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STABLE NITROXIDE RADICALS FROM 2-SUBSTITUTED QUINOLINE-N-OXIDES WITH ORGANOMETALLIC COMPOUNDS†

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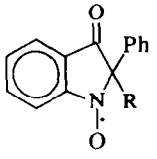
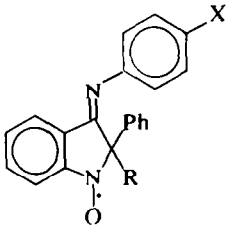
Abstract—Stable nitroxide radicals were obtained by the oxidation of 1-hydroxy-2,2-diphenylquinolines prepared by allowing the PhMgBr to act upon a number of 2-phenylquinoline-N-oxides in THF. Methyl-, ethyl- and benzyl-magnesium compounds gave rise to other nitroxides which were identified from their ESR spectra, but not isolated in the solid state. t-Butyl-magnesium chloride reacted with quinoline-N-oxides giving only the deoxidation products. The ESR spectra of numerous nitroxide radicals were interpreted and discussed.

In previous work[1] it has been shown that when phenylisatogen and 2-phenyl-3-aryliminoindolenine-N-oxides are allowed to react with organo-metallic compounds they afford 1-hydroxyindolines 2,2-disubstituted which are easily oxidised with air or PbO_2 to the corresponding stable nitroxide radicals **1** and **2**, having a coupling constant a^N = 9.2–9.8 gauss:



1: a^N = 9.2–0.8 gauss



2: a^N = 9.3–9.7 gauss

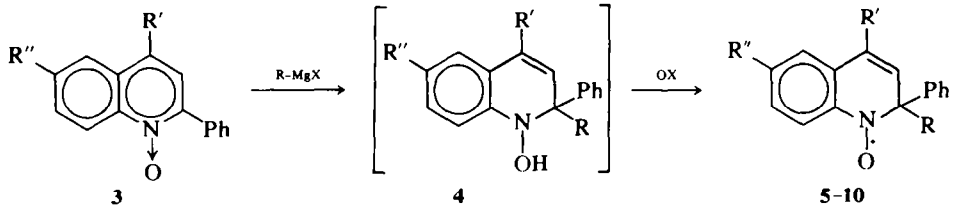
On the other hand, it is well known that 1-alkyl-2-substituted-quinolinium salts react with Grignard reagents RMgX giving the corresponding 1-alkyl-2,2-substituted-1,2-dihydro-quinolines.[2] Now the present paper deals with the nitroxide radicals **5–10**, which have a coupling constant a^N = 10.1–10.8 gauss and which are obtained from the action of the organometallic compounds upon 2-phenyl-quinoline-N-oxide and its derivatives subsequent oxidation by exposure to the air.

The reaction of phenylmagnesium bromide upon 2-phenylquinoline-N-oxide in ether had already been studied in our laboratory;[3] the mixture became deep coloured and 2-phenylquinoline was isolated in poor yields. When the reaction is carried out in THF, the resulting dark red solution gives a strong ESR signal and nitroxide radical **5a** can be isolated, together with a little 2-phenylquinoline. The hydroxy derivative **4a** which can be obtained by reduction of **5a** with 1,2-diphenylhydrazine is a non-stable compound which is very sensitive to the oxidative action of the air.

We also reacted phenylmagnesium bromide with 2-phenylquinoline-N-oxides **3b–f**, some of which were prepared for the first time (Table 1) and we obtained the corresponding nitroxide radicals **6a–10a** in 80–90% yields, together with traces of the deoxidation products. In these reactions, too, easy oxidability of N-hydroxy derivatives **4** prevents their isolation.

In order to demonstrate the attack of C-2 by the Grignard reagent, we allowed 2-phenylquinoline-N-oxide to react with MeMgI, and 2-methylquinoline-N-oxide to react with PhMgBr: in both cases the same compound **5b**

†Dedicated to the memory of Prof. EIJI OCHIAI



3

a: R′ = R″ = H
b: R′ = CO_2Et, R″ = H
c: R′ = CO_2Et, R″ = OMe
d: R′ = OEt, R″ = H
e: R′ = H, R″ = OMe
f: R′ = Cl, R″ = OMe

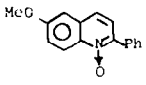
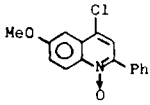
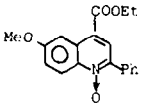
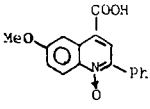
4

5: R′ = R″ = H
6: R′ = $R_2C(OH)$, R″ = H
7: R′ = $R_2C(OH)$, R″ = OMe
8: R′ = OEt, R″ = H
9: R′ = H, R″ = OMe
10: R′ = Cl, R″ = OMe

5–10

a: R = Ph
b: R = Me
c: R = Et
d: R = Ph—CH_2

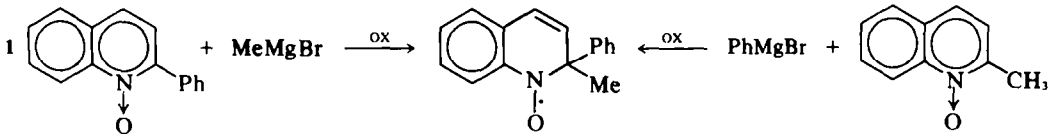
Table 1. Analytical and spectroscopic data of quinoline-N-oxides

Compound	m.p. (solvent)	Analysis	Formula	found % / calcd %			NMR (δ, in $CDCl_3$)
	176° (benzene/ligroin)		$C_{16}H_{13}NO_2$	C 76.90 76.48	H 5.26 5.2-	N 5.97 5.68	3.95 (3H,s,OMe); 7.1-7.75 (7H, complex multiplet, arom.); 7.95-8.1 (2H,m,ortho hydrogens of the Ph ring); 8.81 (1H,d,H-8, J=10 cps).
	199° (ethylacetate)		$C_{16}H_{12}NClO_2$	C 66.96 67.27	H 4.13 4.2C	N 5.22. 5.90	4.0(3H,s,OMe); 7.3-7.6 (6H, complex multiplet, arom.); 7.90-8.05 (2H,m,ortho hydrogens of the Ph ring); 8.76 (1H,d,H-8, J=10 cps).
	132° (ethylacetate)		$C_{19}H_{17}NO_4$	C 70.80 70.57	H 5.15 5.30	N 4.57 4.33	1.45 (3H,t,$CH_2\underline{CH}_3$, J= 7cps); 4.01 (3H,s, OMe); 4.51 (2H, q, $\underline{CH}_2CH_3$, J= 7cps); 7.3-7.7 (4H, m, *); 8.0 (2H ,m, ortho hydrogens of the Ph ring); 8.28 (1H,s,H-3); 8.55 (1H,m, H-5); 8.81 (1H, d, H-8, J= 10 cps)
	284° (acetic ac.)		$C_{17}H_{13}NO_4$	C 68.98 69.14	H 4.39 4.43	N 4.92 4.74	3.96 (3H,s,OMe); 7.35-7.7 (5H, multiplet arom. and COOH); 8.25-8.4 (2H, multiplet arom.); 8.60 (1H,s,arom.); 9.05-9.2 (2H, q, arom.)**.

* H-7 and meta and para hydrogens of the Ph ring.

** in C_5D_5N

was obtained:



5b

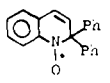
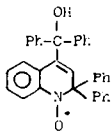
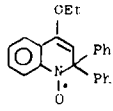
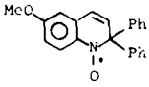
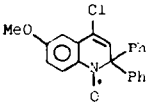
2,2-Diphenyl-1,2-dihydroquinoline-1-oxyls **5a–10a** are intensely-red crystalline compounds which can be easily purified from ethanol; they are perfectly stable in the solid state and can be kept without any particular precaution. Benzene solutions of these radicals, kept in vacuum-sealed test-tubes, have the same intensity of signal after 6 months. Table 2 sets out their analytical and spectroscopic data. In the IR spectra of these compounds no signal occurs in the OH region, which points to a high percentage of radical; indeed this percentage was determined for radical **6a** by comparison with 2,2,6,6-tetramethyl-4-piperidinol-1-oxyl (TANOL) and it was found to be 100% radical in benzene at room temperature, not dimerizing to any appreciable extent in solution at concentrations of up to 10^{-2} M. Other nitroxide radicals are obtained, together with small quantities of the deoxidation compounds, from the reaction of quinoline-N-oxides **3a–f** with methyl-(**5d–10b**), ethyl-(**5c–10c**) and benzyl-(**5d–10d**) magnesium compounds. Methyl and ethyl radicals could be obtained in the pure state as red amorphous solids which do not crystallize but which are as stable as phenyl radicals **5a–10a** are. On the contrary benzyl radicals **5d–10d** were obtained only in solution and were identified by their ESR spectra; they are not stable, the ESR signal vanishing after 2–3 hr.

When t-butylmagnesium chloride is allowed to react with quinoline-N-oxides **3a–f** only the reduction to the corresponding quinolines take place.

DISCUSSION OF THE ESR SPECTRA

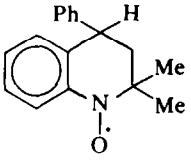
Radicals **5–10** exhibit enough resolved ESR spectra (Table 3), interpretation of which enabled their structure to be determined. They all have a 1:1:1 nitrogen triplet and a coupling constant a^N = 10.1–10.8 gauss. This value agrees with values given in the literature for radicals with

Table 2. Analytical and spectroscopic data of nitroxide radicals

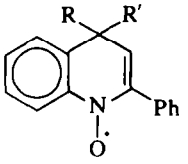
Compound	m.p.*	Analysis	Formula	found % / calcd %	IR (ν, cm⁻¹)**
	152°	$C_{21}H_{16}NO$		C 84.11 / 84.53 H 5.53 / 5.41 N 4.91 / 4.74	1590
	210°	$C_{34}H_{26}NO_2$		C 84.65 / 84.94 H 5.46 / 5.43 N 2.81 / 2.92	1595-3490-3580
	148°	$C_{23}H_{28}NC_2$		C 80.08 / 80.67 H 5.81 / 5.89 N 4.48 / 4.09	1645
	152°	$C_{22}H_{18}NC_2$		C 80.39 / 80.46 H 5.30 / 5.52 N 4.39 / 4.27	1560-1590
	159°	$C_{22}H_{17}NO_2Cl$		C 72.20 / 72.80 H 4.53 / 4.72 N 3.79 / 3.86	1560-1590

* From : EtOH ; ** in nujol

a structure of the type **11** where C-2 near the N–O group is in the sp^3 hybridation.[1,4]



11: a^N = 10.1 gauss



12

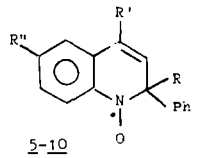
This a^N value allowed us to exclude (in agreement with te cross reaction 1) that the Grignard reagent attacks the C-4 of the ring, which could produce structures like **12**; in fact nitroxides bearing two carbons in the sp^2 hybridation bonded to the N–O group are known to exhibit lower coupling constants, 5–6 gauss in magnitude.[1,5] The greater resonance energy of the styrenic structure **5** with respect to the non-styrenic structure **12** can probably account for the greater reactivity of position 2 of the quinoline ring in comparison with position 4, even if position 2 is substituted.

ESR spectra of radicals **6a–d** are quite simple and exhibit the interaction of the unpaired electron not only with a N atom but also with two hydrogens having a^H = 3.20–3.29 gauss, and three other hydrogen with a^H = 1.07–1.19 gauss. Spin density calculations, according to MacLachlan (Table 4) revealed that in these radicals the greater coupling constant is to be assigned to the hydrogens bonded to carbons C-6 and C-8 (*para* and *ortho*, respectively, to nitrogen) and the lesser to the two C-5 and C-7 hydrogens (*meta* to nitrogen) of the quinoline ring. This attribution agrees also with values given in the literature for the corresponding hydrogens of radicals **1** and **2**[1] and **11**,[4] and it was confirmed experimentally by means of the study of the 6-OMe substituted radicals **7**, **9** and **10**, ESR spectra of which exhibit the presence of only one hydrogen having a^H = 3.5 gauss.

The third hydrogen with a^H = 1 gauss in the radicals **6** is the one bonded to the C-3. From simple MacLachlan calculations on radical **5a** (Table 4) a greater spin density is obtained for C-3 than for C-5 and C-7, whilst they appear to be equal from the ESR data. As a matter of fact, the spin density ratio $\rho_{C\text{-}3}/\rho_{C\text{-}5}$ depends on the presence of a substituent at C-4: in the ESR spectra of radicals **5**, **9** and **10**; actually, the coupling constants of the C-3 hydrogens are greater than those of C-5 and C-7 hydrogens. Better agreement between experimental and calculated data can be obtained by using a different set of parameter values in the MacLachlan calculations, i.e 0.9 and 1.10 instead of 1.0 for $k_{C_4\text{-}C_{4a}}$ and $k_{C_3\text{=}C_4}$, respectively (Table 4), which values are probably more reliable with regard of the true geometry of the molecule. More sophisticated methods of calculation would probably improve the agreement with experimental data but for lack of knowledge of the real molecular geometry we considered it not very useful to refine further our results.

ESR spectra of radicals **6b**, **c**, **d**, are slightly less resolved than spectrum of **6a**, which is attributable to the presence of other coupling constants due to the hydrogens of the R groups bonded to the C-2 of the quinoline ring and, perhaps, of the R groups of the lateral chain on the C-4. In the case of **6d**, nevertheless, if the spectrum is recorded in high resolution conditions, the presence of a further fine structure can be shown for the ESR lines, but we were not able to assign an exact numerical value to this new coupling constant, owing to the great intrinsic width of the ESR lines (in reproducing the experimental spectra

Table 3. ESR data*



5-10

Compound	a_N	$a_H(3)$	$a_H(4)$	$a_H(5,7)$	$a_H(6,8)$	$a_H(R)$	$a_H(R'')$
5a	10.17	1.42	0.55	1.07 - 1.07	3.20 - 3.20	----	----
5b	10.15	----	----	---- - ----	3.30 - 3.30	----	----
5c	10.15	----	----	---- - ----	3.25 - 3.25	----	----
5d	10.31	1.36	0.55	1.02 - 1.02	3.25 - 3.25	0.55	----
6a	10.25	1.07	----	1.07 - 1.07	3.20 - 3.20	----	----
6b	10.51	1.09	----	1.09 - 1.09	3.21 - 3.21	----	----
6c	10.38	1.08	----	1.08 - 1.08	3.29 - 3.29	----	----
6d	10.28	1.19	----	1.19 - 1.19	3.26 - 3.26	<0.15	----
8a	10.50	1.06	----	1.06 - 1.06	3.20 - 3.20	----	----
8b	10.42	1.00	----	1.00 - 1.00	3.16 - 3.16	----	----
8c	10.20	1.01	----	1.01 - 1.01	3.22 - 3.22	----	----
8d	10.40	1.07	----	1.07 - 1.07	3.31 - 3.31	<0.20	----
9a	10.78	1.42	0.55	1.05 - 1.05	3.26	----	0.35 (3H)
9b	10.7	----	----	---- - ----	3.5	----	----
9c	10.1	----	----	---- - ----	3.6	----	----
9d	10.75	1.40	0.55	1.06 - 1.06	3.60	0.55	0.35 (3H)
10a	10.65	1.40	----	1.10 - 1.10	3.25	----	0.40 (3H)
10b	10.55	----	----	---- - ----	3.40	----	----
10c	10.51	----	----	---- - ----	3.35	----	----
10d	10.60	1.40	----	1.05 - 1.05	3.40	<0.15	0.35 (3H)
7a	10.71	----	----	---- - ----	3.4	----	----
7b	10.8	----	----	---- - ----	3.5	----	----
7c	10.8	----	----	---- - ----	3.5	----	----
7d	-----	----	----	-	----	----	----

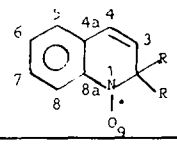
The values of the coupling constants were measured in $CHCl_3$ solution.

with the calculation best results were obtained with a band width of 0.35 gauss). In the particular case of radicals **6c** (R=Et) and **6d** (R=CH_2Ph) we were not able to point out the non-equivalence of the diastereotopic hydrogens of the CH_2 groups bonded to the C-2 of the quinoline ring, which was possible for radicals **1** and **2**.[1]

ESR spectra of the other prepared radicals **5**, **7–10** are somewhat more complex, so that a complete analysis of the spectrum was not always possible. The experimental values of the coupling constants are set out in Table 3; it can be shown that the basic features of all spectra are the same as those of radicals **6**, i.e. they are due to one nitrogen having a^N = 10.1–10.8 gauss and to one or two hydrogens with a^H = 3.1–3.6 gauss. Moreover Table 3 shows the presence of two hydrogens (those bonded to C-5 and C-7) with a^H = 1.05–1.20 gauss, and of another hydrogen (bonded to the C-3) which presents a coupling constant varying between 1.07 and 1.42 gauss. Besides, we were able to assign in some cases the value of a^H for the C-4 hydrogen, a^H = 0.55 gauss, and the a^H value for the 6-OMe group, a^H = 0.35–0.40 gauss.

Comparison of the spectra of radicals **5d** and **9d** with spectra of **5a** and **9a** is the most interesting, indicating that in **5d** and in **9d** the unpaired electron interacts with one and only hydrogen atom more than in **5a** and **9a**, and the value of the related coupling constant is 0.55 gauss, i.e. the same value of a^H for the C-4 hydrogen. This phenomenon was confirmed by the reconstruction of the experimental spectra with the calculation, and it is identical to that which we showed for radicals **1** and **2**.[1] It indicates that the two hydrogens of the CH_2–Ph group bonded to the C-2 of the quinoline ring are non-equivalent, and also in the present case we attribute the non-equivalence not to a hindered rotation about the C-2/CH_2Ph bond, but to the presence of a chiral carbon (the C-2 of the ring) linked to the CH_2. This analogy with radicals **1** and **2** is confirmed by the similar value of the corresponding coupling constants (0.55 vs 0.50 gauss) and by the fact that in the ethyl derivatives **5c** and **9c** the $a^H_{CH_2}$ value is smaller than the value for the benzyl derivatives is. As a matter of fact, for radicals **5c** and **9c** it was not possible to assign a value to this coupling constant because of the poor resolution of

Table 4. Spin density values



Atom N°	ρ (a)	ρ (b)
1	0.2341	0.2383
3	0.1241	0.0787
4	-0.0553	-0.0380
4a	0.1022	0.1046
5	-0.0561	-0.0540
6	0.1038	0.1058
7	-0.0549	-0.0540
8	0.1138	0.1159
8a	-0.0585	-0.0577
9	0.5467	0.5603

a) Calculated with $K_{C_4-C_{4a}} = K_{C_3-C_4} = 1.0$

b) Calculated with $K_{C_4-C_{4a}} = 0.9$; $K_{C_3-C_4} = 1.10$

the experimental spectra. Moreover, in the case of radicals **1** and **2** the non-equivalence of the two diastereotopic hydrogens was confirmed by the NMR spectra of the hydroxylamines obtained by reduction of the radicals, which was impossible for the radicals we are dealing with, because neither radicals nor the corresponding hydroxylamines could be isolated in the pure state and because of their instability in solution.

Finally, the coupling constants values obtained from the spectra and set out in Table 3 were confirmed in all cases by means of reconstruction of the experimental spectra with the calculation. In all cases the agreement between experimental and calculated spectra was satisfactory.

EXPERIMENTAL

The m.ps were not corrected. The IR spectra were recorded in Nujol using a Perkin–Elmer 257 apparatus; the NMR spectra were recorded in $CDCl_3$ on a Perkin–Elmer R 12B spectrometer using TMS as internal standard; the ESR spectra were recorded in $CHCl_3$ on 10^{-4} or 10^{-5} M solutions using a Varian E-4 apparatus. 2-Phenylquinoline-N-oxide,[3,6] 2-phenyl-4-carbethoxyquinoline-N-oxide,[3,6] 2-phenyl-4-ethoxyquinoline-N-oxide[7] and 2-methylquinoline-N-oxide[8] were prepared as described in the literature. The Grignard reagents were prepared according to the usual methods in N_2 atmosphere in THF, except in the cases of MeMgI and EtMgBr for which ether was used.

2-Phenyl-6-methoxyquinoline-N-oxide (**3e**). 2-Phenyl-6-methoxyquinoline[9] (10 g) in AcOH (50 ml) and 120 vol H_2O_2 (20 ml) were refluxed for 1 hr. After cooling the mixture was treated with 10% NaOH and extracted with $CHCl_3$, the $CHCl_3$ extract dried on Na_2SO_4 and evaporated to dryness; washing of the residue with ether gave **3e** (7 g). The analytical and spectroscopic data are set out in Table 1.

2-Phenyl-4-chloro-6-methoxyquinoline-N-oxide (**3f**). 2-Phenyl-4-chloro-6-methoxyquinoline[10] (10 g) in AcOH (150 ml) and 120 vol H_2O_2 (25 ml) were heated under reflux for 1 hr. **3f** was directly precipitated from the boiling soln by addition of water. The analytical and spectroscopic data are set out in Table 1.

2-Phenyl-4-carboxy-6-methoxyquinoline-N-oxide. 2-Phenyl-4-carboxy-6-methoxyquinoline[9] (10 g) in AcOH (150 ml) and 120 vol H_2O_2 (25 ml) were reacted as indicated above and 2-phenyl-4-carboxy-6-methoxy-quinoline-N-oxide was obtained (7.5 g) in a crystalline form by cooling the reaction soln. The analytical and spectroscopic data are set out in Table 1.

2-Phenyl-4-carbethoxy-6-methoxyquinoline-N-oxide (**3c**) was prepared in 60% yields from 2-phenyl-4-carboxy-6-methoxyquinoline-N-oxide working as described for 2-phenyl-4-carbethoxyquinoline-N-oxide.[3] The analytical and spectroscopic data are set out in Table 1.

Synthesis of the nitroxide radicals

General procedure. The Grignard reagent soln (10 mM in 20–30 ml of THF or Et_2O) was added to the quinoline-N-oxide soln (5 mM in 30–40 ml of THF)† under stirring in N_2 atmosphere and at room temp. After 1 hr the mixture was treated with NH_4Claq and extracted with $CHCl_3$. The $CHCl_3$ layer dried on Na_2SO_4 was evaporated to dryness and the benzene soln of the residue was chromatographed on SiO_2. In the case of PhMgBr the radicals **5a–10a** were isolated in 80–90% yields together with traces of the corresponding quinolines. The analytical and spectroscopic data of the radicals are set out in Table 2. In the case of MeMgI and EtMgBr the red nitroxide radicals were isolated in good yields as pure but amorphous non crystallizable solids, together with the corresponding quinolines in 20–40% yields. The same result was obtained when the reaction was carried out between 2-methylquinoline-N-oxide and PhMgBr. In the case of $PhCH_2MgCl$ the presence of the nitroxide radicals in the reaction solns was revealed by the ESR spectra, but chromatography gave only the corresponding quinolines in 25–50% yields and starting materials. No radicals were obtained in the reaction with t-C_4H_9MgCl, the deoxidation compound being the sole reaction product.

Assessment of the percentage of radical. The percentage of radical in compound **6a** was determined by comparing the ESR signals of benzene solns approx 10^{-3} M of radical **6a** with the ESR signals of benzene solns approx 10^{-3} M of TANOL. Double integration of the signal was carried out numerically according to Wyard[11] and the radical content proved to be 100% with a relative deviation of 1%.

Spin density calculations were carried out according to MacLachlan,[12] a value of 1.2 being attributed to λ, with the help of an automatic program. The following values, already used in similar calculations[2] were employed for the parameters:

$h_N = 1.19$ $h_N = 0.44$ $h_O = 0.84$ $k_{CC} = 1.0$
$k_{C-C} = 0.9$ $k_{C=C} = 1.10$ $k_{C-N} = 1.06$ $k_{C=O} = 1.23$
$k_{C-\dot{N}} = 1.29$ $N_{N-O} = 1.10$

†In the reaction with 4-carbethoxy derivatives a molar ratio 5:1 instead of 2:1 was used.

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