Stable Nitroxide Radicals. Reaction between 2-Cyano- and 4-Cyanobenzoquinoline *N*-Oxides and the Grignard Reagent

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2,2-Diphenylbenzoquinolinenitroxide radicals were obtained starting from 2-phenyl-, 2-cyano, 4-cyano-benzoquinoline *N*-oxides, or from unsubstituted benzoquinoline *N*-oxides with phenylmagnesium bromide. The elimination of bromomagnesium hydride from the 2-unsubstituted benzoquinoline *N*-oxides and cyano-magnesium bromide from the 2- or 4-cyanobenzoquinoline *N*-oxides is discussed.

In previous papers we demonstrated that stable nitroxide radicals can be easily synthesized with Grignard reagents starting from indole *N*-oxides (1) and 2-substituted quinoline *N*-oxides (2). Recently we verified that the same results can be obtained from quinoline *N*-oxides, 2-methoxy- and 2-cyanoquinoline *N*-oxides (3). 2-Cyano- and 4-cyanoquinoline *N*-oxides exhibited a different behaviour towards the Grignard reagent. In fact the 2-cyanoquinoline *N*-oxides, with arylmagnesium bromide, form the corresponding 2,2-diaryl-substituted nitroxide radicals with elimination of the cyano group, whereas the 4-cyanoquinoline *N*-oxides lead to 2,2-diaryl-substituted nitroxide radicals without involving the cyano group. These results prompted us to study the behaviour of 2-cyano- and 4-cyanobenzoquinoline *N*-oxides towards the Grignard reagent, both to investigate further the elimination of the cyano group from the 2 and 4 positions and to synthesize stable nitroxide radicals from benzoquinoline *N*-oxides.

Results.

2-Cyano-3,4-benzoquinoline *N*-oxide (1) reacted with phenylmagnesium bromide in a 1:3 ratio to form 2,2-diphenyl-3,4-benzoquinoline-1-oxyl (4) in good yield. The same nitroxide radical was obtained from 2-phenyl-3,4-benzoquinoline *N*-oxide (3) or 3,4-benzoquinoline *N*-oxide (2) in the reaction with phenylmagnesium bromide (Scheme 1).
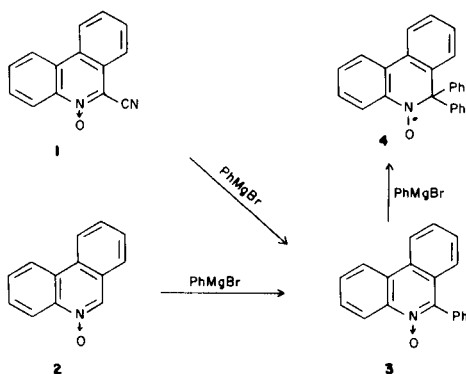
2-Cyano-5,6-benzoquinoline *N*-oxide (5) reacted with phenylmagnesium bromide, to give 2,2-diphenylbenzo-quinoline-1-oxyl (8), similarly to compound 1; nitroxide radical 8 was also obtained both from the unsubstituted *N*-oxide 7 and from 2-phenyl-5,6-benzoquinoline *N*-oxide (9) (Scheme 2).

Scheme 2
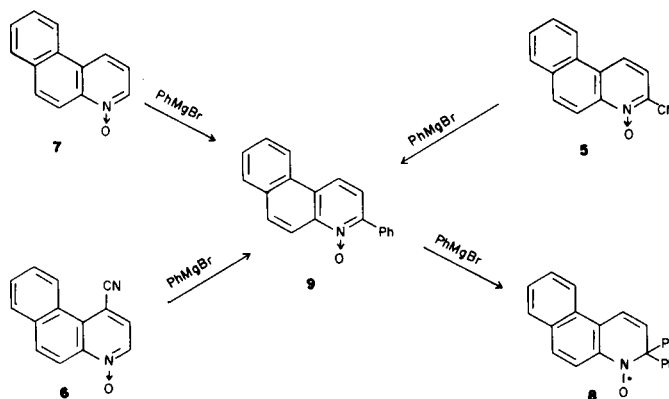
In addition 4-cyano-5,6-benzoquinoline *N*-oxide (6) reacted with phenylmagnesium bromide leading to nitroxide radical 8 with the elimination of the cyano group at C-4, (Scheme 2), whereas 2-phenyl-4-cyano-5,6-benzoquinoline *N*-oxide reacted with phenylmagnesium bromide giving, nitroxide radical 11 without involving

Block I
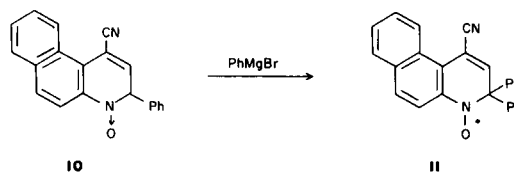
the cyano group at C-4. 2-Cyano-7,8-benzoquinoline *N*-oxide (12) behaved similarly to *N*-oxides 1 and 5. In fact, nitroxide radical 15 was obtained both from *N*-oxide 12 or *N*-oxides 13 and 14 (Scheme 3).

Scheme 1

Scheme 3
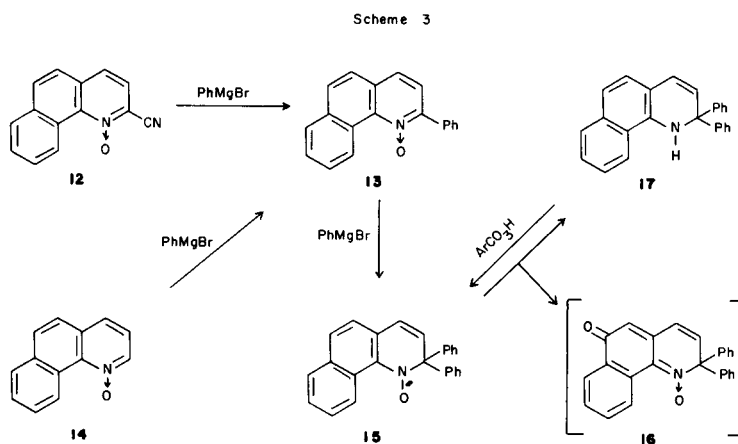
The new starting materials and compounds isolated (Table 1) in the reactions were identified from their analytical and spectroscopic data, which are reported in Table 2.
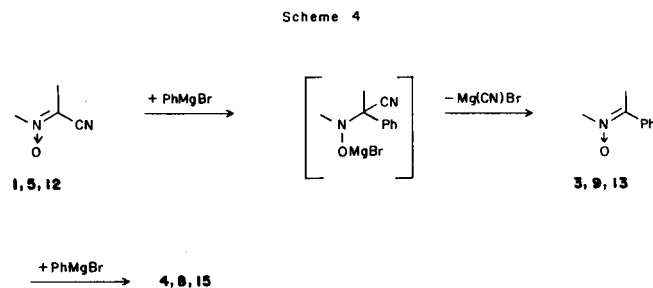
Table 1

Reaction of Benzoquinoline N-Oxides 1, 2, 3, 5, 6, 7, 9, 10, 12, 13 and 14 with Phenylmagnesium Bromide

N-Oxide	Products (% yield)		
1	—	—	4 (95)
2	18 (10) (a)	3 (85)	4 (5)
3	—	—	4 (85)
5	19 (4) (b)	9 (82)	8 (14)
6	—	9 (87)	8 (13)
7	19 (35) (b)	9 (60)	8 (5)
9	—	9 (76)	8 (24)
10	—	—	11 (95)
12 (c)	—	—	15 (e)
13 (c)	—	—	15 (e)
14	20 (78) (d)	13 (22)	—

(a) A. Pictet and L. Hubert, *Ber.*, **29**, 1183 (1901). (b) Ref. (12). (c) The main product was the amine **17** (30% yield). (d) Ref. (12). (e) Radical **15**, the signal of which was detected during the reaction, was not isolated.

Scheme 4

was demonstrated by a separate reaction between 2-phenyl-substituted N-oxides **3,9**, and **13** and phenylmagnesium bromide. This last experiment confirmed the intermediate formation of 2-phenyl-substituted N-oxides **3,9**, and **13**, and the complete elimination of the cyano group (3,4); in fact the nitroxide radicals yields were almost quantitative, starting, both from N-oxides **3** and **9**, and from 2-cyano-derivatives **1** and **5** (Scheme 4).

Nitroxide radicals **4,8**, and **15** were also obtained starting from unsubstituted quinoline N-oxides **2,7**, and **14** and phenylmagnesium bromide. The reaction was interpreted as shown in Scheme 5, assuming bromomagnesium hydride is eliminated with the formation of the 2-phenyl

Discussion.

The formation of nitroxides **4,8**, and **15** from 2-cyano-benzoquinoline N-oxides **1,5**, and **12** with phenylmagnesium bromide can be explained by assuming 2-phenylbenzoquinoline N-oxides **3,9**, and **13** are the reaction intermediates, which are formed by attack of the Grignard reagent at C-2, followed by the elimination of cyanomagnesium bromide, as was already proposed for the 2-cyanoquinoline N-oxides (3) (Scheme 4). The formation of N-oxides **3,9**, and **13**, which react with the excess Grignard reagent to give nitroxide radicals **4,8**, and **15**,

Scheme 5

Table 2

Analytical and Spectroscopic Data of New Compounds

| Compound	Solvent	m.p. (°C)	Analysis Formula	% Found (a)			Ir (cm^{-1})
				C	H	N	
1	AcOH	263	$C_{14}H_8N_2O$	76.13 (76.35)	3.55 (3.66)	12.59 (12.72)	2238 (b)
4	EtOH	175	$C_{25}H_{18}NO$	85.78 (86.18)	5.23 (5.20)	4.19 (4.08)	
6	AcOH	268	$C_{14}H_8N_2O$	76.50 (76.35)	3.64 (3.66)	12.67 (12.72)	2238 (b)
8	EtOH	158	$C_{25}H_{18}NO$	86.31 (86.18)	5.29 (5.20)	4.14 (4.02)	
9	EtOH	194	$C_{19}H_{13}NO$	84.14 (84.11)	5.03 (4.83)	5.20 (5.16)	
10	EtOH	191	$C_{20}H_{12}N_2O$	81.01 (81.06)	4.10 (4.08)	9.51 (9.45)	2225 (b)
11	EtOH	139	$C_{26}H_{17}N_2O$	83.34 (83.62)	4.53 (4.59)	7.50 (7.50)	2190 (b)
12	EtOH	229	$C_{14}H_{18}N_2O$	76.12 (76.35)	3.79 (3.66)	12.14 (12.72)	2230 (b)
13	EtOH	139	$C_{19}H_{13}NO$	84.49 (84.11)	4.79 (4.83)	5.22 (5.16)	
17	benzene-petroleum ether	294	$C_{24}H_{19}N$	89.57 (89.68)	5.76 (5.96)	4.88 (4.36)	

(a) Calculated values in parenthesis. (b) CN.

N-oxides **3,9**, and **13**, which then react with excess Grignard reagent to give nitroxide radicals **4,8** and **15**; on account of the slowness of the bromomagnesium hydride elimination (3), the main products were 2-phenyl-substituted *N*-oxides **3,9** and **13** (5) and 2-phenyl-substituted free bases **18,19**, and **20** (Scheme 5; Table 1).

The elimination of bromomagnesium hydride, already discussed by us (3), has been proposed by others in the reaction of *o*-substitution of azobenzenes with Grignard reagent (6). In addition, 4-cyano-5,6-benzoquinoline (6) forms nitroxide radical **8** and 2-phenyl *N*-oxide **9** in almost quantitative yield with phenylmagnesium bromide (Table 1). The complete elimination of the cyano group could be explained by assuming (Scheme 6) a phenylmagnesium bromide attack at C-2, and the elimination of bromomagnesium hydride, with formation of 2-phenyl-4-cyano *N*-oxide (**10**). Compound **10** could be reduced by bromomagnesium hydride to give, through the intermediate **22**, the 2-phenyl *N*-oxide **9**, which is responsible for the formation of nitroxide radical **8**. Other mechanistic interpretations cannot be excluded even though the 4-cyano-2-phenylbenzoquinoline *N*-oxide (**10**), when treated with sodium borohydride, gives 2-phenylbenzoquinoline *N*-oxide (**9**). In fact, it is our opinion that the more probable tautomeric equilibrium between intermediates **21**
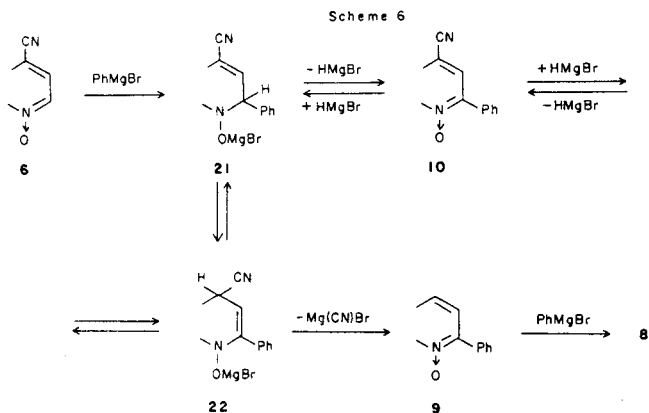
Scheme 7
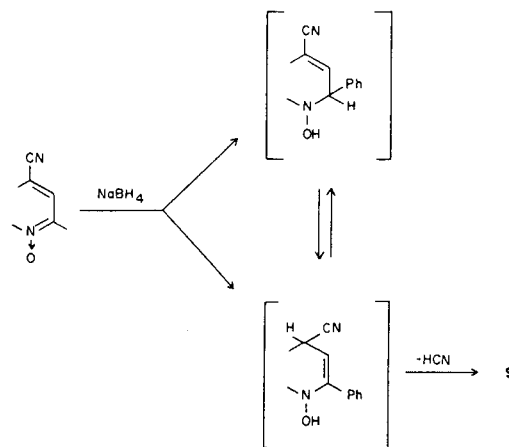
Scheme 6

and **22** (7) cannot be excluded, nor can the 1,2 attack followed by the tautomerization be excluded in the reduction with sodium boronhydride (8) (Scheme 7).

Whatever the reaction pathway may be, 4-cyano-5,6-benzoquinoline *N*-oxide (**6**) reactivity is determined by the presence of the hydrogen at C-2 in intermediate **21**. In fact, when the reaction with phenylmagnesium bromide is carried out on 2-phenyl-4-cyano-5,6-benzoquinoline *N*-oxide (**10**), 2,2-diphenyl-4-cyano-5,6-benzoquinoline-1-oxyl (**11**) is obtained in almost quantitative yield. The lack of a hydrogen at C-2 in intermediate **23** (Scheme 8) prevents the eliminatin of cyano group.

Scheme 8
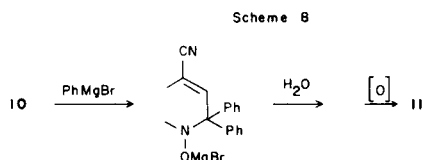
Nitroxide radicals **4,8,** and **11** are stable and were isolated in the solid crystalline state. The percentage of the unpaired electron, which is 100%, was determined as already described in the literature (1). The signal of nitroxide **4** was perfectly simulated with the following hpccs: $a^N = 11.05(G)$ $a^{H-6} = a^{H-8} = 2.78(G)$; $a^{H-5} = a^{H-7} = 1.00(G)$, and two hydrogens of the 3,4-benzo with $a^H = 0.35(G)$. These values reproduce the same spin-density distribution observed in the quinoline nitroxides (2). The signals of nitroxides **8,11**, and **15**, which show $a^N = 9.50(G)$, 9.25(G) and 8.90(G), respectively, were not well resolved so that complete interpretation was not possible.

Nitroxide radical **15** was not stable enough to be isolated, but it was detected in all reactions of Scheme 3 and was regenerated by treatment with the *m*-chloroperbenzoic acid of amine **17**, which is the isolated product. The formation of amine **17** could be explained by assuming a disproportionation process (9), even though the corresponding quinonimine *N*-oxide **16** was not isolated.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded in nujol mulls with a Perkin-Elmer 257 spectrometer. Esr spectra were recorded in a chloroform solution with a Varian E4 spectrometer. Compounds 1 (10), 2 (11), 3 (12), 7 (13) and 14 (13) were prepared as described in the literature. Phenylmagnesium bromide was prepared in THF according to the usual method.

2-Cyano-5,6-benzoquinoline *N*-Oxide (**5**).

Hydrogen peroxide (36% w/w) (6 ml.) was added to a solution of 2-cyano-5,6-benzoquinoline (14) (10 mmoles) in acetic acid (30 ml.). The mixture was heated with a steam-bath for 3 hours. Another 6 ml. of hydrogen peroxide was added to the mixture which was heated for another 3 hours. The solvent was evaporated to dryness under vacuum and the residue was chromatographed on a silica column using benzene as the eluent (yield, 82%). Analytical and spectroscopic data are reported in Table 2.

2-Cyano-7,8-benzoquinoline *N*-Oxide (**12**).

This compound was prepared by the method described for **5** starting from 2-cyano-7,8-benzoquinoline (13) (yield, 20%). Analytical and spectroscopic data are reported in Table 2.

4-Cyano-5,6-benzoquinoline *N*-Oxide (**6**).

This compound was also prepared by the method described for compound **5** starting from 4-cyano-5,6-benzoquinoline (13) (yield, 72%). Analytical and spectroscopic data are reported in Table 2.

2-Phenyl-4-cyano-5,6-benzoquinoline *N*-Oxide (**10**).

2-Phenyl-4-carboxy-5,6-benzoquinoline (15) (13 g.) was refluxed in thionyl chloride (70 g.) for 3 hours. The excess of thionyl chloride was evaporated and the residue was treated with 20 ml. of 34% w/w ammonium hydroxide with stirring, 2-Phenyl-5,6-benzoquinoline-4-carbamide was obtained in quantitative yield, m.p. 268° from ethanol.

Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.51; H, 4.73; N, 9.39. Found: C, 80.67; H, 4.65; N, 9.45.

Thionyl chloride (15 g.) was added to a solution of the carbamide derivative (3 mmoles in 120 ml. of dimethylformamide) at a rate such that the temperature remained below 5°. The reaction mixture was then kept at room temperature for 12 hours. With the addition of water (120 ml.), 2-phenyl-4-cyano-5,6-benzoquinoline precipitated quantitatively, m.p. 184° from benzene-petroleum ether.

Anal. Calcd. for $C_{20}H_{12}N_2$: C, 85.70; H, 4.31; N, 9.99. Found: C, 85.78; H, 4.37; N, 9.75.

The corresponding *N*-oxide **10** was prepared as described for compound **5** (yield, 75%). Analytical and spectroscopic data are reported in Table 2.

Reaction with Phenylmagnesium Bromide.

The Grignard reagent (30 mmoles in 30 ml. of tetrahydrofuran) was added over 10 minutes to a solution of the *N*-oxide (10 mmoles in 70 ml. of THF) at room temperature in a nitrogen atmosphere and with stirring. After 3 hours, the reaction mixture was poured into 10% aqueous ammonium chloride and extracted with chloroform. The chloroform layer was dried on sodium sulphate and evaporated to dryness. The residue was dissolved in benzene and treated with lead dioxide (2 g.). The filtered benzene solution was chromatographed on a silica column using benzene as the eluent. The data in the isolated products are summarized in Table 1.

Reduction of **10** with Sodium Borohydride.

Sodium boronhydride (10 mmoles) was added to a solution of 2-phenyl-4-cyano-5,6-benzoquinoline *N*-oxide (1 mmoles in 30 ml. of tetrahydrofuran-methanol in a 1:1 ratio). After 3 hours the reaction mixture was poured into 10% aqueous ammonium chloride and extracted with chloroform. The chloroform layer was dried over sodium sulphate and evaporated to dryness, yielding the corresponding 2-phenyl-5,6-benzoquinoline in quantitative yield.

Oxidation of **17** with *m*-Chloroperbenzoic Acid.

m-Chloroperbenzoic acid in a 10^{-2} M solution and of 1,2-dihydro-2,2-diphenyl-7,8-benzoquinoline **17** were mixed in the esr cavity using an inverted U aqueous cell (16). The recorded signal corresponded to that of nitroxide radical **15**.

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recovered at the end of the reaction comes from the hydrolysis and subsequent oxidation of the intermediate (3) (Scheme 5).

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