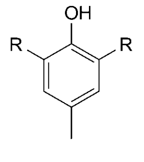
Spin Trapping of Radical Intermediates Generated by the Oxidation of Substituted 4-Methylphenols

by **Petr Majzlík**, **Ladislav Omelka***, **Renata Superatová**, and **Petra Holubcová**

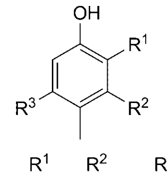
Faculty of Chemistry, Brno University of Technology, CZ-612 00 Brno, Czech Republic
(omelka@fch.vutbr.cz)

A series of substituted 4-methylphenols **1** and **2** was oxidized with PbO_2 in the presence of nitroso compounds **3**–**10**. The formation of adducts of benzyl radicals with the nitroso spin traps in the reaction mixture was established, suggesting the abstraction of an H-atom from the methyl substituent of **1** or **2**. In the consecutive steps, the adducts underwent a further rearrangement to the corresponding nitrones. When the starting phenol contained bulky ^{t}Bu groups in *ortho*-position (see 2,6-di(*tert*-butyl)-4-methylphenol (**1a**)), the stable 2,6-di(*tert*-butyl)-4R-phenoxy radicals ($R = -CH{=}N^+(O^-)-X$) were detected as the final radical products. The indirect evidence of nitrones in the reaction mixture was performed in one case by the reaction with a $RO_2^\bullet$ radicals.

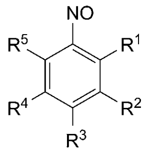
Introduction. – It is generally known that the oxidation of monohydric phenols with different agents, such as PbO_2, MnO_2, or $RO_2^\bullet$ leads to the formation of corresponding phenoxy radicals. The large number of EPR parameters continuously published in catalogues during the last decades [1] contributed to the detailed knowledge of this class of radicals, and seemingly, any new principal information cannot be expected in this field. The stability of phenoxy radicals substantially depends on the substitution in the *ortho*-position. High stability is the typical feature of the phenoxy radicals derived from 2,6-dialkyl-substituted phenols, especially those with bulky ^{t}Bu substituents (sterically hindered phenols). For this reason, 2,6-di(*tert*-butyl)-4R-phenols are frequently utilized as very efficient antioxidants [2]. Monohydric phenols with 2,6-dialkyl substituents containing an α-CH bond, as well as phenols with unsubstituted or partially substituted *ortho*-position (sterically unhindered phenols) provide on oxidation unstable phenoxy radicals, which can be detected only by using special EPR techniques, *e.g.*, flow or spin-trapping methods [3][4]. Although the generation of phenoxy radicals resulting from the abstraction of the phenolic H-atom is the dominating radical process during the oxidation, the tendency towards the abstraction of an H-atom from a Me group in 4-methyl-substituted phenols was also observed. The benzyl radicals formed were detected by a spin-trapping technique by using nitroso spin traps [4][5]. The recombination products of benzyl radicals observed in the reaction mixture of the oxidized phenols also support this mechanism, although other theories interpreting their formation have been proposed [6]. To understand the specific behavior of 4-methyl-substituted phenols in more detail, the oxidation of a series of phenols having this structural requisite was investigated by the spin-trapping method. Thus H-atom abstraction from a 4-Me group was investigated within the series of differently substituted 4-methylphenols **1** and **2** in the presence of substituted nitroso spin traps **3**–**10**.



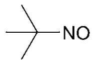
1a R = ^{t}Bu
1b R = Me
1c R = NO_2



	R^1	R^2	R^3
2a	H	H	H
2b	Me	H	H
2c	^{t}Bu	H	H
2d	H	Me	H
2e	H	Me	Me



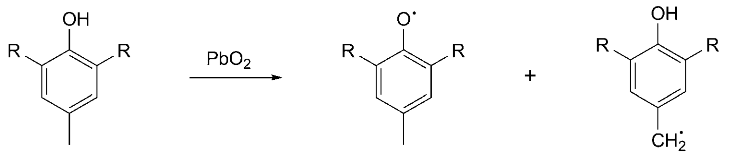
	R^1	R^2	R^3	R^4	R^5
3	H	H	H	H	H
4	Me	H	H	H	H
5	Cl	H	Cl	H	Cl
6	H	H	PhNH	H	H
7	Me	Me	H	Me	Me
8	H	H	Me_2N	H	H
9	^{t}Bu	H	^{t}Bu	H	^{t}Bu



10

Results and Discussion. – *2,6-Disubstituted 4-Methylphenols* **1**. Generally, the mechanism given in *Scheme 1* has to be taken into account in the case of the oxidation of 2,6-disubstituted 4-methylphenols **1**.

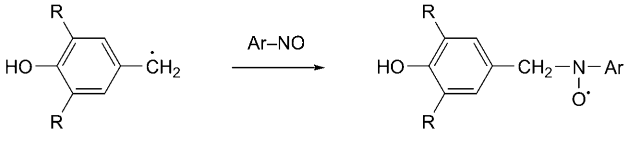
Scheme 1



1 **11** **12**

The oxidation of 2,6-di(*tert*-butyl)-4-methylphenol (**1a**) in the presence of nitrosobenzene (**3**) afforded a mixture of radical products where the corresponding phenoxy radical **11a** (a_H(Me) = 1.094 mT, a_H(*m*) = 0.155 mT) and the benzyl radical **12a**, prevailed, the latter being indirectly detected through the adduct **13a** (Ar = Ph; a_N(NO) = 1.049 mT, $a_H(CH_2)$ = 0.565 mT, a_H(*o*,*p*) = 0.273 mT, a_H(*m*) = 0.092 mT, *Scheme 2*).

Scheme 2



12 **13**

The EPR parameters of **13a** are similar to those of the spin-trapping adduct of **12a** with 3,5-di(*tert*-butyl)nitrosobenzene (= 1,3-bis(1,1-dimethylethyl)-5-nitrosobenzene)

[5]. The concentration ratio between the two radicals **11a** and **12a** depended on the experimental conditions, and in the presence of an excess of phenol **1a** over the spin-trap agent **3**, the EPR spectrum of the pure benzyl radical adduct **13a** was observed (*Fig. 1,a*). Nevertheless, gradually, the EPR spectrum changed: One hour after the preparation of the sample, the EPR spectrum given in *Fig. 1,b*, was detected, whose parameters suggest that a secondary phenoxy radical **15a** was formed *via* nitrone **14a** (Ar = Ph) in the consecutive steps of the oxidation ($g = 2.0049$) (*Scheme 3*). This statement is evidently supported by the splitting constant of H-atoms ($a_H = 0.150$ mT), which is the typical value of *meta* H-atoms in phenoxy radicals. Other dominating splittings verified by the simulation of the experimental EPR spectra were attributed to one H- and one N-atom of **15a** (Ar = Ph) (*Table 1*). Based on these experimental facts, it is evident that the secondary phenoxy radicals resulted from the transformation of the benzyl radical adduct **13a**. Moreover, the number of interacting nuclei suggests that the 4-position in the secondary phenoxy radical **15a** (Ar = Ph) is occupied by the nitrone fragment $-CH{=}N^+(O^-)-Ph$, which originates from the conversion of the nitroxide radical moiety $-CH_2-N(O^\bullet)-Ph$ in **13a** (→ intermediate **14a** (Ar = Ph)).

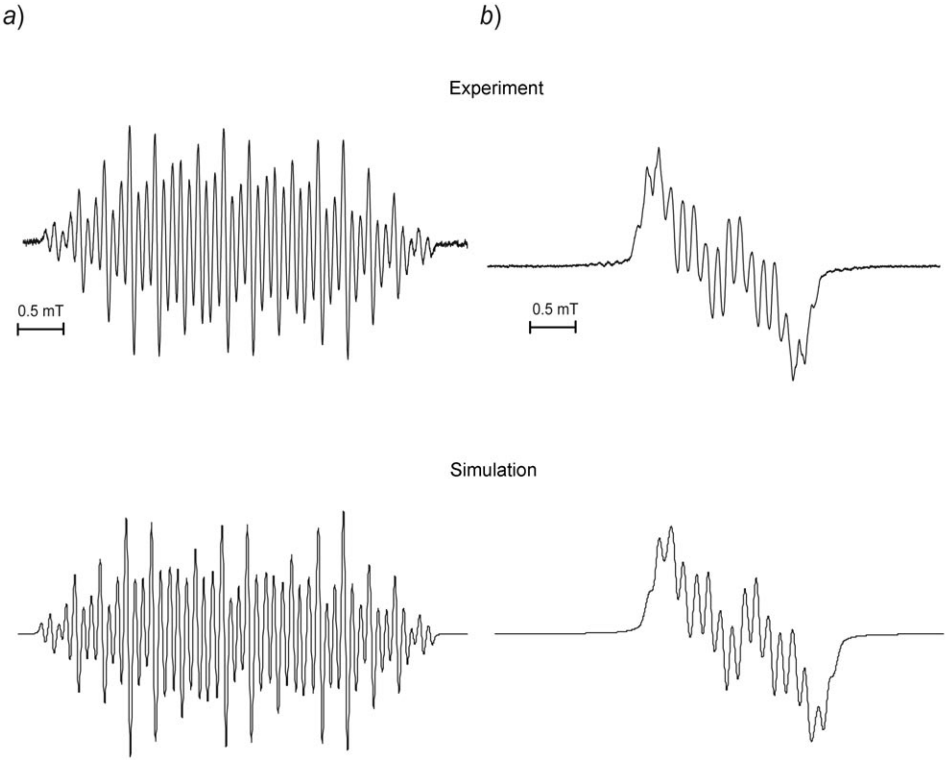
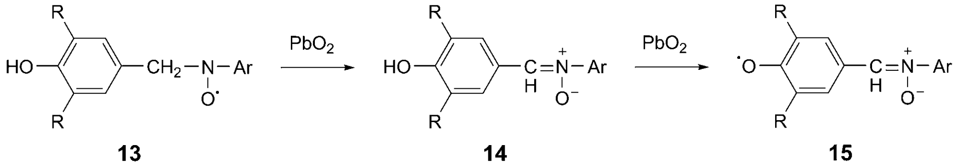


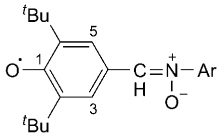
Fig. 1. a) *Experimental and simulated EPR spectrum of nitroxide radical* **13a** *in benzene solution;* b) *experimental and simulated EPR spectrum of secondary phenoxy radical* **15a** (Ar = Ph) *in benzene solution*

Scheme 3



13 **14** **15**

Table 1. *EPR Parameters of Phenoxy Radicals* **15a** *Prepared by the Oxidation of 2,6-Di(*tert*-butyl)-4-methylphenol* (**1a**) *with PbO_2 in Benzene Solution in the Presence of the Different Aromatic Nitroso Compounds* **3**–**9** *or of 2-Methyl-2-nitrosopropane* (**10**)



15a

Nitroso compound Ar-NO	Ar	Splitting constants [mT] of **15a**			
		$a_H(3,5)$	$a_H(CH)$	$a_H(N)$	$a_H(Ar)$
3	Ph	0.150	0.290	0.510	0.090 (3 H)
4	2-MeC_6H_4	0.150	0.280	0.490	–
5	2,4,6-$Cl_3C_6H_2$	0.165	0.305	0.485	–
6	4-$PhNHC_6H_4$	0.140	0.280	0.570	0.095 (2 H)
7	2,3,5,6-Me_4C_6H	0.155	0.270	0.490	–
8a)	4-$Me_2NC_6H_4$	–	–	–	–
9b)	2,4,6-$^tBu_3C_6H_2$	–	–	–	–
10c)	^tBu	0.170 (1 H), 0.150 (1 H)	0.260	0.505	–

a) Due to the strong line broadening effect, the individual splitting constant could not be determined. b) Interpretation of EPR signal is still an open problem. c) Splitting constants taken from [7].

In the course of further experiments, the number of aromatic nitroso compounds as spin traps was expanded. The analysis of EPR spectra established that the above-mentioned reaction route is unambiguously valid in the cases of **3**–**8**, although the quality of the EPR signal of phenoxy radical **15a** (Ar = 4-$Me_2NC_6H_4$), obtained with **8**, did not allow the determination of the splitting constants (*Fig. 2,a*; *Table 1*). The 2,4,6-tri(*tert*-butyl)nitrosobenzene (= 1,3,5-tris(1,1-dimethylethyl)-2-nitrosobenzene; **9**), however, afforded an EPR spectrum (*Fig. 2,b*) whose interpretation is still an open problem. Probably due to the strong steric effect arising from the presence of bulky ^{t}Bu groups in the *ortho*-positions of the starting nitroso compound **9**, the distribution of spin density in the corresponding phenoxy radical **15a** (Ar = 2,4,6-tri(*tert*-butyl)phenyl) differed from that observed for the previously discussed ones. On the other hand, neither the adduct **13a** nor the phenoxy radical **15a** was observed in the trapping reaction of **1a** with 2-methyl-2-nitrosopropane (**10**). Instead of them, only the nitroxide radical $(Me_3C)_2NO^\bullet$ ($a_N(NO) = 1.555$ mT) was detected, as a product of the decomposition of the spin trap on the surface of PbO_2. This fact is surprising because the EPR parameters of the phenoxy radical **15a** (Ar = ^{t}Bu, *Table 1*), produced by the oxidation of the nitrone **14a** (synthesized by the reaction of 3,5-di(*tert*-butyl)-4-hydroxybenzaldehyde with *N*-(*tert*-butyl)hydroxylamine) with benzoyloxy radicals, are reported in the literature [7].

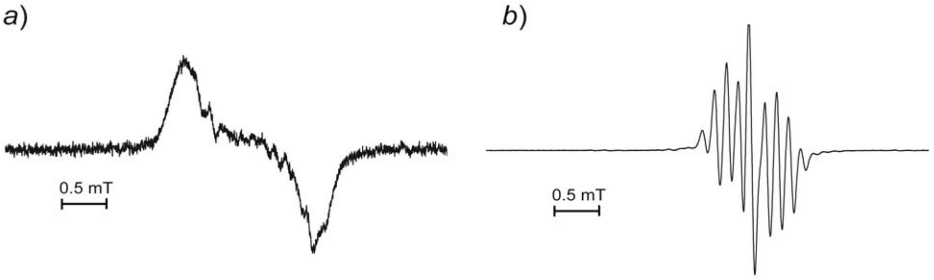
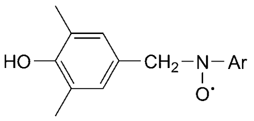


Fig. 2. *Experimental EPR spectra of radical products produced by the PbO_2 oxidation of 2,6-di(*tert-*butyl)-4-methylphenol* (**1a**) *in the presence of nitroso spin trap* a) **8** *and* b) **9** *in benzene solution*

The experimental results obtained by PbO_2 oxidation of the sterically hindered 2,6-di(*tert*-butyl)-4-methylphenol (**1a**) in benzene solution in the presence of different nitroso compounds Ar–NO initiated further investigation in this field. Thus the tendency towards the abstraction of one H-atom from a 4-Me group was also studied with the 2,4,6-trisubstituted phenols **1b** and **1c**. In contrast to **1a**, due to the absence of bulky substituents in *ortho*-position, the detection of the corresponding phenoxy radicals cannot be expected in this case. When 2,4,6-trimethylphenol (**1b**) was subjected to the oxidation, immediately after the addition of PbO_2 to the benzene solution of **1b** and nitrosobenzene (**3**), a high concentration of benzyl radical adduct **13b** (Ar = Ph, *Table 2*) was observed.

Table 2. *EPR Parameters of Nitroxide Radicals* **13b** *Prepared by the PbO_2 Oxidation of* **1b** *in Benzene in the Presence of Some Nitroso Spin Traps Ar–NO*



13b

Ar	Splitting constants [mT] of **13b**		
	a_N(NO)	a_H(CH_2)	a_H(Ar)
Ph	1.023	0.550	0.263 (3 H), 0.092 (2 H)
2-MeC_6H_4	1.150	0.630	0.190 (5 H), 0.085 (2 H)
2,4,6-$Cl_3C_6H_2$	1.261	0.950	0.070 (2 H)

The EPR signal of **13b** was stable for more then 24 h without being overlapped by the signal of another radical. This fact seemingly points out that the suggested reaction route (unambiguously evidenced for **1a**; *Scheme 3*), based on the conversion of **13b** to nitrone **14b** and consecutively to the secondary phenoxy radical **15b**, is not valid in this case. However, this effect can also be satisfactorily interpreted as a result of a substantially lower stability of 2,6-dimethyl-4R-phenoxy radicals in comparison with those derived from 2,6-di(*tert*-butyl)-4R-phenols. The presence of nitrone **14b** in the reaction mixture was indirectly established by an experiment, where *tert*-butyl hydroperoxide was added to the reaction mixture 24 h after the generation of adduct **13b**: A high concentration of nitroxide radical **16** with the splitting constants $a_N(NO) = 1.046$ mT, $a_H(CH) = 0.175$ mT, $a_H(o,p) = 0.273$ mT, and $a_H(m) = 0.092$ mT (*Fig. 3*) was observed in accordance with *Scheme 4*. The EPR parameters of **16** agreed well with the

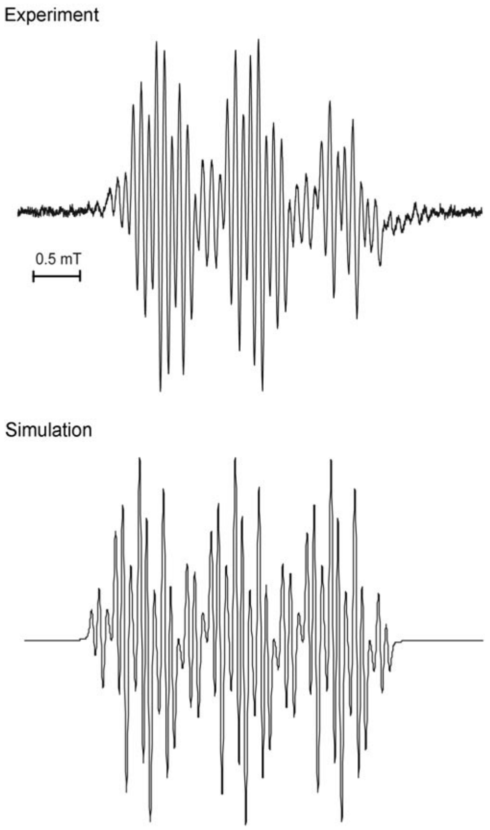
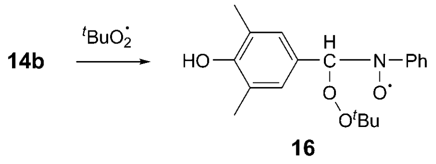


Fig. 3. *Experimental and simulated EPR spectrum of nitroxide radical* **16** *in benzene solution*

Scheme 4



published data for a RO$_2^\bullet$ adduct with *C,N*-diphenylnitrone, reported by *Cholvad et al.* [8]. Simultaneously, the authors point out the instability of this adduct, leading to the loss of the CH H-atom in nitroxide radical Ph–CH(OOR)–N(O$^\bullet$)–Ph in subsequent steps of the reaction. The spin adducts **13b** were observed also by the PbO$_2$ oxidation of **1b** in the presence of other spin traps (*Table 2*).

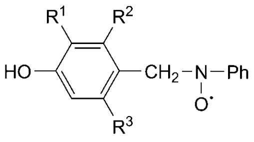
The H-atom abstraction from the 4-methyl substituent, unambiguously established by the behavior of phenols **1a** and **1b**, was not observed with 2,6-dinitro-4-methylphenol (**1c**). In this case, the EPR spectrum of a nitroxide radical with dominating N-splitting (a_N(NO) = 1.155 mT, other splittings unresolved) was registered after the addition of PbO$_2$ to the benzene solution of **1c** in the presence of nitrosobenzene (**3**). This fact points out the specific behavior of phenols with electron-accepting *ortho*-substituents, which influence the polarity of the C–H bonds in the 4-Me group. Consequently, the tendency towards its homolytic scission, leading in the case of phenols **1a** and **1b** to the formation of benzyl radicals, is partially reduced in phenol **1c**. The EPR signal of nitroxide radicals can possibly be ascribed to adducts of generated phenoxy radicals with nitrosobenzene [4].

Substituted 4-Methylphenols **2**. Similarly to the above discussed phenols **1a**–**1c**, the simultaneous generation of corresponding phenoxy and benzyl radicals is also expected in the course of the oxidation with PbO$_2$ of sterically unhindered phenols **2a**–**2e**. Due to their instability caused by structural factors (unsubstituted or partially substituted *ortho* position), the phenoxy radical cannot be directly detected by the EPR method, and only indirect evidence by means of the spin-trapping technique is suitable [4]. Due to the tendency towards the abstraction of an H-atom from the 4-methyl substituent, the benzyl radicals also reacted with nitroso spin traps and the generated adducts mostly dominated in the EPR spectrum. With nitrosobenzene (**3**) as spin trap, the PbO$_2$ oxidation of phenols **2a**–**2c** in benzene produced the radical adducts **17a**–**17c** (*Table 3*). The 3,4-dimethylphenol (**2d**) afforded only in CHCl$_3$ solution a high

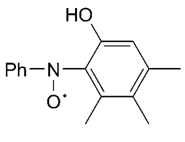
Table 3. *EPR Parameters of Nitroxide Radicals* **17** *Prepared by the PbO$_2$ Oxidation of* **2a**–**2d** *in Benzene in the Presence of Nitrosobenzene* (**3**)

Phenol	Splitting constants [mT] of **17**		
	a_N(NO)	a_H(CH$_2$)	a_H(phenyl)
2aa)	1.120	0.610	0.290 (3 H), 0.093 (2 H)
2b	1.091	0.600	0.280 (3 H), 0.095 (2 H)
2c	1.049	0.565	0.273 (3 H), 0.092 (2 H)
2db)	1.107	0.730	0.279 (3 H), 0.093 (2 H)

a) Splitting constants taken from [4]. b) Splitting constants in CHCl$_3$.



17



18

concentration of nitroxide radical **17d**, in benzene, only the unresolved EPR signal of the radical adduct of the phenoxy radical ($a_N(NO) = 1.00$ mT) was detected.

Also no adduct of benzyl radicals was observed on PbO_2 oxidation of 3,4,5-trimethylphenol (**2e**) in benzene in the presence of nitrosobenzene (**3**). Instead of them, the EPR signal of hydroxyphenyl adduct **18** was detected. The EPR parameters of the latter ($a_N(NO) = 0.980$ mT, $a_H(1\,H) = 0.060$ mT, $a_H(o,p) = 0.261$ mT, and $a_H(m) = 0.085$ mT) were similar to those of the species obtained by the spin trapping of the 3,5-dimethylphenoxy radical with nitrosobenzene [4]. Nevertheless, the PbO_2 oxidation of **2e** in $CHCl_3$ in the presence of **3** revealed the simultaneous formation of small amounts of benzyl radical adduct **17e** as deduced from the detailed analysis of the EPR side lines present besides the dominating EPR signal of radical adduct **18**.

Conclusions. – The oxidation of the series of 4-methyl substituted phenols with PbO_2 in different solvents showed that besides the formation of phenoxy radicals, also the abstraction of an H-atom from the 4-methyl substituent leading to the benzyl radicals has to be taken into account. Theoretically, both radical intermediates can be evidenced by EPR spectroscopy applying spin-trapping method. The adducts of the benzyl radicals entered the follow-up reactions, resulting in the formation of nitrones, which could be further oxidized at the phenolic part of the molecule. Stable secondary phenoxy radicals produced in this way were formed on PbO_2 oxidation of 2,6-di(*tert*-butyl)-4-methylphenol in the presence of different aromatic nitroso compounds. Due to their instability, similar secondary phenoxy radicals could not be detected with other phenols in our study, the only detectable radical products being adducts of benzyl radicals with nitroso compounds. Nevertheless, the presence of an intermediate nitrone was established by the reaction with a peroxy radical.

This work was supported by the *Ministry of Education of the Czech Republic* under research project *MSM* 0021630501.

Experimental Part

General. All chemicals (phenols, nitroso compounds, *tert*-butyl hydroperoxide, PbO_2) were commercially available and used without further purification. Benzene and $CHCl_3$ of anal. grade purity (*Sigma*) were used as the solvent in all experiments. EPR Spectra: EPR spectrometer *SpectraNova*; at r.t.; simulation of exper. spectra with the programme Simphonia.

Oxidation of **1** *or* **2** *with PbO_2 in the Presence of Nitroso Compounds* **3**–**10***: General Procedure.* In a $5 \cdot 10^{-2}$ M benzene or $CHCl_3$ soln. of the phenol, the corresponding amount of a nitroso compound was dissolved, adjusting the molar ratio phenol/nitroso compound to 2 : 1. To 2 ml of this soln., PbO_2 (150 mg) was added under stirring. The stirring was stopped after 1 min, and after the sedimentation of the solid phase, 0.3 ml of the reaction mixture was placed into the EPR tube. To study the consecutive transformations of primary radical products, the sampling of the reaction mixture was performed in 30 min intervals under continuous stirring. To obtain the high quality EPR spectra, the soln. in the tube was bubbled with N_2 for 30 s.

REFERENCES

[1] Landolt-Börnstein, 'Magnetic Properties of Free Radicals', New Series, Vol. 9, Part c2, Springer, Berlin, 1979; Landolt-Börnstein, 'Magnetic Properties of Free Radicals', New Series, Vol. 17, Part c2, Springer, Berlin, 1989.

[2] J. Pospíšil, *Pure Appl. Chem.* **1973**, *36*, 207.
[3] T. J. Stone, W. A. Waters, *J. Chem. Soc.* **1964**, 213.
[4] L. Omelka, J. Kováčová, *Magn. Reson. Chem.* **1994**, *32*, 525.
[5] E. I. Zhuzhgov, N. M. Bazhin, M. P. Terpugova, Y. D. Tsvetkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1974**, *23*, 2438.
[6] R. Stubbins, F. Sicilio, *Tetrahedron* **1970**, *26*, 291.
[7] J. G. Pacifici, H. L. Browning, *J. Am. Chem. Soc.* **1970**, *92*, 5231.
[8] V. Cholvad, A. Staško, A. Tkáč, A. L. Buchachenko, L. Malík, *Collect. Czech. Chem. Commun.* **1981**, *46*, 823.

Received November 23, 2010