.43	1.39
	1.52	6.14	8.41	1.37
	75.9	0.068	101	1.33
	Mean k_{11} = 1.37 ± 0.02 dm^3 mol^{-1} s^{-1}			
with 2M-H_2O	1.47	2.33	56.4	2.32
3-Deuterioindole (**1d**)	1.67	12.7		1.35
	1.52	0.25		1.37
	Mean k_{11} = 1.36 ± 0.01 dm^3 mol^{-1} s^{-1}			
N-Methylindole (**1b**)	1.70	0.41	2.7	6.67
	1.70	3.40	22.0	6.41
	1.70	19.0	125	6.55
	1.70	25.0	161	6.30
	8.48	0.0072	0.56	6.59
	Mean k_{11} = 6.50 ± 0.13 dm^3 mol^{-1} s^{-1}			
2-Methylindole (**1c**)	1.26	18.0	75.2	417
	1.26	1.85	81.9	447
	6.29	72.0	27.8	439
	63.0	778	35.0	437
	Mean k_{11} = 435 ± 0.10 dm^3 mol^{-1} s^{-1}			
with 2M-H_2O	63.0	778	42.7	549
1,3-Dideuterio-2-methylindole (**1e**)	78.9	778	34.5	440
3-Methylindole (**5a**)	1.37	36.8	6.99	0.19
	1.37	27.6	5.80	0.21
	1.37	19.0	4.37	0.23
	1.37	11.9	2.86	0.24
	1.37	6.52	1.69	0.26
	1.37	6.01	1.74	0.29
	1.37	0.31	0.96	0.31
	77.0	0.068	0.27	0.35
with 2M-H_2O	1.35	0.52	4.32[b] 3.01[c]	8.3[b] 5.79[c]
with 6M-H_2O	1.27	0.52	5.56[b] 3.54[c]	10.7[b] 6.81[c]
2-Deuterio-3-methylindole (**5b**)[d]				

[a] Water content 0.004M. [b] Estimated from initial rate. [c] Estimated from first half-life. [d] See Table 2.

spectrophotometer for 30 min. The solutions were mixed by inverting the assembly and shaking rapidly for about 10 s and the cell was returned to the cell holder.

The kinetics of the coupling reactions were followed by the photomeric estimation of the coupled product (azoindole) and shown to be first-order in diazonium ion and first-order in indole as had been observed by Binks and Ridd[10] using the diazonium chloride in aqueous solution. The main body of results was obtained by using an excess of diazonium salt and following the appearance of product.

The first-order rate constants were calculated from the rearranged integrated rate equation (see discussion) where D_t

$$\log(D_\infty - D_t) = -k_1 t + c$$

and D_∞ are the optical densities of azoindole at time *t*, and at the end of the reaction respectively. The first-order rate constant k_1 is thus calculated from the slope of the plot, log $(D_\infty - D_t)/t$. The second-order rate constant k_{11} was obtained by dividing the first-order coefficient by the diazonium ion or indole concentration, depending upon which was the reagent in excess.

Errors and reproducibility. The majority of the rates were run at least in duplicate and were reproducible to 3% although the reproducibility was slightly poorer in the azo-couping of 3-methylindole. The rate constants were calculated by the method of least-squares. For indole, and its *N*- and 2-methyl derivatives, the first-order plots showed good linearity for 3—4 half-lives in most of the coupling reactions. 3-Methylindole also showed good-first order plots in dry acetonitrile (<0.01M-H_2O) but the second-order rates varied with diazonium ion concentration, and in the presence of water the plots showed divergence from linearity (as described in the theoretical section).

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