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HOMOLYTIC SUBSTITUTIONS IN INDOLINONE NITROXIDE RADICALS—III

REACTIONS WITH TERBUTOXY AND METHYL RADICALS

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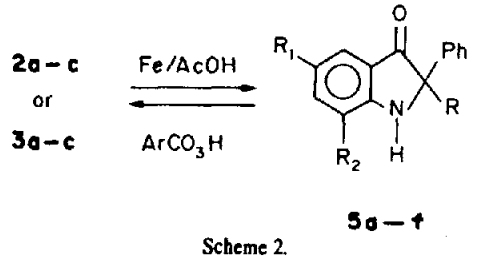
Abstract—Nitroxide radicals **1a–c** react with terbutoxy radical to form terbutoxy substituted radicals **2**, **3** and **4**. The reaction mechanism is interpreted in terms of homolytic substitution. The terbutoxy substituted nitroxides can be easily oxidized to quinoneimine *N*-oxides **6**, **7**, **8** and **9**. The interpretation of the evolution of radicals **2**, **3** and **4** in the reaction mixture is confirmed by experimental evidence. The reaction of nitroxide **1a–c** with the methyl radical is also described.

Indolinone nitroxide radicals (1,2 - dihydro - 2,2 - disubstituted - 3 - oxo - 3H - indol - 1 - oxyls) **1a–c**, which have the nitroxide function in the conjugated position with a π system of the molecule[1] show interesting reactivity, which differs from that of the classical nitroxides, e.g. 2,2,6, 6 - tetramethylpiperidine-1-oxyl and similar.[2] In fact, radicals of the latter type have the nitroxide group between two trisubstitute sp^3 carbons.

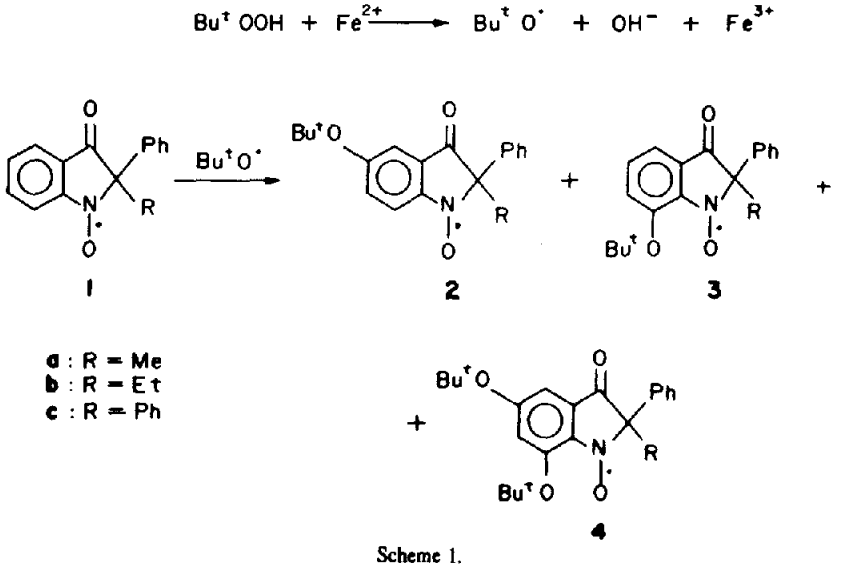
Nitroxides **1a–c** react with nucleophiles ($ArCO_2^{-3}$, Br^{-4}, $MeOH^3$) at the indole nucleus in the presence of oxidants, whereas with electrophilic readicals, such as aroyloxyl radicals, they undergo homolytic substitution.[5] In the present paper the reactions of **1a–c** with terbutoxy and methyl radicals are described.

RESULTS

Nitroxide radicals **1a–c** were reacted with terbutoxy radical (originating from the decomposition of terbutylhydroperoxide with iron (II)[6]) to form terbutoxy substituted nitroxides **2a–c**, **3a–c** and **4c** (Scheme 1). All reactions were carried out at room temperature in aqueous acetonitrile, for 10 min, using the nitroxide and terbutoxy radical in a 1:3 ratio. Compounds **2a–c**, **3a–c** and **4c** (the last isolated only for nitroxide **1c**) were separated by preparative TLC and identified by their ESR spectra (Table 1) and by the NMR spectra of the corresponding amines **5a–f** (Table 2). In fact, nitroxides **2** and **3** gave amines **5** by iron acetic acid reduction (Scheme 2). Amine **5c**, in which the terbutoxy group was at C-5 of the indole nucleus, showed an NMR spectrum with a doublet at δ 6.88 (J = 9.4 Hz) corresponding to the C-7 hydrogen. Amine **5d**, the isomer corresponding to **5c**, in which the terbutoxy group was at C-7 of the indole nucleus, clearly showed a *pseudo*-quartet in the NMR



Scheme 2.



Scheme 1.

Table 1. Hfccs* (in gauss) of nitroxides **2a–c**, **3a–c** and **4c** in $CHCl_3$ solution

Nitroxide	a^N	$a^{H-4} = a^{H-6}$	a^{H-5}	a^{H-7}	a^R
2a	9.30	1.02(2H)	-	2.88	0.12(3H)
3a	9.40	0.92(2H)	3.18	-	0.18(3H)
2b	9.72	0.93(2H)	-	2.88	0.30(1H)
3b	9.30	1.02(2H)	3.20	-	0.28(1H)
2c	9.70	0.95(2H)	-	2.85	-
3c	9.30	0.95(2H)	3.15	-	-
4c	9.57	0.82(2H)	-	-	-

*These values were confirmed by computer simulation of the experimental spectra.

spectrum, at δ7.33 ($J = 8.0$ Hz and $J = 7.0$ Hz) corresponding to the C-5 hydrogen, which is typical of an ABC system. The amines **5a–f** gave nitroxides **2a–c** and **3a–c** by oxidation with *m*-chloroperbenzoic acid (Scheme 2). Monosubstituted nitroxides **2** and **3** were also identified on the basis of the hfccs of C-7 and C-5 hydrogens, which were *ca.* 3.2 Gauss and *ca.* 2.9 Gauss respectively (Table 1). The reason for this difference has been discussed previously.[5]

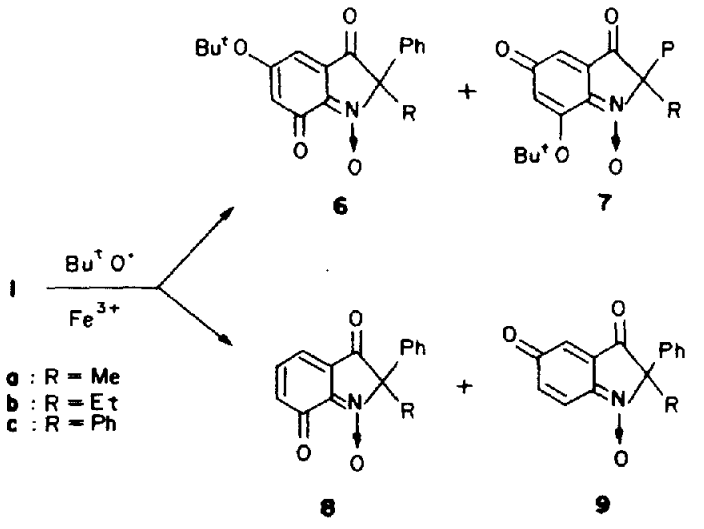
The diterbutoxy substituted nitroxide **4c** was identfied by its ESR spectrum, which showed three groups of three bands with relative intensity of 1:2:1, due to one nitrogen ($a^N = 9.57$ Gauss) and two equivalent hydrogens ($a^H = 0.82$ Gauss) (Table 1).

When the reactions of **1a–c** with terbutoxy radical were carried out using the reagents in a 1:6 ratio and a reaction time of 2 h, quinoeimine *N*-oxides **6**, **7**, **8** and **9** were isolated. Compounds **6a–c**, **7a–c**, **8a–c** and **9a–c**

Table 2. Spectroscopic data of amines **5a–f**

Amine[a]	R	R_1	R_2	m.p.°C[b]	IR (ν) cm^{-1}[c]	NMR(δ) in $CDCl_3$
5a	Me	Bu^tO	H	-	1620[d]-1695[e] 3425[f]	1.29(9H,s,Bu^t);1.71(3H,s,Me);4.96(1H, broad,NH);6.84(1H,d,arom,J=9.5Hz); 7.1-7.6(7H,m,arom.).
5b	Me	H	Bu^tO	122	1607[d]-1695[e] 3310[f]	1.48(9H,s,Bu^t);1.75(3H,s,Me);5.05 (1H,broad,NH);6.76(1H,pseudo-q,arom, J=7.5Hz);7.2(1H,d,arom,J=7.5Hz);7.3-7.6(6H,m,arom.).
5c	Et	Bu^tO	H	-	1620[d]-1695[e] 3425[f]	0.84(3H,t,$CH_2\underline{CH_3}$);1.29(9H,s,Bu^t);2.14 (2H,q,$\underline{CH_2}CH_3$);4.92(1H,broad,NH);6.28 (1H,d,arom,J=9.4Hz);7.1-7.7(7H,m,arom.).
5d	Et	H	Bu^tO	-	1610[d]-1700[e] 3430[f]	0.85(3H,t,$CH_2\underline{CH_3}$);1.49(9H,s,Bu^t);2.16 (2H,q,$\underline{CH_2}CH_3$);5.08(1H,broad,NH);7.33 (1H,pseudo-q,arom,J=7.0Hz,J=8.0Hz); 7.1-7.6(7H,m,arom.).
5e	Ph	Bu^tO	H	188	1620[d]-1680[e] 3370[f]	1.30(9H,s,Bu^t);5.0(1H,broad,NH);6.84 (1H,d,arom.,J=9.0Hz);7.13(1H,d,arom., J=2.0Hz);7.1-7.6(11H,m,arom.).
5f	Ph	H	Bu^tO	191	1610[d]-1670[e] 3235[f]	1.45(9H,s,Bu^t);5.17(1H,broad,NH);6.76 (1H,pseudo-q,arom.,J=8.0Hz);7.12(1H, d,arom.,J=1.6Hz);7.2-7.5(1H,m,arom.).

a,Each compound gave the expected molecular ion peak in its mass spectrum. Compounds **5b**, **5e** and **5f** gave satisfactory elemental microanalysis: C,H and N ± 0.3%. Compounds **5a**, **5c** and **5d** were purified by preparative TLC from benzene. b, from benzene petroleum ether; c, from nujol; d, Ph-NH-$\overset{|}{C}$- ; e, $\rangle C=O$; f, NH.



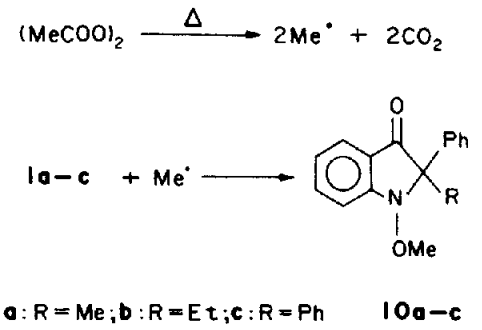
Scheme 3.

Table 3. Spectroscopic data of quinoneimine *N*-oxides 6a–c, 7a–c, 8a–c and 9a–c

Compound[a]	UV[b] max(log ε)	IR(ν)cm^{-1}[c]	NMR(δ) in CD_3CO CD_3
6a	-	1615-1625 1740	1.54(9H,s,Bu^t);1.96(3H,s,Me);6.4(1H,d,arom., J=1.5Hz);6.78(1H,d,arom.,J=1.5Hz);7.35(5H,s, arom.).
6b	-	1620-1632 1748	0.87(3H,t,$CH_2\underline{CH_3}$);1.56(9H,s,Bu^t);2.52(2H,q, $\underline{CH_2}CH_3$);6.39(1H,d,arom.,J=2.0Hz);6.74(1H,d, arom.,J=2.0Hz);7.38(5H,s,arom.).
6c	217(4.27);273(4.12) 353(4.22);4.70(3.31)	1620-1633 1733	1.54(9H,s,Bu^t);6.41(1H,d,arom.,J=2.0Hz);6.81 (1H,d,arom.,J=2.0Hz);7.2-7.5(10H,m,arom.).
7a	-	1600-1622 1746	1.59(9H,s,Bu^t);1.98(3H,s,Me);6.32(1H,d,arom., J=1.5Hz);6.74(1H,d,arom.,J=1.5Hz);7.4(5H,s, arom.).
7b	-	1600-1620 1742	0.89(3H,t,$CH_2\underline{CH_3}$);1.58(9H,s,Bu^t);2.52(2H,q, $\underline{CH_2}CH_3$);6.33(1H,d,arom.,J=1.5Hz);6.71(1H,d, arom.,J=1.5Hz);7.40(5H,s,arom.).
7c	217(4.31);265(4.08) 3.68(4.23)	1604-1632 1750	1.60(9H,s,Bu^t);6.34(1H,d,arom.,J=1.5Hz);6.75 (1H,d,arom.,J=1.5Hz);7.2-7.5(10H,m,arom.).
8c	218(4.35);3.40(3.90) 445(3.64)		
9a	-	1607-1620 1757	2.04(3H,s,Me);6.7(1H,d,arom.,J=1.2Hz);6.85 (1H,pseudo-q,arom.,J=9.8Hz,J=1.2Hz);7.45(5H, s,arom.);7.90(1H,d,arom.,J=9.8Hz).
9b	-	1605-1618 1752	0.87(3H,t,$CH_2\underline{CH_3}$);2.62(2H,m,$\underline{CH_2}CH_3$);6.70(1H, d,arom.,J=1.7Hz);6.85(1H,pseudo-q,arom.,J= 10Hz,J=1.7Hz);7.44(5H,s,arom.);7.94(1H,d, arom.,J=10Hz).
9c	219(4.40); 3.88(4.24)	1607-1620 1750	6.77(1H,d,arom.,J=1.7Hz);6.87(1H,pseudo-q, arom.,J=9.9Hz,J=1.7Hz);7.3-7.6(10H,m,arom.); 7.94(1H,d,arom.,J=9.9Hz).

a,Each compound gave a satisfactory elemental microanalysis;C,H,and N ± 0.23%. IR and NMR spectra of 8a-c have been previously described[5b]; b, in 95% EtOH; c, in nujol.

were identified by their analytical and spectroscopic data (Table 3). The UV spectrum of **8c** compared with that of **9c**, showed absorption at a higher wavelength (Table 3). This result is in agreement with the larger system existing between the carbonyl and the *N*-oxide groups. On the other hand, the NMR spectra of compounds **8a–c**[5] and **9a–c** clearly showed an ABC and an ABX system, respectively (Table 3). The structures of compounds **6a–c** and **7a–c**, for which the NMR spectra were less significant, were determined by thier UV spectra. In fact, compound **6c** showed an absorption maximum at a higher wavelength than compound **7c**, in agreement with that stated before for compounds **8c** and **9c**.



Scheme 4.

DISCUSSION AND CONCLUSIONS

Much work has been done in the last decade on the reactivity of terbutoxy radical in the H-atom abstraction;[7] less has been done on the addition[8,9] and substitution[10] reactions of this radical.

Despite its high rate of decomposition, the terbutoxy radical[11] might be trapped unchanged by nitroxides **1a–c**. The formation of compounds **2**, **3** and **4** was interpreted as a homolytic substitution and the attack mechanism of the terbutoxy radical on nitroxides **1a–c** could be the same as that proposed for the disproportionation reaction of aryl-alkyl nitorxides[12] and the one previously discussed for nitroxides **1a–c** with aroyloxyl radicals.[5]

The fragmentation of terbutoxy radical[6] did not effect the reaction products. In fact, the methyl radical (generated in benzene by the decomposition of diacylperoxide at 60°) in the presence of nitroxides **1a–c** quantitatively yielded the corresponding *O*-methyl hydroxylamines **10a–c** (Scheme 4, Table 5). Compounds **6**, **7**, **8** and **9** formed from nitroxides **2**, **3** and **4**. Reacting these nitroxides under the same conditions followed for nitroxides **1a–c**, compounds **6**, **7**, **8** and **9** were isolated.

After it was verified that the terbutylhydroperoxide was not able to oxidize nitroxides **2**, **3** and **4**, a successful oxidation was achieved with iron (III) in aqueous acetonitrile at room temperature. (The iron (III) is formed during the decomposition of terbutylhydroperoxide with iron (II) in the main reaction).[6] Quinoneimine *N*-oxides **9c** and **8c** were quantitatively obtained from **2c** and **3c**, respectively (eqns 1 and 2); whereas compounds **6c** and **7c** were isolated by oxidizing **4c** under the same conditions (eqn 3).

$$\mathbf{2c} + Fe^{3+} \rightarrow \mathbf{9c} + Fe^{2+} \quad (1)$$

$$\mathbf{3c} + Fe^{3+} \rightarrow \mathbf{8c} + Fe^{2+} \quad (2)$$

$$\mathbf{4c} + Fe^{3+} \rightarrow \mathbf{6c} + \mathbf{7c} + Fe^{2+}. \quad (3)$$

Summarizing, the reaction of nitroxides **1a–c** with terbutoxy radical can be considered to be an easy method for preparing terbutoxy substituted indoxyls **5a–f** and quinoneimine *N*-oxides **6a–c** and **7a–c**.

Table 4. Percent yields of quinoneimine *N*-oxides **6a–c**, **7a–c**, **8a–c** and **9a–c**

Nitroxide	Products (% yields)			
1a	6a (5)	7a (8)	8a (20)	9a (56)
1b	6b (10)	7b (16)	8b (25)	9b (45)
1c	6c (15)	7c (18)	8c (27)	9c (33)

Table 5. Physical and spectroscopic data of compounds **10a–c**

Compound[a]	m.p. °C[b]	NMR(δ) in $CDCl_3$
10a	81	1.78(3H,s,Me); 3.82(3H,s,NOMe); 6.8–8.0(9H,m,arom.).
10b	oil	1.8(3H,t,$CH_2\underline{CH_3}$);2.48(2H,m,$\underline{CH_2}CH_3$); 3.85(3H,s,NOMe);6.8–7.9(9H,m,arom.).
10c	100	3.87(3H,s,NOMe);7.0–7.9(14H,m,arom.).

a, Compounds 10a and 10c gave satisfactory microanalyses: C,H, and N ± 0.26%. Each compound gave the expected molecular ion peak in its mass spectrum; b, from n-heptame.

EXPERIMENTAL

M.ps were uncorrected. The IR spectra were recorded using a Perkin–Elmer 257 spectrophotometer. The ESR spectra were recorded in $CHCl_3$ solution on a Varian E4 spectrometer. The ^1H NMR spectra were recorded on a Varian XL 100 spectrometer. The UV spectra were recorded on a Perkin—Elmer 204 spectrophotometer. The mass spectra were recorded on a Varian 112 S apparatus. Nitroxides **1a–c**[13] and diacetylperoxide[14,15] were prepared as described in the literature.

Reactions of nitroxides **1a–c** *with terbutoxy radical.* 6 Mmoles of $FeSO_4 \cdot 7H_2O$ in 40 ml of H_2O were added to a solution of 2 mmoles of **1a–c** and 6 mmoles of terbutylhydroperoxide in 100 ml of MeCN at room temperature and with stirring. After 10 min the reaction mixture was poured into 100 ml of water and extracted with benzene (100 ml). The benzene layer, washed with H_2O (3 × 50 ml), was dried on Na_2SO_4 and chromatographed on a SiO_2 column from benzene. The monosubstituted nitroxides **2a–c** and **3a–c** were separated together in 50–70% yields and in a 3:1 ratio, respectively. In the case of **1c**, the diterbutoxy substituted **4c** was also isolated in 8% yield. The mixture of **2** and **3** was resolved by chromatography on SiO_2 preparative tlc from petroleum ether/ethylacetate 9:1.

Amines **5a–f** *from nitroxides* **2a–c** *and* **3a–c**. The nitroxide **2** and **3** mixture (500 mg) and iron powder (1 g) were refluxed for 5 min in 15 ml of acetic acid. After cooling, the reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was taken up with benzene (50 ml) and 10% aqueous $NaHCO_3$ (50 ml). The residue from the benzene layer, evaporated to dryness, was chromatographed on SiO_2 preparative tlc, eluting with petroleum ether/ethylacetate 9:1. The yellow C-5 and C-7 monoterbutoxy substituted amines were isolated in yields greater than 75%, and in a 3:1 ratio. The spectroscopic data of amines **5a–f** are reported in Table 2.

Nitroxides **2a–c** *and* **3a–c** *from amines* **5a–f**. Amine **5** (10 mg in 1 ml of $CHCl_3$) and the equimolar quantities of *m*-chloroperbenzoic acid were each placed in one of the two legs of the inverted U cell, similar to that described by Russel,[16] and degassed with nitrogen. The mixed solution was transferred to the ESR cavity. The recorded signal was the same as the precursor nitroxide **2** or **3**.

Quinoneimine N-*oxides* **6a–c**, **7a–c**, **8a–c** *and* **9a–c** *from nitroxides* **1a–c**. 12 Mmoles of $Fe_2SO_4 \cdot 7H_2O$ in 40 ml of H_2O were added to a solution of 2 mmoles of nitroxide **1** and 12 mmoles of terbutylhydroperoxide in 100 ml of MeCN at room temperature and with stirring. After 2 h the reaction mixture was worked up as described above. Two fractions were isolated by chromatography on a SiO_2 column from benzene/acetone 9:1. The first, yellow fraction was a mixture of compounds **7** and **9** and the second, red fraction was a mixture of **6** and **8**. Compounds **7** and **9** were separated on SiO_2 preparative tlc from petroleum ether/ethylacetate 7.5:2.5. The mixture of **6** and **8** was resolved by SiO_2 preparative tlc from benzene/acetone 9.5:0.5. Spectroscopic data of compounds **6a–c**, **7a–c**, **8a–c** and **9a–c** are reported in Table 3; the yields are reported in Table 4.

Quinoneimine N-*oxides* **6a–c**, **7a–c**, **8a–c** *and* **9a–c** *from monoterbutoxy substituted nitroxides* **2a–c** *or* **3a–c**. By reacting 1 mmole of **2** or **3** in 50 ml of MeCN and 3 mmoles of terbutylhydroperoxide with 3 mmoles of $FeSO_4 \cdot 7H_2O$ in 20 ml of H_2O as described above for 2 h, compounds **6**, **7**, **8** and **9** were formed whether starting from nitroxide **2** or from nitroxide **3**.

Oxidation of nitroxide **2c**, **3c** *and* **4c** *with iron (III).* $FeCl_3$ (100 mg in 3 ml of H_2O) was added to a solution of **2c** (50 mg in 10 ml of MeCN) at room temperature and with stirring. After 1 h the reaction mixture was poured into 30 ml of H_2O and extracted with benzene (20 ml). The benzene layer was separated and dried on Na_2SO_4 and then chromatographed on SiO_2 preparative. The quinoneimine *N*-oxide **9c** was isolated quantitatively.

Nitroxide **3c**, reacted as described above, gave quantitatively quinoneimine *N*-oxide **8c**.

The diterbutoxy substituted nitroxide **4c** with $FeCl_3$ gave quinoneimine *N*-oxides **6c** and **7c** in 65% and 25% yields, respectively. Compounds **6c** and **7c** were separated on SiO_2 preparative tlc from benzene/acetone 9.5:0.5.

Reactions of nitroxides **1a–c** *with diacetylperoxide.* Nitroxide **1a** (1 mmole in 30 ml of benzene) and diacetylperoxide (4 mmoles) were heated at 60° for 8 h. Then the reaction mixture was washed with 10% $FeSO_4 \cdot 7H_2O$ (2 × 20 ml) and then with H_2O (2 × 20 ml). The benzene layer, dried on Na_2SO_4, was chromatographed on a SiO_2 column from petroleum ether/ethylacetate 9:1. Compound **10a** was isolated in 75% yield.

From nitroxides **1b** and **1c** compounds **10b** and **10c** were isolated in 70% and 72% yields. Spectroscopic data of compounds **10a–c** are summarized in Table 5.

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