Electrophilic *ipso*-Substitutions. Part 1. Reaction of 3-Substituted Indoles with Nitronium and Nitrosonium Ions

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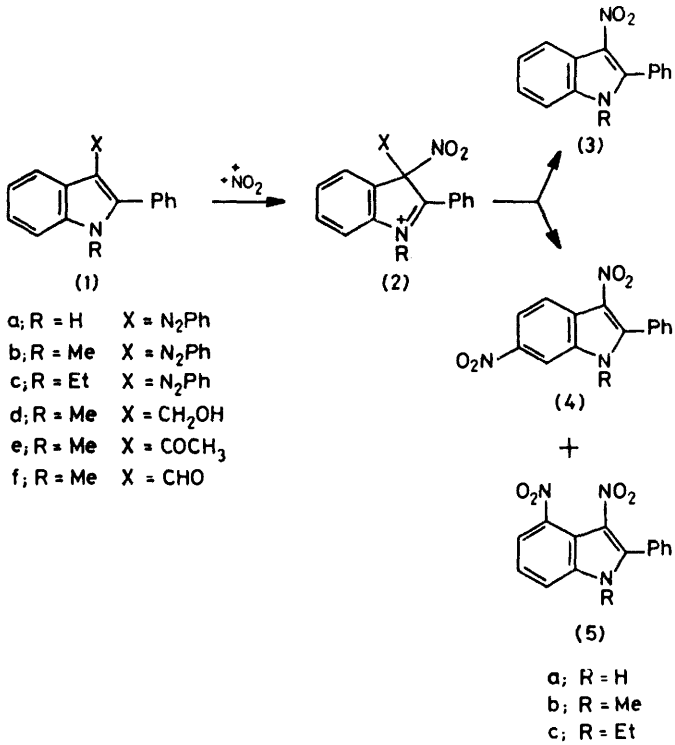
3-Substituted indoles react with nitronium and nitrosonium ions to yield 3-nitroindole. In both cases the reaction was interpreted as an electrophilic *ipso*-substitution. The reaction mechanism is interpreted by hypothesizing the formation of a σ-complex-like intermediate, which is some cases is preceded by an electron-transfer process. An order for the leaving abilities of the different electrofugal groups is discussed.

ELECTROPHILIC aromatic substitution of indoles has been studied extensively and occurs mainly at C-3 of the indole nucleus.[1] Until recently most attention was given to those nuclear substitutions in which C-3 was substituted by hydrogen, and other types of electrophilic substitutions in which the C-3 of the indole nucleus is substituted by groups other than hydrogen have been less studied.

To our knowledge only a few cases of electrophilic *ipso*-attack on the indole nucleus have been reported.[2-4] In this paper we describe a series of 3-substituted indoles which undergo electrophilic *ipso*-attack at C-3 by nitronium and nitrosonium ions to form 3-nitroindoles. Because of the similar reactivity of naphthols and indoles,[5] our study was suggested by the reaction of 1-phenylazo-2-methoxynaphthalene [6] with nitronium ion, which leads to 1-nitro-2-methoxynaphthalene through electrophilic *ipso*-attack.

RESULTS AND DISCUSSION

2-Phenyl-3-phenylazoindole (1a) and 70% nitric acid in a 1 : 2 ratio in acetic acid at room temperature give 2-phenyl-3-nitroindole (3a) [7] and 2-phenyl-3,6-dinitroindole (4a).[8] 2-Phenyl-3-nitroindole (3a) is formed by displacement of the diazo-group with nitronium ion; in fact the reaction solution reacts with an alkaline solution of 2-naphthol giving 1-phenylazo-2-naphthol. This electrophilic substitution takes place through a σ-complex (2) described in Scheme 1. 1-Methyl- (1b) and 1-ethyl-2-phenyl-3-phenylazoindole (1c) showed similar behaviour. The two 3-nitro-indoles (3b and c) were formed from (1b and c), respectively, in good yields (Table 1). In the case of (1b), 3,4-dinitroindole (5b) was also isolated and identified by n.m.r. (Table 2). Compounds (3b and c) were identified by comparison with



SCHEME 1

authentic samples prepared by *N*-alkylation of (3a). In all these reactions, when phenylazoindoles (1a—c) were mixed with nitric acid, a deep colour was observed, which disappeared with time, except in the case of (1c), in which it was still present after 70 h. In this case when the reaction was poured into water after 70 h, the starting materials were completely recovered, whereas when the solution was warmed for 30 min, compound (3c) was the only isolated product upon working up the reaction as described above. This behaviour can be explained by assuming for the σ-complex either easy formation or a particular stability in solution, due to the low leaving ability of the diazo-group. All attempts to isolate the σ-complex failed.

Compounds (1d—f) treated with nitric acid, as de-

TABLE 1

Reactions between 3-substituted indoles and nitric acid *

Compound	Reaction time (h)	Products [% yield]
(1a)	24	(3a)[a] [86]; (4a)[b] [14]
(1b)	50	(3b) [80]; (5b) [20]
(1c)	50	(3c)[a] [90]
(1d)	2	(3b) [35]
(1e)	72	(3b) [40]; (6) [30]; (7) [24]
(1f)	1.5	(3b) [15]; (8) [60]
(3b)	0.5	(4b) [81]
(9a)	24	(3b) [15]; (4b) [30]; (5b) [30]
(9b)	48	(3b) [26]; (4b) [30]; (5b) [24]
(13b)	96	(3b) [17]; (14) [6]

* All reactions were carried out at room temperature, except in the case of (1f) and (3b), for which the reaction mixture was heated at 60 °C.

[a] Ref. 7. [b] Ref. 8.

TABLE 2

Analytical and spectroscopic data

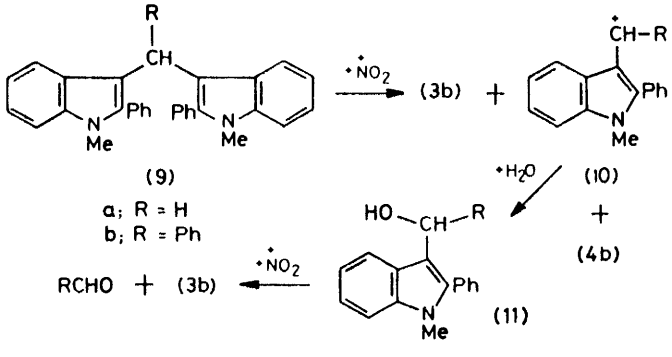
Compound *	M.p. (°C)	Formula	Found (%) †				Chemical shift (δ)
(3b)	119 [a]	$C_{15}H_{12}N_2O_2$	C, 71.0 (70.75)	H, 4.65 (4.52)	N, 11.0 (11.1)	$\nu_{max.}$/cm^{-1}	3.69 (3 H, s, NCH_3), 7.4—7.7 (8 H, m, arom), 8.37 (1 H, m, arom) [f]
(4b)	242 [b]	$C_{15}H_{11}N_3O_4$	C, 61.15 (60.6)	H, 3.9 (3.75)	N, 14.4 (14.15)		3.70 (3 H, s, NCH_3), 7.64 (5 H, s, arom), 8.30 br (2 H, arom), 8.73 br (1 H, arom) [g]
(5b)	221 [b]	$C_{15}H_{11}N_3O_4$	C, 60.85 (60.6)	H, 3.6 (3.75)	N, 14.25 (14.15)		3.68 (3 H, s, CH_3), 7.48—7.73 (6 H, m, arom), 8.0 (1 H, d, arom, *J* 7.5 Hz), 8.20 (1 H, d, arom, *J* 7.5 Hz) [g]
(6)	165 [b]	$C_{17}H_{14}N_2O_3$	C, 70.0 (69.6)	H, 4.85 (4.8)	N, 9.45 (9.5)	1674 [e]	1.88 (3 H, s, $COCH_3$), 3.63 (3 H, s, NCH_3), 7.68 (5 H, s, arom), 8.13 (1 H, pseudo-q, arom, *J* 8.5, 1.8 Hz), 8.47 (1 H, d, arom, *J* 8.5 Hz), 8.58 (1 H, d, arom, *J* 1.8 Hz) [g]
(7)	160 [b]	$C_{17}H_{14}N_2O_3$	C, 69.85 (69.6)	H, 4.65 (4.8)	N, 9.6 (9.5)	1674 [e]	1.90 (3 H, s, $COCH_3$), 3.61 (3 H, s, NCH_3), 7.30—7.67 (6 H, m, arom), 7.67 (1 H, d, arom, *J* 7.5 Hz), 7.98 (1 H, d, arom, *J* 7.5 Hz) [g]
(8)	233 [b]	$C_{16}H_{12}N_2O_3$	C, 68.45 (68.55)	H, 4.25 (4.3)	N, 10.05 (10.0)	1650 [e]	3.78 (3 H, s, NCH_3), 7.78 (5 H, s, arom), 8.1 (1 H, pseudo-q, arom, *J* 8.5, 1.8 Hz), 8.33 (1 H, d, arom, *J* 8.5 Hz), 8.6 (1 H, d, arom, *J* 1.8 Hz), 9.62 (1 H, s, CHO) [g]
(13b)	236 [c]	$C_{21}H_{16}N_4O_2$	C, 71.0 (70.75)	H, 4.65 (4.5)	N, 15.6 (15.7)		3.85 (3 H, s, NCH_3), 7.22—7.75 (8 H, m, arom), 8.04 (4 H, pseudo-q, A_2B_2, arom), 8.54–8.70 (1 H, m, arom) [h]
(13c)	186 [c]	$C_{22}H_{18}N_4O_2$	C, 71.2 (71.35)	H, 4.9 (4.9)	N, 15.2 (15.15)		1.40 (3 H, t, CH_2CH_3), 4.25 (2 H, q, CH_2CH_3), 7.2—7.58 (8 H, m, arom), 7.98 (4 H, pseudo-q, A_2B_2, arom), 8.50—8.72 (1 H, m, arom) [h]
(14)	259 [d]	$C_{15}H_{11}N_3O_4$	C, 60.7 (60.6)	H, 3.65 (3.75)	N, 14.05 (14.15)		3.68 (3 H, s, NCH_3), 7.62 (5 H, s, arom), 8.02 (1 H, d, arom, *J* 9.0 Hz), 8.30 (1 H, pseudo-q, arom, *J* 9.0, 2.2 Hz), 9.0 (1 H, d, arom, *J* 2.2 Hz) [g]

* All compounds gave correct molecular peaks in the mass spectra. † Calculated values in parentheses.

[a] From ligroin, b.p. 100—140 °C. [b] From C_6H_6. [c] From EtOH. [d] From $CHCl_3$. [e] C=O. [f] [$^2H_6$]acetone. [g] [$^2H_6$]DMSO. [h] $CDCl_3$.

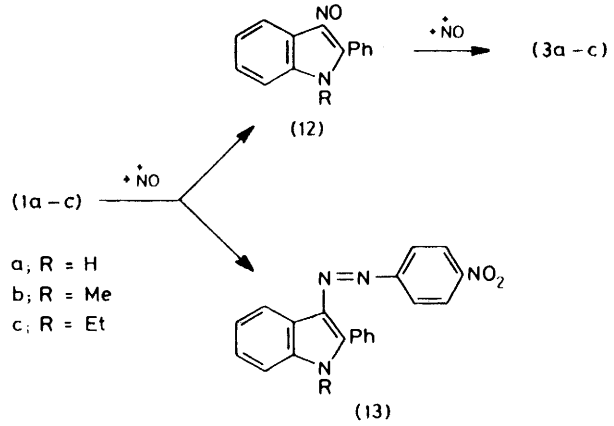
scribed for compounds (1a—c), also underwent electrophilic *ipso*-substitution at C-3 and, in particular, it was observed that compound (1d) reacted more readily than the phenylazo-derivatives (1a—c), whereas compounds (1e and f) reacted with greater difficulty. In the case of (1e) with 3-nitroindole (3b), a mixture of 1-methyl-3-acetyl-5-nitroindole (6) and 1-methyl-3-acetyl-4-nitroindole (7) was also isolated (Table 2); whereas from (1f), (3b) and 3-formyl-1-methyl-2-phenyl-5-nitroindole (8) were isolated (Tables 1 and 2).

Bis-(1-methyl-2-phenylindol-3-yl)methane (9a) slowly reacted with 70% nitric acid in a 1 : 4 ratio to give 1-methyl-2-phenyl-3-nitroindole (3b) and a mixture of 3,6-dinitroindole (4b) and 3,4-dinitroindole (5b). The same results were obtained from (9b), for which compounds (3b)—(5b) and benzaldehyde were isolated and identified. These reactions were also interpreted as



SCHEME 2

electrophilic *ipso*-substitutions, which take place in two different steps (Scheme 2). The first step involves *ipso*-attack by the nitronium ion on the indolylmethanes (9a and b) forming 3-nitroindole (3b) and the carbo-



SCHEME 3

cations (10a and b). The second step is characterized by the reaction between the nitronium ion and the hydroxy-derivatives (11). The yields of the nitro- and dinitro-indoles (Table 1) are consistent with the mechanism proposed.

The formation of 3,6-dinitroindole (4b) was explained by the reaction of 3-nitroindole (3b) with nitronium ion; in fact, compound (3b) on treatment with nitric acid forms (4b) in good yield (Table 1).

2-Phenyl-3-phenylazoindole (1a) and the correspond-

ing *N*-alkyl derivatives (1b and c) were also allowed to react with nitrosonium ion in acetic acid at room temperature. They formed 3-nitroindoles (3a—c) together with a small amount of 3-(*p*-nitrophenylazo)-indoles (13a—c) (Scheme 3).

These results confirm that the nitrosonium ion is more electrophilic than the diazonium ion. The formation of intermediate nitrosoindoles (12a—c) was demonstrated by treating them with nitrous acid under the conditions in which the 3-phenylazoindoles were allowed to react. The formation of 3-nitroindoles (3a—c) by nitrosonium ion can be explained by assuming, at first, a displacement of the diazonium ion which leads to nitrosoindoles, which further undergo oxidation by the nitrous acid. The formation of compounds (13a—c) can be interpreted as a conventional nitrosation of the phenyl group followed by oxidation to the corresponding 3-(*p*-nitrophenylazo)-derivatives (13a—c). The yields of products are reported in Table 3.

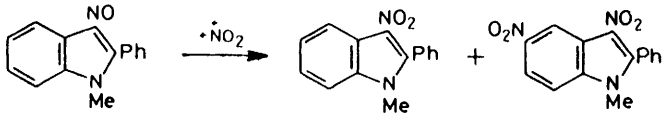
TABLE 3

Reactions between 3-phenylazoindoles and nitrous acid

Compound	Reaction time (h)	Products [% yield]
(1a)	24	(3a) [a] [82]; (13a) [b] [18]
(1b)	48	(3b) [74]; (13b) [26]
(1c)	72	(3c) [78]; (13c) [22]

[a] Ref. 7. [b] A. Korczynski, W. Brydowna, and L. Kierck, *Gazz. Chim. Ital.*, 1926, **56**, 914.

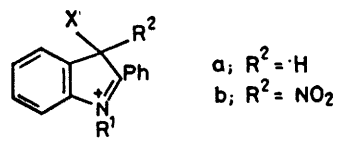
3-Nitrosoindole (12b) reacts with 70% nitric acid in acetic acid to form 3-nitroindole (3b) and a dinitro-derivative. In our opinion this reaction is particularly significant. The formation of 3-nitroindole (3b) can be



(12b) (3b) (14)

SCHEME 4

explained by an oxidation process of nitroso- (12b) to nitro-indole (3b). The dinitro-derivative, which represents 30% of transformed (12b), could be the 3,6-dinitro-derivative, which is the expected compound for the nitration of 3-nitroindole in these conditions but in fact the compound isolated in this case is 3,5-dinitroindole (14) (Scheme 4). It is well known that the indole

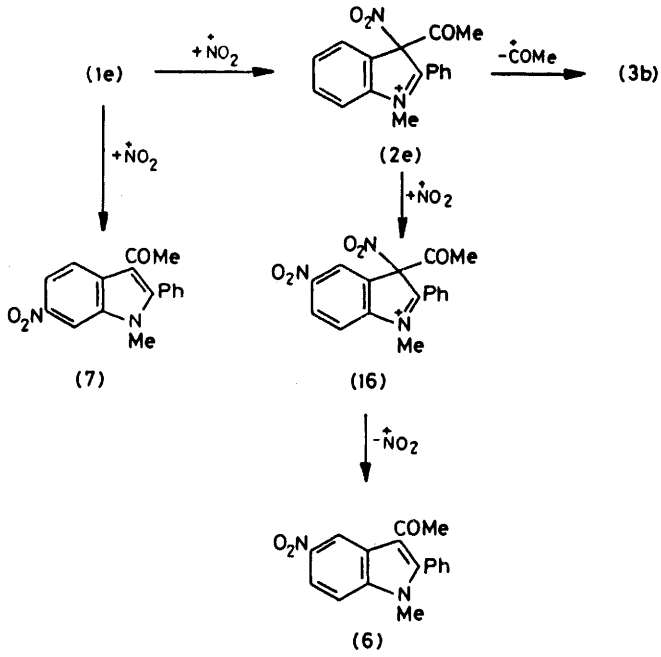


(15)

a; R^2 = H
b; R^2 = NO_2

nucleus undergoes nitration at C-5 when it reacts in the protonated form (15a);[9] the conjugated acid of indole is isoelectronic with the σ-complex (15b) and is formed by *ipso*-attack. Thus, the formation of 3,5-dinitroindole (14) can be explained by nitration of the σ-complex, and the reaction between nitrosoindole (12b) and nitric acid can therefore be interpreted as an electrophilic *ipso*-substitution.

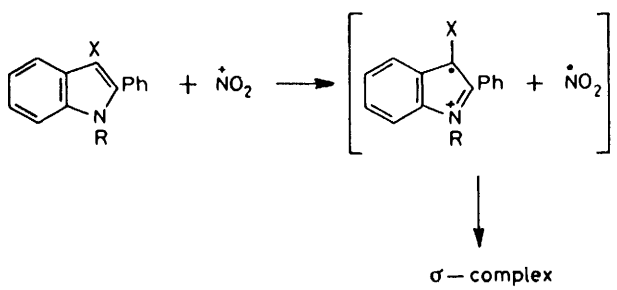
Thus, in the case of 3-acetylindole (1e), the formation of (7) could be explained by nitration of the free base (1e),[9] while the formation of 5-nitro-3-acetylindole (6) could take place by nitration of the σ-complex (2e), as shown in Scheme 5. The loss of nitronium ion instead of



SCHEME 5

the acetyl group from the σ-complex (15), could be influenced by the similar leaving abilities of the nitronium ion and the acetyl group. For compound (1f) we propose the same mechanism.

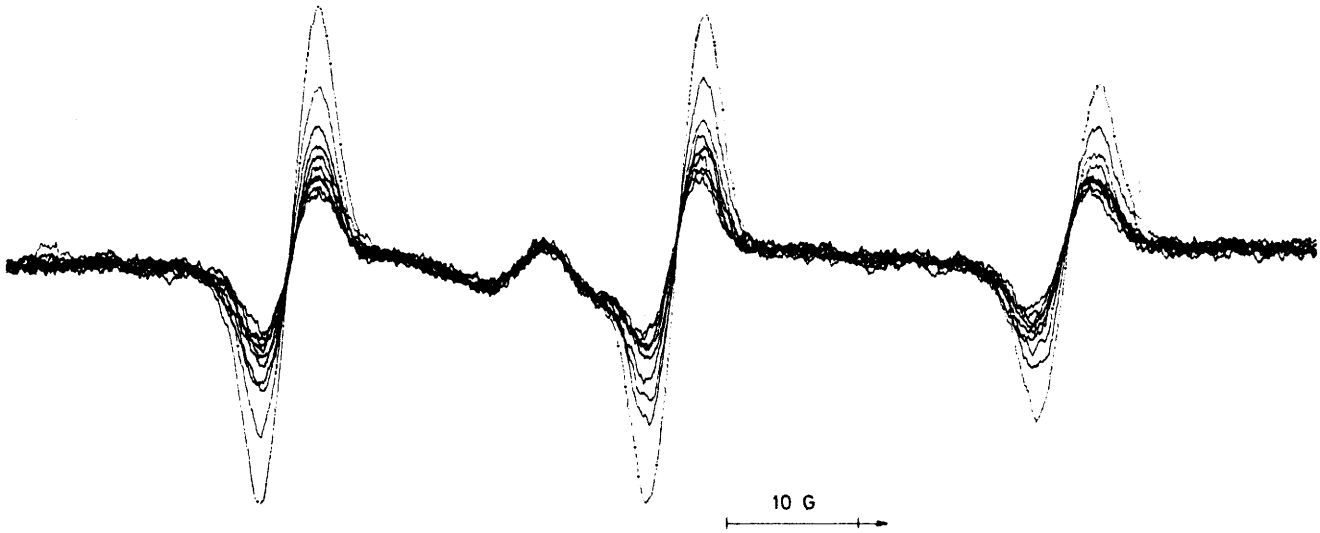
The reactions between (1d—f) and (9a and b) and nitric acid were also carried out in the e.s.r. cavity at room temperature. In the case of (1d) and (9a and b) a



SCHEME 6

signal of three bands with relative intensity 1 : 1 : 1 was observed (Figure), which could be attributed to the formation of the $^{\cdot}NO_2$ radical (a^N 29.2 G). This evidence clearly shows that the σ-complex is preceded by an electron transfer process, when groups at C-3 increase the basicity of the substrate.[10] Thus, in these cases the more probable mechanism is that shown in Scheme 6, according to Perrin.[11]

An order for the leaving abilities of the cationic species is difficult to establish because of the sensitivity of the electrophilic *ipso*-substitutions to the reaction conditions and the mechanism by which the electrofugal group is removed from the σ-complex.[12] As all our reactions were carried out in the same conditions, we propose the following sequence for increasing leaving abilities: $\overset{+}{C}HO < \overset{+}{C}OCH_3 < \overset{+}{N}O < \overset{+}{N}_2Ph < PhCH(\overset{+}{}$-indol-3-yl$) \leqslant \overset{+}{C}H_2$-indol-3-yl $< \overset{+}{C}H_2OH$. This sequence is based above all on the yields and reaction times reported in Table 1.



E.s.r. signal attributed to the $^{\cdot}NO_2$ radical, recorded for the reaction of (1d) with 70% HNO_3 in acetic acid

EXPERIMENTAL

M.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer for Nujol mulls. N.m.r. spectra were recorded on Varian XL 100 spectrometer (tetramethylsilane as internal standard). E.s.r. spectra were recorded on a Varian E 4 spectrometer. Mass spectra were recorded on a Varian 112 S instrument.

Compounds (1a),[13] (1b),[14] (1c),[15] (1d),[16] (1f),[17] (9a),[18] (9b),[18] and (12b) [15] were prepared as described in the literature.

Reactions with HNO_3 (*General Procedure*).—70% HNO_3 (6 mmol) was added dropwise, at room temperature and with stirring, to an acetic acid solution (30—100 ml) of a 3-substituted indole (3 mmol). After the time reported in Table 1 the mixture was evaporated under vacuum at 60°. The residue were taken up in benzene and chromatographed on an SiO_2 column using benzene or benzene–acetone (9 : 1) as eluant. The isolated products and yields are reported in Table 1. In the cases of (9a and b), the substrate : HNO_3 ratio was 1 : 4. Compounds (6) and (7) were separated by chromatography on an SiO_2 column eluting with light petroleum–ethyl acetate (7 : 3). Analytical and spectroscopic data of new isolated compounds are reported in Table 2. Many of these compounds were synthesized by an independent route for comparison (see below).

Reactions with HNO_2 (*General Procedure*).—Sodium nitrite (6 mmol) was added to an acetic acid solution (50 ml) of 3-phenylazoindoles (1a—c) (3 mmol), at room temperatures and with stirring. After the time reported in Table 3, the solution was evaporated to dryness. The residue was worked up as described above. Isolated compounds are reported in Table 3. Analytical and spectroscopic data are reported in Table 2.

3-*Acetyl*-1-*methyl*-2-*phenylindole* (1e).—Dimethyl sulphate (23 ml) was added over 30 min to 3-acetyl-2-phenylindole (9.4 g) [19] suspended in 40% NaOH (120 ml), at 60° and with stirring. The addition of Me_2SO_4 was done gradually to maintain the temperature at 60°. The mixture was then slowly heated until a vigorous reaction began. When the boiling subsided, the mixture was heated at 80—90° for 1 h. Product (1e), obtained by cooling and water dilution of the reaction solution was separated by filtration (9.2 g, 95%), m.p. 70° (lit.,[20] 136°), δ($CDCl_3$) 1.92 (3 H, s, $COCH_3$), 3.45 (3 H, s, NCH_3), 7.25—7.6 (8 H, m, arom), and 8.5—8.73 (1 H, m, arom) (Found: C, 81.8; H, 5.95; N, 5.45. Calc. for $C_{17}H_{15}NO$: C, 81.9; H, 6.05; N, 5.6%).

1-*Methyl*-2-*phenyl*-3-*nitroindole* (3b).—Compound (3b) was prepared by methylation of (3a) as described above. Starting from (3a) (1 g) in 40% NaOH (15 ml) and Me_2SO_4 (3 ml), (3b) (0.95 g, 90%) was obtained. Analytical and spectroscopic data are reported in Table 2.

1-*Ethyl*-2-*phenyl*-3-*nitroindole* (3c).—Compound (3a) (2 g) in EtONa (200 mg of Na and 40 ml of absolute EtOH) and EtI (2.64 g) were refluxed for 2 h. On cooling, compound (3c) crystallized and was separated by filtration (1.3 g, 59%). Analytical and spectroscopic data are reported in Table 2.

1-*Methyl*-2-*phenyl*-3,6-*dinitroindole* (4b)—Starting from (4a) (125 g) in 40% NaOH (15 ml) and Me_2SO_4 (2.3 ml) and working up as described above, compound (4b) was obtained in 68% yield The same compound was obtained by nitration of (3b). On starting from (3b) (0.5 g) and 70% HNO_3 (0.6 ml) in acetic acid (40 ml) at 70° for 1 h and working up as described above, (4b) was isolated in 81% yield. Analytical and spectroscopic data are reported in Table 2.

1-*Methyl*-2-*phenyl*-3,5-*dinitroindole* (14).—Starting from 2-phenyl-3,5-dinitroindole (1.7 g) in 40% NaOH (15 ml) and Me_2SO_4 (1.5 ml) and working up as described above, compound (14) was obtained in 82% yield. Analytical and spectroscopic data are reported in Table 2.

1-*Methyl*-2-*phenylindole*.—This compound, used as the

starting material in several preparations, was conveniently prepared by methylation of 2-phenylindole. Starting from 2-phenylindole (5.79 g) in 40% NaOH (90 ml) and Me_2SO_4 (18 ml) and working up as described above, 1-methyl-2-phenylindole was obtained in 90% yield.

1-Methyl- and 1-Ethyl-2-phenyl-3-(p-nitrophenylazo)indoles (13b *and* c).—*p*-Nitrobenzenediazonium salt, prepared by the usual method from *p*-nitroaniline (15 mmol), 30% HCl (15 ml), and $NaNO_2$ (15 mmol) in H_2O (5 ml), was neutralized with CH_3CO_2Na and added to a solution of 1-methyl-2-phenylindole (5 mmol) in EtOH at 0—5° with stirring. After 30 min at this temperature the mixture was stirred for 2 h at room temperature. The precipitated compound (13b) was collected by filtration (yield 80%). Compound (13c) was prepared from 1-ethyl-2-phenylindole in the same way (yield 60%).

Reactions in the E.s.r. Cavity.—Solutions of 3-substituted indoles and 70% HNO_3 in acetic acid were each placed in one of the two legs of the inverted U cell, similar to that described by Russel,[21] and degassed with nitrogen. The mixed solutions were transferred to the e.s.r. cavity. The signal reported in the Figure, attributed to the $^{\bullet}NO_2$ radical, was obtained for compounds (1d) and (9a and b).

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