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NITROXIDE AND ANION RADICALS DERIVED FROM ISATOGEN AND RELATED INDOLE DERIVATIVES

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Abstract – Neutral indolic nitroxides were obtained by oxidation of 1-hydroxyindoles with lead dioxide. Anion indolic nitroxides were obtained by reduction of indoline-N-oxides in DMSO/t-BuOK (reducing agent being the $CH_3SOCH_2^-$ anion). In both cases an a^N of about 6 gauss was found. This value, which differs from values previously reported, is justified in the course of the work. Some other anion radicals derived from bi-indolic derivatives are also reported and their structures discussed on the basis of MO calculations or by comparison with analogous examples.

It has been reported[1] that 2-substituted isatogens, when treated with water/methanol or water/acetone solutions of sodium hydroxide give a nitroxide to which structure 1 was assigned; at the same time structure 2 was proposed for radicals obtained by heating isatogens in proton donor solvents like toluene, xylene or mesitylene. Concerning these structures some observations have already been made[2] and this indicated that radicals obtained by alkali treatment of isatogens must be more reasonably considered as open ring nitroxides and that structure 1 is more probably attributable to the product of thermolysis of isatogens. In further support of previous observations we now report a new nitroxide radical that was produced by treating 2-phenylisatogen with the reducing agent t-BuOK/DMSO (the reducing agent, being the $CH_3SOCH_2^-$ anion[3]). The spectrum is reported in Fig 1 and in spite of its low resolution clearly shows a triplet of lines with a hyperfine splitting constant equal to 5·6 gauss attributable to the coupling of the unpaired electron with one nitrogen nucleus. This value is in perfect agreement with that of 5·9 gauss found in nitroxide 3[4] in the same solvent and with those of 4–5 gauss found in nitroxides of type 4[5] in various solvents: on the contrary it is a long way from values around 9 gauss previously proposed for the structurally similar nitroxides 2. We believe that structure 5 is the actual one for this radical and experimental evidence supports this statement.† In order to find other evidence of this behaviour

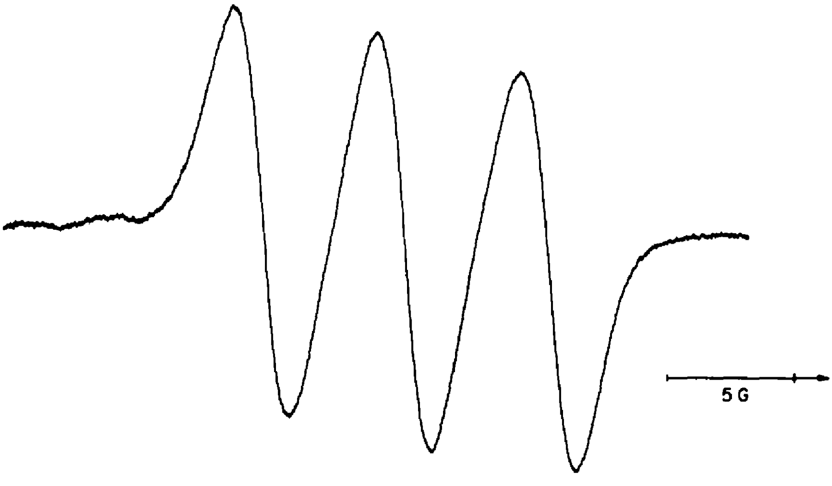

Fig 1. ESR spectrum of the radical obtained by reduction of phenyl-isatogen in t-BuOK/DMSO.

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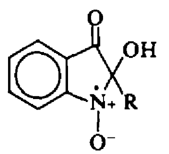
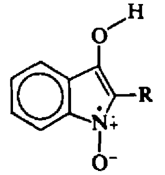
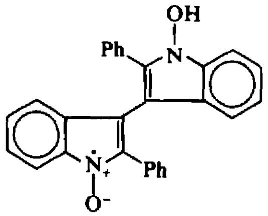
†Polarographic reduction of 2-phenylisatogen shows that the same radical can be obtained when only one electron per mole is consumed and that such reduction is a reversible one (results to be published).



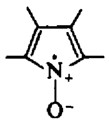
1: R = H (a^N = 9·66 gauss)
R = Ph (a^N = 10 gauss)



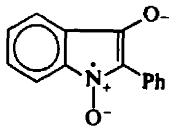
2: R = CO_2Me, Ph ($a^N \sim$ 9 gauss)



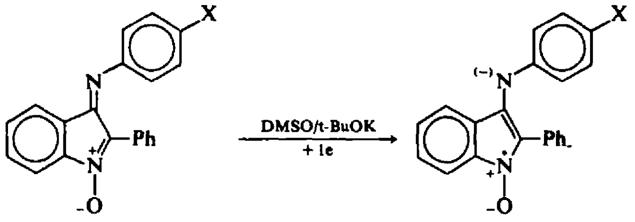
3: a^N = 5·9 gauss



4: a^N = 4–5 gauss



5: a^N = 5·6 gauss



6a: X = H
b: X = Cl

7a: a^N = 5·7 gauss
b: a^N = 5·9 gauss

we treated compounds **6a** and **b**, which are structurally related to isatogens, with the same reducing agent. As expected anion nitroxides were obtained that show an analogous nitrogen splitting constant; ESR spectra (Fig 2) show their substantial identity, some fine structure, due to the coupling of the unpaired electron with other nuclei, being observable.

At this point it seemed of interest to study some neutral indolic nitroxides in order to see if some influence could be attributed to the negative charge in determining the a^N value. The only example previously reported is that of nitroxide **3**[4,2] which shows substantial identity of a^N value with those of our anion nitroxides; however this molecule has some ambiguities[6,7,4] in its formation and this fact forced us to find some new examples. Oxidation of DMSO solutions of N-hydroxyindoles **8**,[8] **9**,[9] and of the previously unknown **10**, with lead dioxide, gave radicals **11**, **12** and **13** (Figs 3 and 4) for which a^N of about 6 gauss were obtained. These results seem to exclude any particular participation of the negative charge in determining the value of a^N. Compound **10** was obtained by the reaction of hydrazo-benzene on the condensation product of 1-hydroxy-2-phenylindole and *p*-NO-benzonitril. The *p*-CN group stabilizes the hydroxy derivative **10** against a dehydration reaction that can occur in other examples. This fact has already been discussed in a previous work.[8]

The bi-nitrone **14** must be considered a compound structurally related to isatogens for which the presence in all purified samples of some amount (0·5%) of radical **3**[7] can cause some complication. When a $5 \cdot 10^{-3}$ M solution of compound **14** in DMSO is treated in the absence of oxygen with $6 \cdot 10^{-3}$ moles of t-BuOK, the initial spectrum (Fig 4) slowly vanishes, and a new spectrum appears, which after 3 hr shows its maximum intensity. The new radical can be obtained also by oxidation of the bihydroxy derivative **16** in the same solvent and in the presence of the same amount of base: in the latter case only 5 to 10 min is required for the signal to appear. The spectrum (Fig 5) can be interpreted in many different ways and some reconstructions were attempted: four of them seem to better fit experimental and calculated spectra, and are reported in Table 1; Fig 5, however, shows only the calculated spectrum that is considered the best interpretation (caseD).

Interpretation A should correspond to structure **15** with a maximum spin density on the two benzo rings and a minimum one on the N atoms, which is

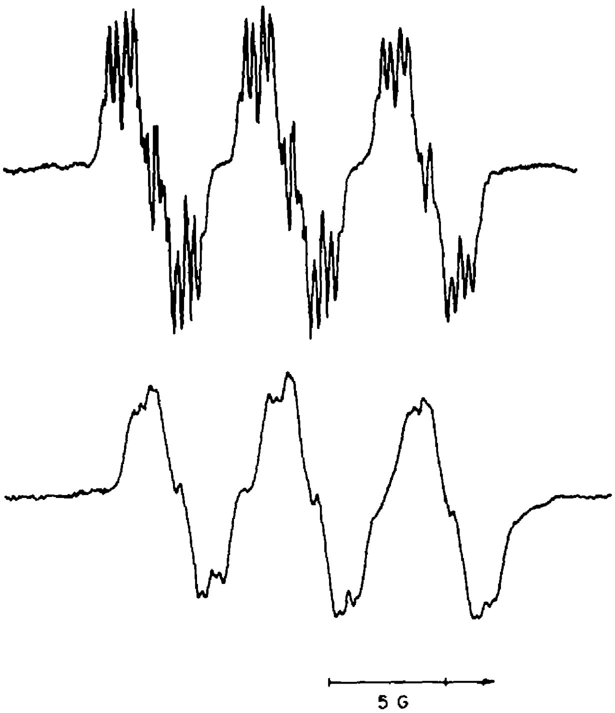
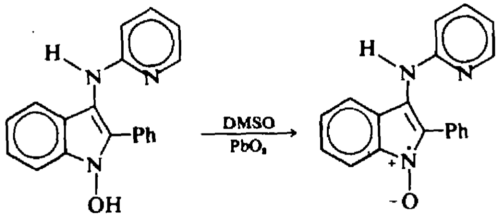
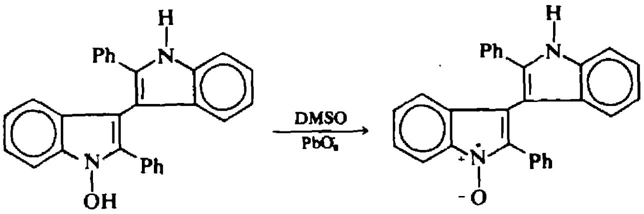


Fig 2. ESR spectra of radicals **7a** (bottom) and **7b** (top).

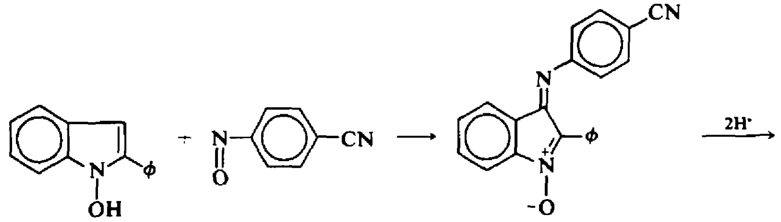


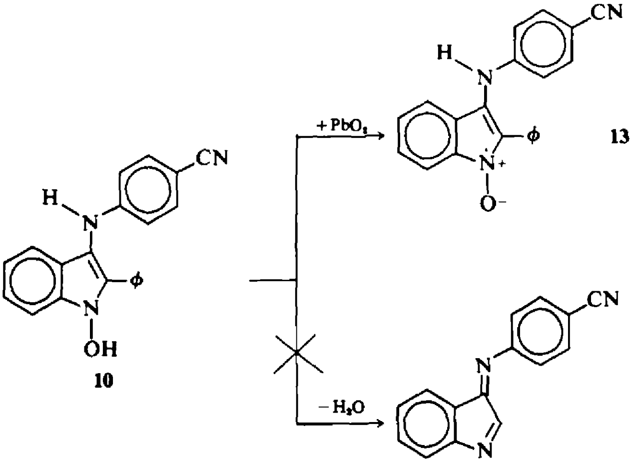
8 **11**: $a^N = 6{\cdot}00$ gauss



9 **12**: $a^N = 5{\cdot}95$ gauss

unlikely in a nitroxide. Case B can account for a ring opening of the bi-nitrone that could form a conjugated semidione radical anion of type **17** but neither the line intensity ratio, nor the chemistry of such compounds can account for this interpretation. As a matter of fact neither phenylisatogen, nor compound **6** suffered ring opening reaction in these experimental conditions. Situations C and D are the most likely to be considered: both can readily refer to radical **15**, but the better fit between experimental and calculated spectrum, as far as line intensity ratio is concerned, is found for case D. This interpretation clearly asks for the magnetic equivalence of six benzoprotons (three for each ring), which is not usual, the *ortho* and *para* hydrogens showing generally a higher spin density than





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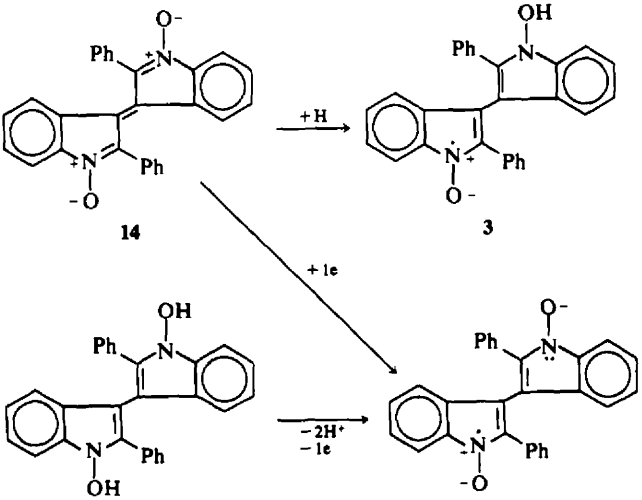
13: $a^N = 6{\cdot}00$ gauss



14

3

16

15: $a^N = 3{\cdot}35;\ 3{\cdot}35$ gauss
$a^H = 0{\cdot}55$ (6 equivalent protons)

Table 1

A: (4) $a^H = 3{\cdot}35$ gauss (4) $a^H = 0{\cdot}55$ gauss (2) $a^N = 0{\cdot}55$ gauss	B: (4) $a^H = 3{\cdot}35$ gauss (6) $a^H = 0{\cdot}55$ gauss
C: (2) $a^N = 3{\cdot}35$ gauss (8) $a^H = 0{\cdot}55$ gauss	D: (2) $a^N = 3{\cdot}35$ gauss (6) $a^N = 0{\cdot}55$ gauss

the *meta*, with respect to the N—O group. McLachlan MO calculations were made, using parameters recently suggested[10] for aromatic N-oxide radical anions and previously proposed in a detailed study[11] on the same subject and reported in Table 2.

As can be seen, position 4, 5, 6 and 14, 15, 16

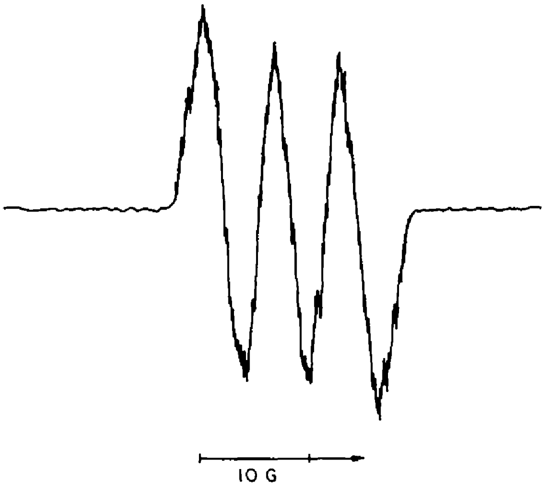
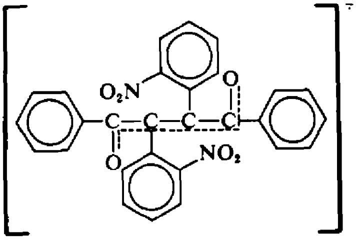
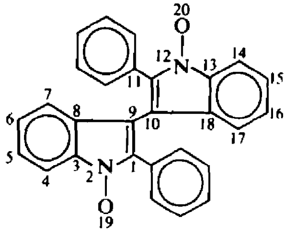


Fig 3. ESR spectrum of radical **11**.



17

Table 2. McLachlan MO calculations for radical **15**



Positions	McLachlan spin densities	parameters
1–11	−0·0508	$\lambda = 1{\cdot}2$
2–12	0·1285	$h_N = 1{\cdot}0$
3–13	0·0109	$h_O = 0{\cdot}6$
4–14	0·0114	$k_{CN} = 0{\cdot}8$
5–15	0·0092	$k_{NO} = 0{\cdot}8$
6–16	0·0149	$k_{CC} = 1{\cdot}0$
7–17	0·0053	
8–18	0·0180	
9–10	0·0543	
19–20	0·2982	

show spin density values very close to each other thus justifying the spectrum. If we calculate the a^H with the usual formula

$$a^H = 25{\cdot}67\,Pc$$

we find an $a^H = 0{\cdot}1$ gauss for positions 7 and 17 which are certainly missed, if we consider that the lines have a width of 0·3 gauss. Unfortunately no other solvents can be used owing to the very low solubility of bi-nitrone **14** and to the particular reducing system. The a^N value of 3·35 gauss for two equivalent nitrogens is in good agreement with the values 5–6 gauss found for one nitrogen in the other anion nitroxides previously discussed. The perfect equivalence of the two $>$N—O groups can be explained by the fact that in radical **15** the electron density must be equally distributed between the two nuclei, while in radical **3** we have a tautomeric rather than a mesomeric situation which allows the two nitrogens to behave independently.

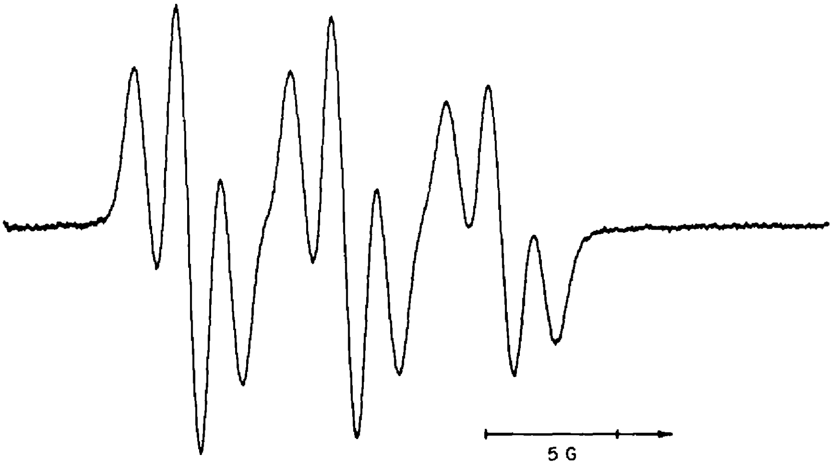


Fig 4. ESR spectrum attributed to radical **12**.

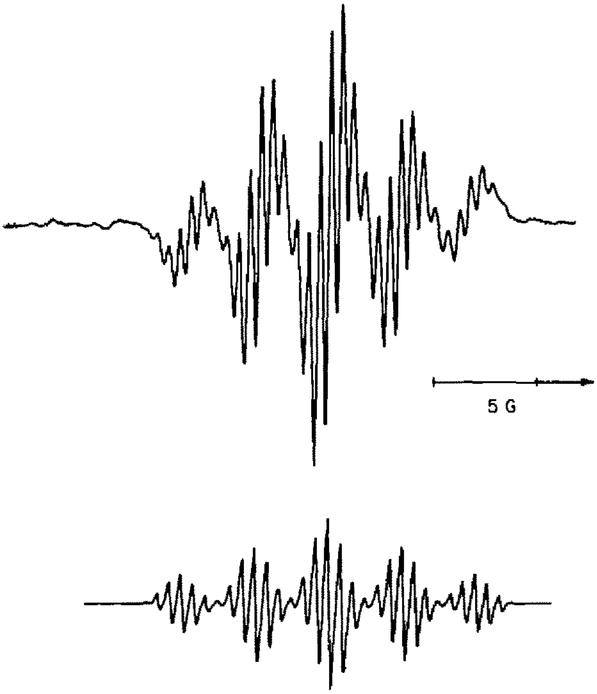


Fig 5. Experimental (top) and simulated (bottom) ESR spectrum of radical 15. Simulation was made using values given in the text.

An attempt to obtain the same radical starting from 1-hydroxy-2-phenylindole **18** was unsuccessful, since the compound decomposed with formation of a final nitroso anion radical **19** (Fig 6).

Compounds **9** and **16**, when dissolved in a solvent, undergo spontaneous oxidation to the corresponding nitroxides. No ESR signal was observed if solutions of both compounds were previously treated with hydrogen on a Pd/C 5% catalyst.

Compound **18** showed a particular behaviour when a DMSO solution of the compound was oxidized with PbO_2; in the presence of air, radical **3** was observed and the signal was stable within a period of 24 hr, while if air was carefully excluded a different radical appeared (Fig 7), which corresponds to that previously obtained in the oxidation with lead tetraacetate[2] and to which structure **20** was assigned ($a^N = 9{\cdot}50$; $a^H = 3{\cdot}06, 3{\cdot}06$; $a^H = 1{\cdot}00, 1{\cdot}00$). We believe that in the former case a fast

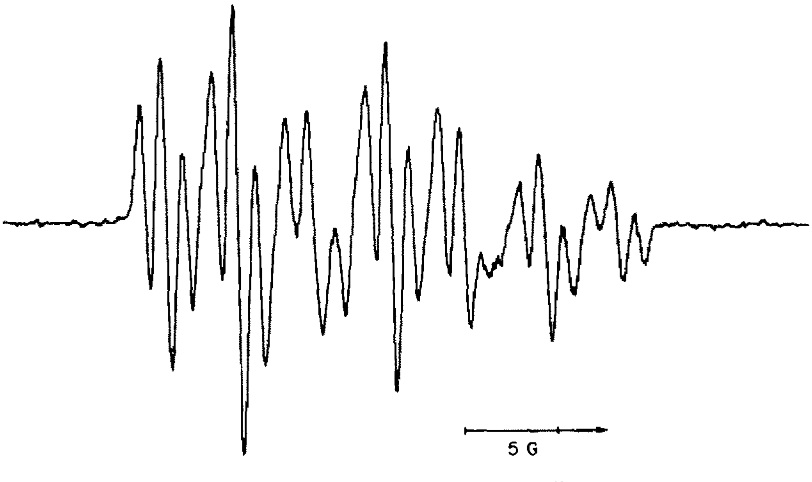
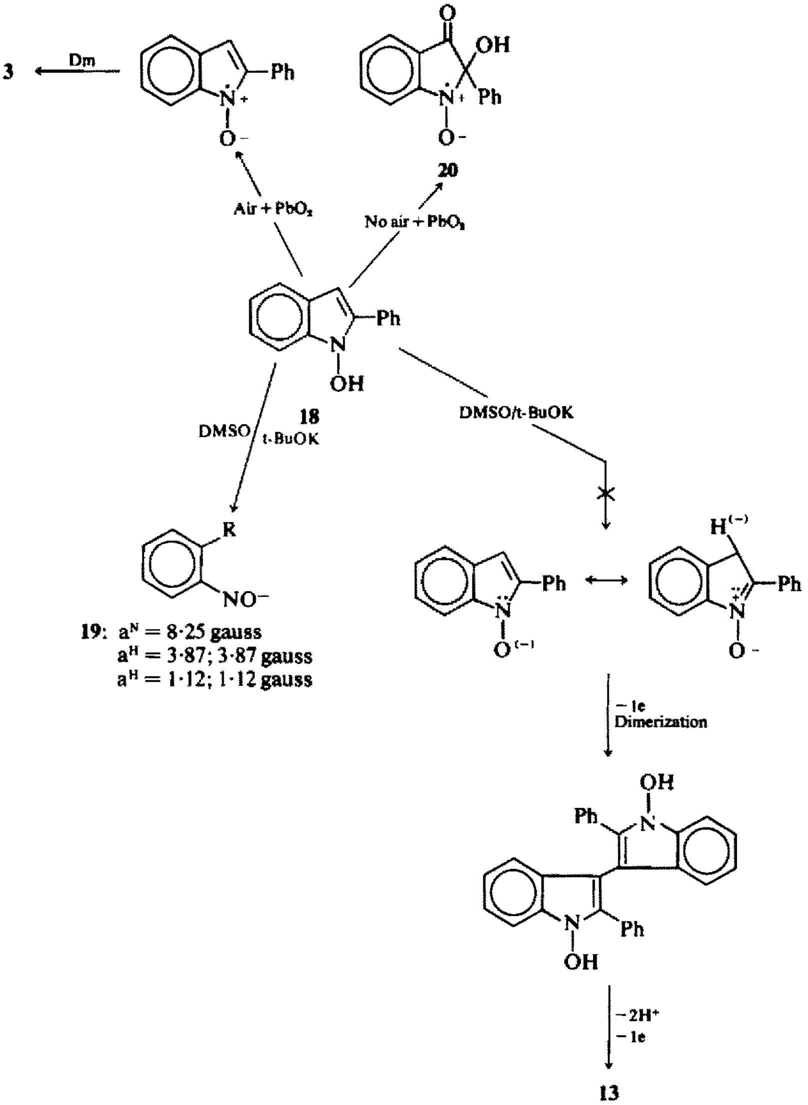


Fig 6. ESR spectrum attributed to radical 19.



19: $a^N = 8{\cdot}25$ gauss
$a^H = 3{\cdot}87; 3{\cdot}87$ gauss
$a^H = 1{\cdot}12; 1{\cdot}12$ gauss

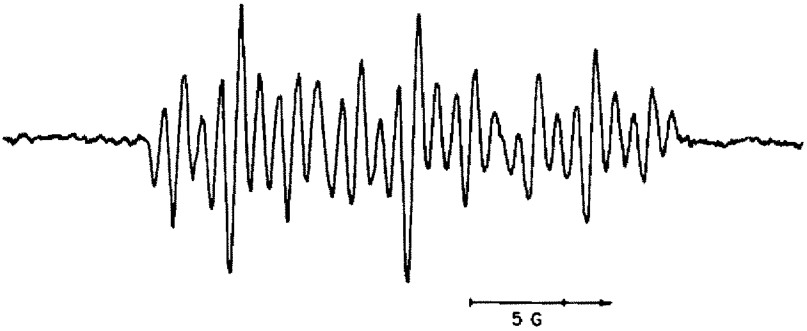
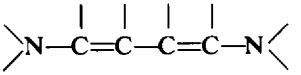


Fig 7. ESR spectrum attributed to radical **20**.

dimerisation takes place, while in the latter the oxidation at position −3 is faster than the dimerisation. It is known that 1-hydroxy-2-phenylindole rapidly dimerizes in air when dissolved in many solvents* and that lead tetraacetate oxidizes it to 2-phenylisatogen.[6]

In order to have more detailed information concerning radical **15**, compound **21** was submitted to the same experimental conditions in the absence of oxygen. An extremely simple ESR spectrum (Fig 8) was obtained that can be reproduced by using the value given in the following scheme.

The partial resolution of the spectrum makes the use of MO calculations of small utility in interpreting the spectrum. In any case, some calculations were made using the McLachlan approximation,[12] and partially reported in Table 3. The two phenyl rings were not included in these calculations, since they must be perpendicular to the molecular plane in order to have the equivalence of the two N atoms. All sets of parameters lead to the conclusion that the four H atoms must be the ones bonded to C atoms 5, 7, 15, 17 and that the maximum spin density must occur on the system  $>N{-}\overset{|}{C}{=}\overset{|}{C}{-}\overset{|}{C}{=}\overset{|}{C}{-}N<$ with a lower spin density, within this system, on the N atoms. This can explain why a higher spin density is observed on C atoms 5, 7 (and 15, 17) rather than on $C_{14,16}$ and $C_{4,6}$, C atoms 5, 7, 15, 17 being in *ortho* and *para* position to C_9 and C_{10} respectively, where the maximum spin density is observed.

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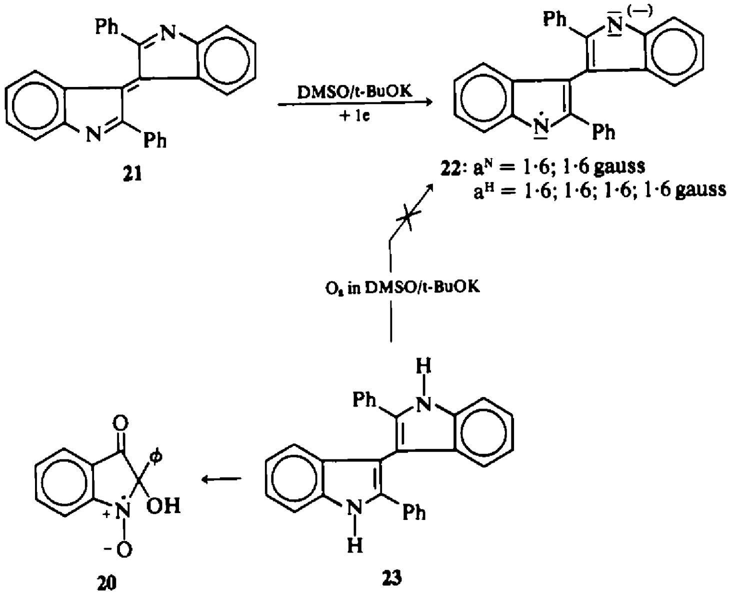
*Although not described in detail this is an observation of all our experimental work on 1-hydroxy-2-phenylindole.



21

22: $a^N = 1{\cdot}6; 1{\cdot}6$ gauss
$a^H = 1{\cdot}6; 1{\cdot}6; 1{\cdot}6; 1{\cdot}6$ gauss

23

20

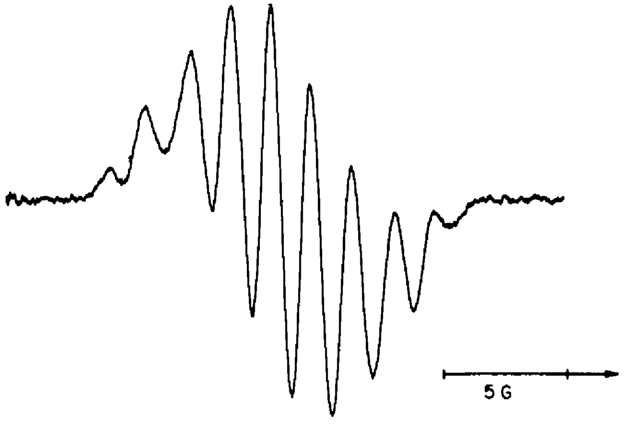
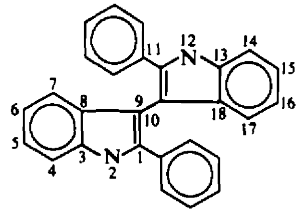


Fig 8. ESR spectrum attributed to radical **22**.

Table 3

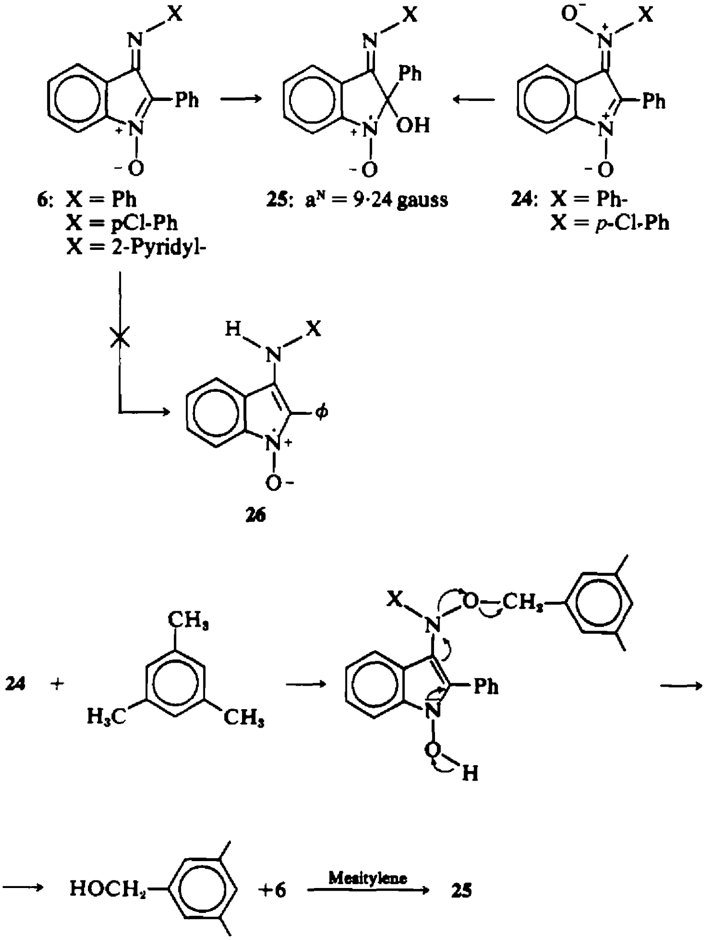


Atoms	(a) $h_N = 0{\cdot}70$; $k_{CN} = 0{\cdot}90$	(b) $h_N = 1{\cdot}20$; $k_{CN} = 1{\cdot}20$
1–11	0·1234	0·1686
2–12	0·1153	0·0475
3–13	0·0176	0·0237
4–14	0·0189	0·0157
5–15	0·0297	0·0343
6–16	0·0073	0·0037
7–17	0·0409	0·0460
8–18	0·0035	0·0073
9–10	0·1503	0·1678

Radical **22** cannot be obtained through the opposite reaction, consisting in the oxidation in DMSO/t-BuOK of bi-indole **23**, in the same way as was seen for the conversion **14** → **15** ← **16**. In fact no signal was obtained until a large amount of base was added; a new radical was then detected for which either the hfsc (identical to those previously reported for radical **20**) or the fact that only a large amount of base can affect the reaction, leads to consideration of the possibility of obtaining that degradation radical.

The last consideration is concerned with the possibility that compound **6** can behave as a 2-phenylisatogen when photolysed in protic solvents like mesitylene. To check this we boiled $3{\cdot}10^{-2}$ M solutions in mesitylene of compounds **6** and **24**, carefully deoxygenated, for 6 min, obtaining always the same ESR signal (Fig 9).

The fact that the same compound can be obtained starting from **6** and **24** is not surprising: we have already found[9] that bi-nitrone **24** reacts in boiling toluene leading to **6** and to oxidation products derived from toluene. The following Scheme



6: X = Ph
X = pCl-Ph
X = 2-Pyridyl-

25: $a^N = 9{\cdot}24$ gauss

24: X = Ph-
X = *p*-Cl-Ph

26

24 +

→ 25

SCHEME 1

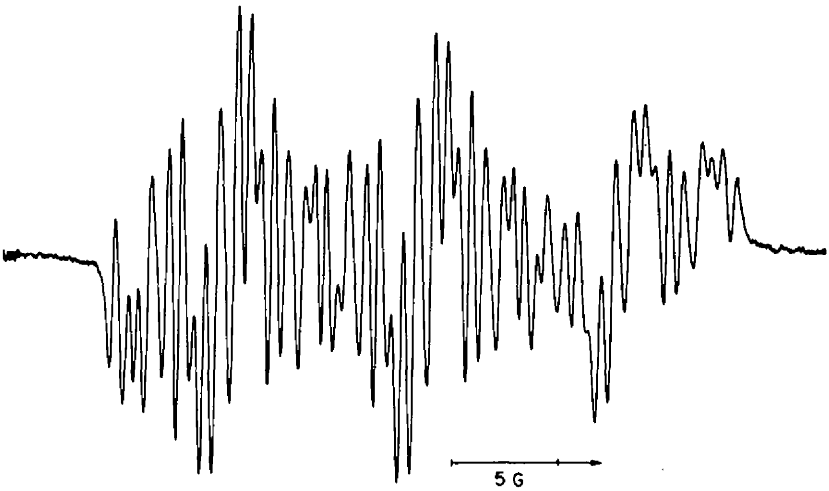
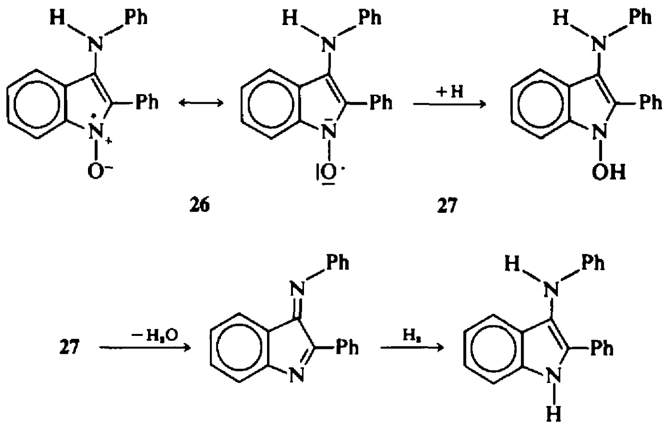


Fig 9. ESR spectrum attributed to radical 25.



26 27

28

I can be considered for the reactions involved in our process.

In previous work[9] we also found that 6 cannot react with toluene. We think that if radical 26 should be formed during photolysis of 6 it must be reduced by following the path 26 to 28.

It has been demonstrated[8] that 27 spontaneously loses water thus leading to an imino compound that must be reduced to the final amino compound 28.

In particular, 6 where X = 2-pyridyl- gives[8] a stable N-hydroxy derivative: no differences were observed in the behaviour of 6 (X = 2-pyridyl-) and of the analogous phenyl derivatives observed. Finally, radical 26 should have an a^N of the same value as the corresponding anion 7 and neutral (11, 12 and 13) radicals previously discussed ($a^N \sim 6$ gauss, against $a^N = 9{\cdot}24$ gauss of this last radical), and should correspond to an irreversible reduction process. The fact that in the mesitylene only starting material was recovered is clearly in contrast with the choice of formula 26 as the one of the actual radical observed and this fact is one more proof than formula 25 probably represents the radical obtained. The fact that a complete analysis of the spectrum was not possible is, in this respect, of a little importance; as will be discussed in a future publication, compounds of series 24 show different behaviour when reduced in alkali solution.

EXPERIMENTAL

Compounds. 2-Phenylisatogen,[13] 1-oxy-2-phenyl-3-phenyl-imino-3H-indole,[14] 1-oxy-2-phenyl-3-(*p*-Cl-phenyl-)imino-3H-indole,[15] 1-hydroxy-2-phenyl-3-(2-pyridyl-)aminoindole,[8] 1-hydroxy-2-phenyl-3-(2'-phenyl-3'-indolyl-) indole,[9] 1,1'-dioxy-2,2'-diphenyl-$\Delta^{3,3'}$-bi-3H indole, 1,1'-di-hydroxy-2,2'-diphenyl-3,3'-bi-indole,[6] 1-hydroxy-2-phenylindole,[16] 2,2'-diphenyl-$\Delta^{3,3'}$-bi-3H-indole,[17] 2,2'-diphenyl-3,3'-bi-indole,[18] 1-oxy-2-phenyl-3-(2-pyridyl-) iminoindole,[19] 1-oxy-2-phenyl-3-phenyl-imino-3H-indole-N-oxide[20] and 1-oxy-2-phenyl-3-(*p*-Cl-phenyl-)imino-3H-indole-N-oxide[15] were prepared with methods reported in the literature.

Solvents. All solvents were commercial products and were purified and dried with conventional methods.

1-*Oxy-2-phenyl*-3-(p-CN-*phenyl-)imino*-3H-*indole.* To a soln of 1-hydroxy-2-phenylindole (1·56 g; 0·075 mole) in 120 ml abs EtOH, to which was previously added NaOEt (prepared with 0·18 g of Na and 15 ml of abs EtOH), a soln of *p*-nitrosobenzonitril[21] (0·99 g; 0·075 mole) in 100 ml EtOH was added. 1·3 g of an orange ppt separated and was filtered off after 4 hr and crystallized from EtOH: m.p. 235–6° (60%). (Found: C, 78·24; H, 4·03; N, 13·03; Calc. for $C_{21}H_{13}N_3O$: C, 78·00; H, 4·05; N, 13·00%).

1-*Hydroxy-2-phenyl*-3-(p-CN-*phenyl*)-*aminoindole* (**10**). 1-Oxy-2-phenyl-3-(*p*-CN-phenyl-)imino-3H-indole (0·81 g) dissolved in 50 ml anhyd benzene was treated with hydrazobenzene (0·50 g) dissolved in 15 ml anhyd benzene and boiled 15 min. A white compound separated and was filtered off and washed with benzene and light petroleum: m.p. 196–7° after crystallization from acetone/water 0·65 g; (75%). (Found: C, 77·54; H, 4·59; N, 13·18; Calc. for $C_{21}H_{15}N_3O$: C, 77·51; H, 4·64; N, 12·91%).

Radical anions by reduction with DMSO/t-BuOK were obtained by treatment of 1 ml of a $1 \cdot 10^{-3}$ to $1 \cdot 10^{-2}$ M soln in DMSO of the particular compound put in one leg of a particular cell previously described[3] with a 10% excess of t-BuOK put into the other leg of the same cell, after deoxygenation with a 30 min stream of pre-purified N_2.

Radical anions by oxidation with DMSO/t-BuOK were obtained in the same way but allowing some air to be introduced into the cell at the end of the operation previously described. In the oxidation of 2,2'-diphenyl-3,3'-di-indole a high excess of t-BuOK was used.

Neutral nitroxide radicals were obtained by the addition of a small amount of freshly prepared PbO_2 to a deoxygenated soln of the N-hydroxy-compound in the most suitable solvent.

Radicals by photolysis of 1-*oxy-2-phenyl-3-aryl-imino*-3H-*indoles and* 1-*oxy-2-phenyl-3-aryl-amineindole*-N-*oxides* were obtained by boiling under N_2 0·05 g of the compound in 5 ml mesytilene previously deoxygenated with 40 min stream of pre-purified N_2. After 5 min the soln was transferred to an ESR flat cell, cooled to room temp and introduced into the ESR cavity.

Spectra. ESR measurements were performed on a Varian E-4, ESR spectrometer at room temp. All radicals appeared within a few min, when not otherwise described.

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