Nitroxides as reaction intermediates

HANS GÜNTER AURICH
Fachbereich Chemie of the University Marburg, Hans-Meerwein-Straße, D-3350-Marburg, Federal Republic Germany

Received August 10, 1981

HANS GÜNTER AURICH. Can. J. Chem. **60**, 1414 (1982).

Vinyl nitroxides **4** are obtained by oxidation of the nitrones **3**, as was shown by esr studies and by identification of the reaction products. The formation of **4***d–f* is even observed in oxidation of the hydroxylamines **1***d–f*, nitroxides **2***d–f* and nitrones **3***d–f* being the intermediates. The high reactivity of the vinyl nitroxides **4** at their β-position is illustrated by the reactions of **4***a* with various compounds affording the nitroxides **7–10**, respectively. Compound **4***c* reacts with its precursor **3***c* to give **11**, **12**, or **13**, depending on the reaction conditions. From oxidation of **3***a*, *c*, and *e* the dimerization products **5***a*, *c*, and *e*, respectively, could be isolated. Whereas further oxidation of **5***d* yields **6***d*, the acyl nitroxides **14***a* and *c* are formed in the oxidation of **5***a* and *c*, respectively.

The formation of quinone **23** in the reaction of 2-methyl-2-nitrosopropane with potassium *tert*-butoxide in isopropyl alcohol in the presence of oxygen is discussed. The nitroxide **20** has been detected in the reaction mixture. Imines **24** react with nitrosobenzene giving nitroxides **26**. These are further oxidized by nitrosobenzene to afford nitrones **27**. Whereas **27***a* and *b* could be isolated, **27***c* and *d* undergo further reaction yielding the diimines **30***c* and *d* along with dinitrone **29**.

The formation and reactions of imino nitroxides **31** and of the nitronyl nitroxide **41** are discussed. Electron spin resonance studies revealed the high reactivity of the imidazolyl-1,3-dioxides **46** and the imidazolyl-1-oxides **50**, which easily form radicals **47–49** and **51**, respectively, which are derived from secondary reactions.

HANS GÜNTER AURICH. Can. J. Chem. **60**, 1414 (1982).

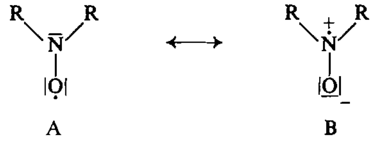
On obtient les vinylnitroxydes **4** par oxydation des nitrones **3** comme le révèlent les études de rpe et l'identification des produits de la réaction. On observe aussi la formation des composés **4***d–f* lors de l'oxydation des hydroxylamines **1***d–f* qui procède par l'intermédiaire des nitroxydes **2***d–f* et des nitrones **3***d–f*. On illustre la grande réactivité de la position β des vinylnitroxydes **4** par les réactions du composé **4***a* avec divers composés qui conduisent respectivement aux nitroxydes des **7–10**. Le composé **4***c* réagit avec son précurseur **3***c* en donnant, en suivant les conditions de la réaction, les composés **11**, **12** ou **13**. L'oxydation des composés **3***a*, *c* et *e*, permet d'isoler respectivement les produits de dimérisation **5***a*, *c* et *e*. Alors qu'une oxydation plus poussée du composé **5***d* conduit au composé **6***d*, l'oxydation des composés **5***a* et *c* conduit respectivment aux acylnitroxydes **14***a* et **14***c*.

On discute de la formation de la quinone **23** lors de la réaction du méthyl-2 nitroso-2 propane avec le *tert*-butoxyde de potassium dans l'alcool isopropylique, en présence d'oxygène. On décelé la présence du nitroxyde **20** dans le mélange réactionnel. Les imines **24** réagissent avec le nitrosobenzène en donnant les nitroxydes **26**. Ces derniers sont de plus oxydés par le nitrosobenzène en donnant les nitrones **27**. Alors qu'on peut isoler les composés **27***a* et *b*, les composés **27***c* et *d* subissent une réaction supplémentaire en donnant les diimines **30***c* et *d* ainsi que la dinitrone **29**.

On discute de la formation et des réactions des iminonitroxydes **31** et du nitronyl nitroxyde **41**. Les études de rpe révèlent la grande réactivité des imidazolyldioxydes-1,3 **46** et des imidazolyloxydes-1 **50** qui forment facilement les radicuax **47–49** et **51** respectivement qui proviennent de réactions secondaires.

[Traduit par le journal]

Nitroxides are stabilized by delocalization of the unpaired electron between oxygen and nitrogen (structures A and B), the delocalization energy being of the order of 30 kcal/mol for dialkyl nitroxides (1). A consequence of this inherent stabilization of the nitroxide group is the easy formation of nitroxides by oxidation of hydroxylamines, as is indicated by the low bond dissociation energy for the OH bond of these compounds (2).



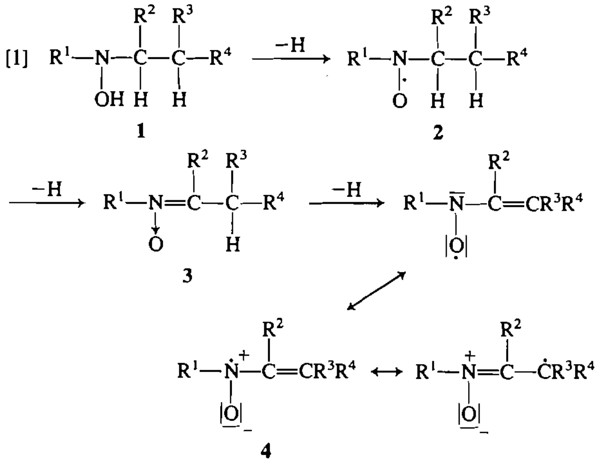
Among the many other reaction routes affording nitroxides, spin trapping by nitrones or nitroso compounds appears to be the most important (3). The facile formation of nitroxides by spin trapping is reflected by the low activation energies for these reactions (4).

Contrary to di-*tert*-alkylnitroxides, which are very persistent radicals, nitroxides with at least one hydrogen atom at the α-carbon atom usually disproportionate to give hydroxylamines and nitrones (5). Because of the facile dehydrogenation of such nitroxides, the oxidation of appropriate hydroxylamines via intermediate nitroxides to give nitrones should be a common reaction. However, complications can arise by reaction of the nitrone with the intermediate nitroxide (6).

Furthermore, oxidation of nitrones with a hydrogen atom at the β-position should afford vinyl nitroxides, which are expected to be additionally stabilized by delocalization of the unpaired electron into the vinyl group (7).

Whereas di-*tert*-alkyl substituted nitroxides are usually extremely persistent, phenyl substituted

0008-4042/82/121414-07$01.00/0



nitroxides are not. The reason is that the extended delocalization of the unpaired electron into the phenyl ring makes dimerization by attack at the *para* position possible, thus giving rise to further decomposition (8*a*). This behavior illustrates nicely the difference between stabilization and persistence of radicals (8*b*).

The delocalization of the unpaired electron into the vinyl group of vinyl nitroxides should cause an even more enhanced reactivity of these radicals compared to phenyl nitroxides. Therefore we decided to study the formation of vinyl nitroxides by esr spectroscopy as well as their reaction pathways by product analysis. More generally, we have been interested in the question of how the nitroxide group affects the reactivity at neighbouring positions in cooperation with other functional groups.

Results and discussion

A. *Formation and reactions of vinyl nitroxides*

Oxidation of the nitrones 3 (9)[1] or their corresponding tautomers (10) by lead dioxide or nickel peroxide gave the vinyl nitroxides 4. The lifetime of radicals 4*a*, *b*, *e*, and *f* is sufficient for them to be detected by esr. Their coupling constants are summarized in Table 1. Radicals 4*c* and *d* could not be observed directly, since they react immediately with their precursor nitrones 3*c* and *d*, respectively, to yield derived radicals. However spin trap reactions as well as product formation indicate that they are real intermediates.

TABLE 1. Coupling constants of the vinylnitroxides 4 in Gauss[a]

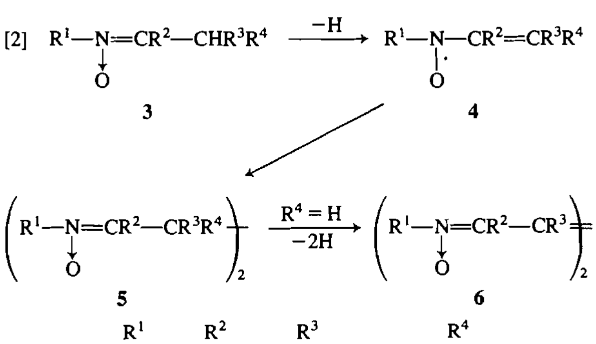
Compound	a^{N}	a^{H}_{α}	a^{H}_{β}	a^{H}_{other}
3*a*[b] (7)	8.6	—	6.5	0.45 (3H) R^2 or R^3
3*b*[c]	8.4	4.8	—	1.45 (3H), 0.93 (3H) R^3 and R^4
3*e*[d]	8.1	2.55	—	1.85 (3H), 0.65 (2H), 1.35 (3H), 0.65 (2H) R^1 and R^4
3*f*[e]	8.8	2.85	—	1.7 (3H), 0.65 (2H) R^4

[a]See footnote 1.
[b]In Et—O—Et.
[c]In CCl_4.
[d]In $CHCl_3$.
[e]In CH_2Cl_2.

In the oxidation of hydroxylamines 1*d*–*f* (10, 11) the esr signals of the nitroxides 2*d*–*f* can be observed initially but after some time they disappear and, instead, that of the radical derived from a secondary reaction of 4*d*, and those of 4*e* and 4*f*, respectively, arise.[1] To the best of our knowledge this is the first time that the formation of a vinyl nitroxide 4 from hydroxylamine via the intermediates 2 and 3 has been observed.

The fate of the vinylnitroxides 4 can be derived from oxidation reactions of 3 on a preparative scale.[1] By performing the oxidation reactions of 3*a*–*e* with lead dioxide or nickel peroxide on a preparative scale we isolated the dimers 5*a*, *c*, and *e* in 81, 85, and 63% yield, respectively; 5*d* could not be isolated but was directly oxidized further to give 6*d*. Only in the case of the oxidation of 3*b* a variety of unidentified products was formed in low yield. Likewise the products 6*d* and 5*e* were isolated in comparable yields by oxidation of the hydroxylamines 1*d* and 1*e*, respectively. These results indicate that *dimerization by formation of a carbon–carbon bond at the β-position of the vinyl group is the major reaction pathway of the intermediate vinyl nitroxides.*

Electron spin resonance studies revealed further that reactions of the vinylnitroxides 4 with other compounds usually also occur at the β-position. The reactions of 4*a* with nitroso compounds,



	R^1	R^2	R^3	R^4
a	*t*-Bu	COOMe	COOMe	H
b	*t*-Bu	H	3,5-*t*-$Bu_2C_6H_3$	3,5-*t*-$Bu_2C_6H_3$
c	*t*-Bu	H	Ph	H
d	Ph	H	Ph—CO	H
e	Ph	H	Ph—CO	Ph
f	*t*-Bu	H	Ph—CO	Ph

---

[1] H. G. Aurich and M. Schmidt, unpublished results; M. Schmidt, Dissertation, Marburg, in preparation.

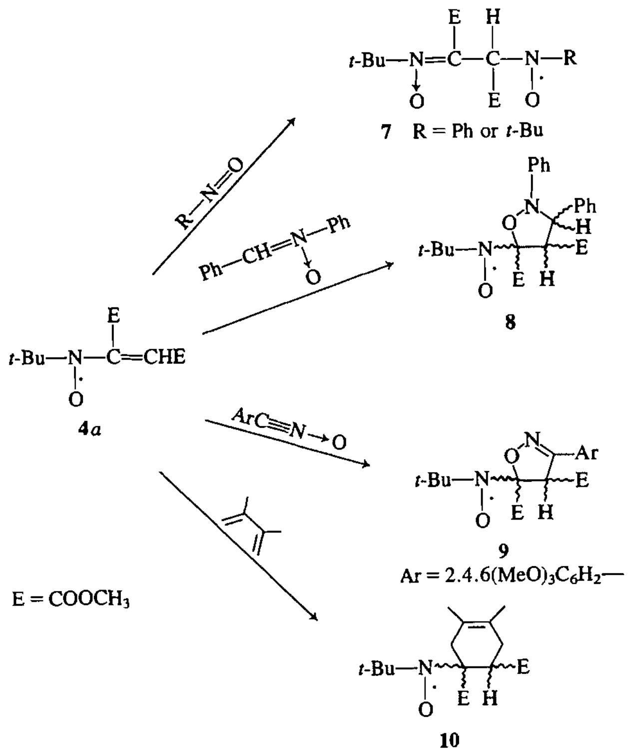
TABLE 2. Coupling constants of the nitroxides **2** in Gauss[a]

Compound	R¹	R²	R³	R⁴	a^N	a^H_α	a^H_β	$a^H_{R^1}$
2*d*[b]	Ph	H	PhCO	H	11.15	10.0 (2H)	0.45 (2H)	2.9 (3H), 0.95 (2H)
2*e*[b]	Ph	H	PhCO	Ph	11.8	12.75 (1H), 10.4 (1H)	0.45 (1H)	3.0 (3H), 1.0 (2H)
2*f*[c]	*t*-Bu	H	PhCO	Ph	15.25	12.75 (2H)	—	—

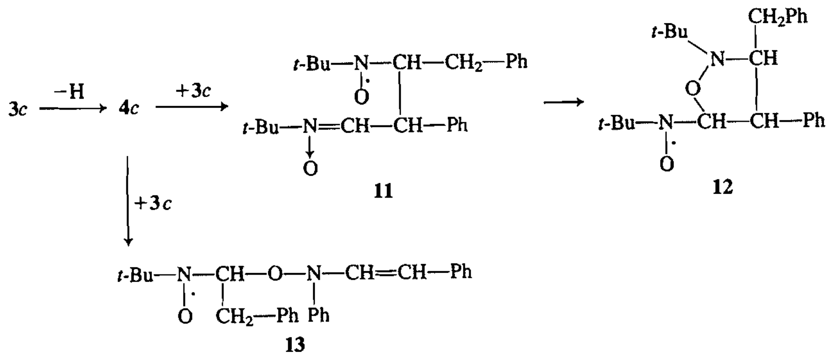
[a] See footnote 1.
[b] In $CHCl_3$.
[c] In Et—O—Et.

N-benzylidene-aniline-*N*-oxide, 2,4,6-trimethoxybenzonitrile-*N*-oxide, and 2,3-dimethylbuta-1,3-diene, which afford the nitroxides **7–10**, are representative examples (7). Whereas the reactions with the nitroso compounds are simple spin-trapping processes, the formation of **8–10** occurs by cyclizations which are formally 1,3-dipolar cycloadditions. However, it seems more likely that they are

[3]



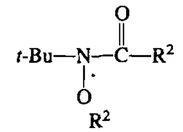
[4]



two-step reactions. In this case the formation of **8** and **9** must be considered as a twofold spin-trapping process.

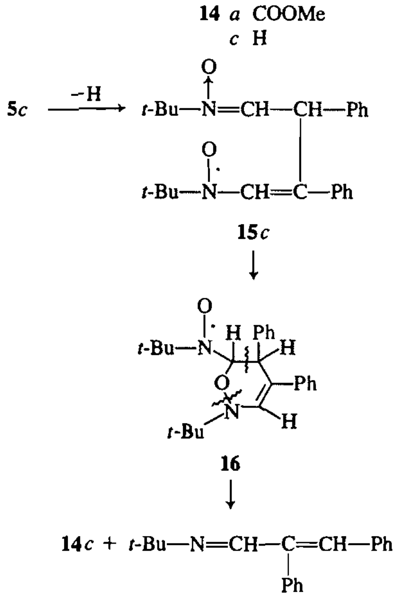
Depending on the reaction conditions, three different radicals, obviously formed by secondary reactions of the rather reactive vinylnitroxide **4***c* with its precursor, have been detected in the oxidation of nitrone **3***c*. The coupling constants of these radicals are: $a^N = 15.45$, $a^H = 2.5$ G (1H) in chloroform; $a^N = 13.5$, $a^H = 5.8$ G (1H) in benzene; and $a^N = 13.9$ G, no proton splitting in benzene.[1] The structures **11**–**13** appear to be most probable for these radicals, but at present unambiguous assignment is not possible.

Whereas the intermediate dinitrone **5***d*, which probably exists in its tautomeric *N*-hydroxyenamine form (10), is easily oxidized to afford product **6***d*, the isolated dinitrones **5***a* and **5***c* surprisingly yield the acylnitroxides **14***a* and **14***c* (12) on oxidation with nickel peroxide. After prolonged oxidation of **5***c*, 2,3-diphenylpropen-2-al was isolated,[2] which is obviously formed by hydrolysis of the corresponding *N*-*tert*-butylimine **17**. Thus it appears that the oxidation of **5***c* initially gives the nitroxide **15***c* which then undergoes an intramolecular spin-trap reaction to yield the nitroxide **16**. The formylnitroxide **14***c* and the imine **17** can then arise by a retro-Diels–Alder reaction of **16**.



R^2

14 *a* COOMe
c H

[5] 

17

B. *Nitroxides as intermediates in other oxidation reactions*

The formation of 2,5-bis-(*tert*-butylamino)-1,4-benzoquinone **23**[3] in 31% yield from the reaction of 2-methyl-2-nitroso propane with potassium *tert*-butoxide in isopropyl alcohol in the presence of oxygen is a rather obscure reaction (14*a*). Electron spin resonance studies indicated that the nitroxide **20** ($a^N = 15.2$ G, $a^H = 10.4$ G (2H), $a^H = 0.65$ G (1H)) is involved. The same radical was obtained by Lagercrantz and Setaka (14*b*) in the reaction of hydroxy radicals with isopropyl alcohol in the presence of 2-methyl-2-nitrosopropane: $a^N = 16.3$ G, $a^H = 13.3$ G (1H), $a^H = 8.9$ G (1H), $a^H = 0.74$ G (1H) in H_2O. The larger values for the coupling constants are due to the more polar solvent. In contrast to our findings, Lagercrantz observed two different coupling constants for the methylene protons, but this may be due to the different reaction conditions. Nevertheless, exactly the same ratio $a^N/a^H_{CH_2}$ is obtained in the two cases, if one uses the mean values of the proton couplings.

It must be assumed that the reaction is induced by the formation of the nitroso anion radical **18** on treatment of the nitroso compound with *tert*-butylate (15). Anion radical **18** reacts readily with oxygen and, as is known from reaction in various solvents, hydrogen abstraction from the solvent occurs under these conditions (15). Radical **19** formed from isopropyl alcohol (eq. [6]) is then trapped by the nitroso compound to give the nitroxide **20**. One would expect hydrogen abstraction from isopropyl alcohol to occur exclusively at its central position, as was also pointed out by a referee. But under the very different conditions, applied by Lagercrantz (14*b*) and us, radical **20** could be detected unambiguously, whereas no evidence for the trapping of the radical CH_3—$\dot{C}$-(OH)CH_3 was found. Under the oxidative reaction conditions a successive dehydrogenation of **20** to afford the acylnitrone **22** via the intermediate vinyl nitroxide **21** is reasonable. Since it was found that nitrone **22**,[4] which was synthesized independently,

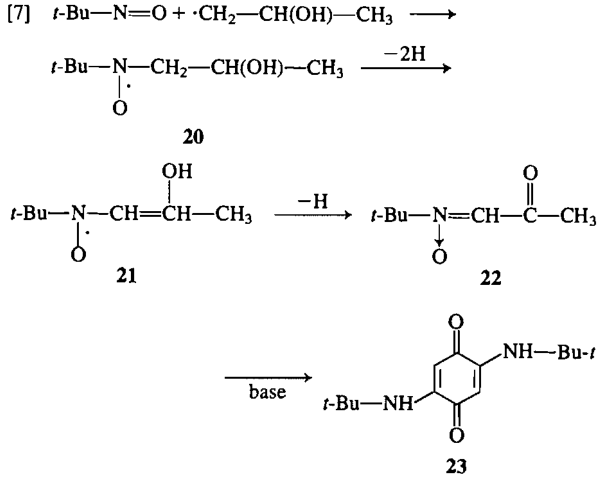
---

[2] Melting point 94°C (lit. (13*a*) mp 94°C, see also p. 281, ref. 13*a*); ir (KBr): 1660 and 1620 cm^{-1}; ^1H nmr ($CDCl_3$): 9.65 (1H, s), 7.4–7.1 (11H, m) ppm; ms: M^+ 208.

[3] Structural proof by comparison with a sample prepared in an independent way (13*b*).

[4] Nitrone **22** was obtained by reaction of *tert*-butylhydroxylamine with 2-oxo-propanal;[1] ^1H nmr ($CDCl_3$): 7.0 (1H, s), 2.35 (3H, s), 1.45 (9H, S) ppm.

$$[6]\quad \underset{\textbf{18}}{t\text{-Bu—}\dot{N}\text{—}\underline{O}|^-} + O_2 + CH_3\text{—}CH(OH)\text{—}CH_3 \longrightarrow t\text{-BuNO}_2 + OH^- + \underset{\textbf{19}}{\cdot CH_2\text{—}CH(OH)\text{—}CH_3}$$



is converted into the quinone **23** on treatment with various bases, the reaction seems to be rationalized best by the proposed reaction sequence (eq. [7]).

As was found some years ago by Layer (16), imines react in their tautomeric enamine form with nitrosobenzene to give hydroxylamines which are oxidized by further nitrosobenzene to afford the corresponding nitroxides. We performed this reaction with less substituted imines **24** having at least two hydrogen atoms at the β-position (17). The nitroxides **26** could be detected by esr, as expected, but there was no evidence for the existence of the tautomeric β-amino substituted vinylnitroxides **28**. Oxidation of the nitroxides **26** by nitrosobenzene afforded the rather unstable imino nitrones **27** which could be isolated only when substituted as in **27***a* and **27***b*.

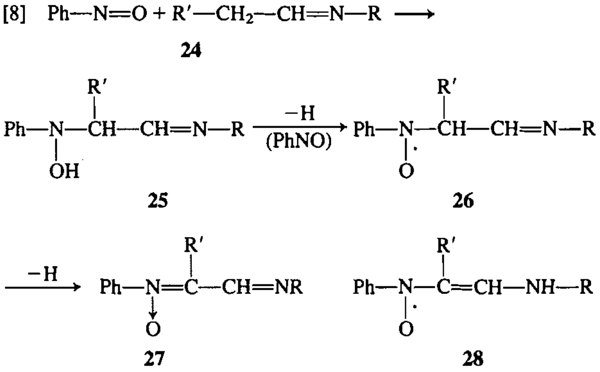
In the reactions with imines **24***c* and **24***d*, however, the diimines **30***c* and **30***d* were formed along with the dinitrone **29** (eq. [9]) (18). Since the existence of small amounts of vinylnitroxides **28***c* and **28***d* in equilibrium with **26***c* and **26***d*, respectively, could not be excluded, a dimerization of **28***c* and **28***d* by bond formation at the β-position may be considered to be the first step in a reaction sequence yielding **30***c* and **30***d* along with **29**. But this possibility was refuted by the labelling experiments. The distribution of the carbon-13 label agrees only with a dimerization at the oxidation level of the nitrone **27** in the indicated way.

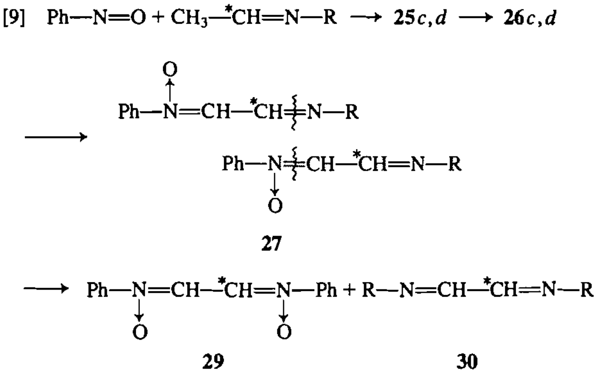
C. *Imino and nitronyl nitroxides*

Contrary to the vinyl nitroxides **4**, imino nitroxides **31** do not dimerize, since the gain in energy for the formation of a nitrogen–nitrogen bond does not compensate the loss of delocalization energy for the two nitroxide molecules (ref. 19, see also p. 91).

As in the case of hydroxylamines **1***e* and **1***f*, amino-substituted hydroxylamines such as **33**, which exist in equilibrium with their educts, can be oxidized by lead dioxide to yield imino nitroxides via the corresponding intermediates (20). Starting with nitrone **32** and methylamine, nitroxide **34** was first detected, which was slowly converted to the imino nitroxide **36**. Surprisingly, the oxidation process did not stop at this level. The methyl group was destroyed by further oxidation, the imino nitroxide **37** being the final radical product in the reaction sequence [10]. Compound **35** could be isolated from the reaction mixture as the lead complex in 31% yield.

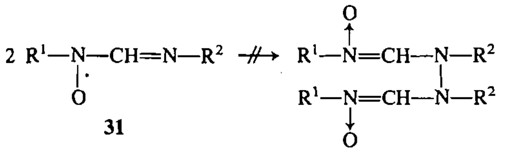
Similarly, oxidation of **38** (21) proceeds via **39** and **40** to afford the nitronyl nitroxide **41** (eq. [11]). But after some hours the esr signal of **41** disappears, and the imino nitroxide **42** is observed instead. The *N*-hydroxy formhydroxamic acid **43**





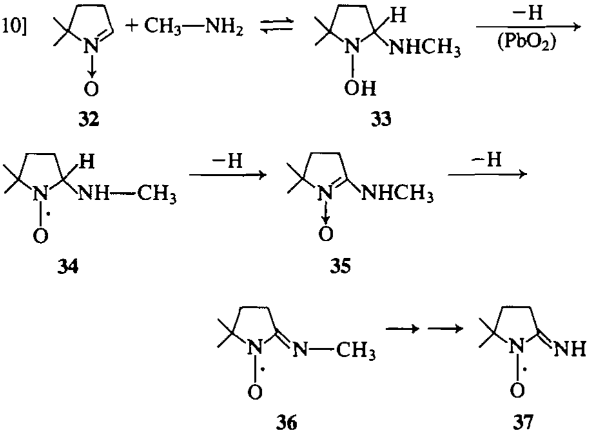
* ^{13}C-labelled

	R′	R
a	*i*-Pr	*t*-Bu
b	Ph	*t*-Bu
c	H	*t*-Bu
d	H	*c*-C_6H_{11}

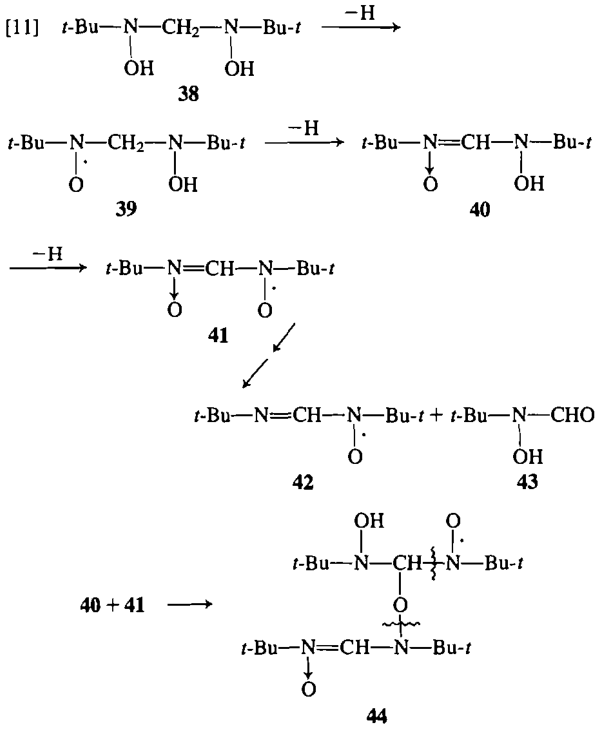


31

[10]



32 **33** **34** **35** **36** **37**



38 **39** **40** **41** **42** **43** **44**

was isolated as the lead complex in 5% yield from the reaction mixture (20). The formation of **42** and **43** can be rationalized if one assumes that **41** is trapped by its precursor **40** to give the adduct **44**, which is then split as indicated.

TABLE 3. Coupling constants of the radicals **46**–**51** in Gauss[a]

Radical	a_1^N	a_3^N	a_2^H	$a_{4,5}^H$	g-value
46*a*	4.0	4.0	0.8 (3H)	1.7 (6H)	
46*b*	4.0	4.0	—	1.65 (6H)	
47	7.1	6.8	3.2 (3H)	—	2.0065
49	6.85	6.85	—	—	2.0065
48	8.2	4.8	—	—	2.0062
50*b*	4.3	2.0	—	7.6 (3H); 2.0 (3H)	
51*a*	8.15	3.6	1.76 (3H)	—	
51*b*	8.7	3.8	0.53 (3H)	0.33 (3H)	

[a] See footnote 5. In $CHCl_3$.

D. *Imidazolyl-1,3-dioxides and imidazolyl-1-oxides*

In imidazolyl-1,3-dioxides the vinyl group and the nitronyl group are both conjugated with the nitroxide moiety. Whereas the 4,5-diaryl substituted imidazolyl-1,3-dioxides (22) as well as the benzimidazolyl-1,3-dioxides (23) are relatively persistent, this is not true for the 4,5-dimethyl substituted radicals **46**. Thus, the radical to which structure **46***a* has been assigned (22) is in fact a radical derived from a secondary reaction.[5]

When we oxidized the 4,5-dimethyl-3-hydroxy-imidazole-1-oxides **45***a* (22) and **45***b* to afford **46***a* and **46***b*, we found that the lifetime of these radicals is markedly influenced by the substituent at the 2-position. Although **46***a* was studied at low temperatures its esr spectrum changes so rapidly that it never could be recorded without superposition of the spectrum of the radical derived from a secondary reaction. On the other hand, radical **46***b* has a lifetime of more than five minutes at room temperature. Whereas **46***a* is converted into a cyclic nitronyl nitroxide **47** (24) with slightly different coupling constants for the two nitrogen atoms, indicating an unsymmetric substitution, **46***b* is converted into the oximino nitroxide **48** (eq. [12]). The structure of **48** was assigned by comparison with the coupling constants of related radicals (23*b*). Finally **48** is converted to give the nitronyl nitroxide **49**, which is presumably symmetrically substituted.

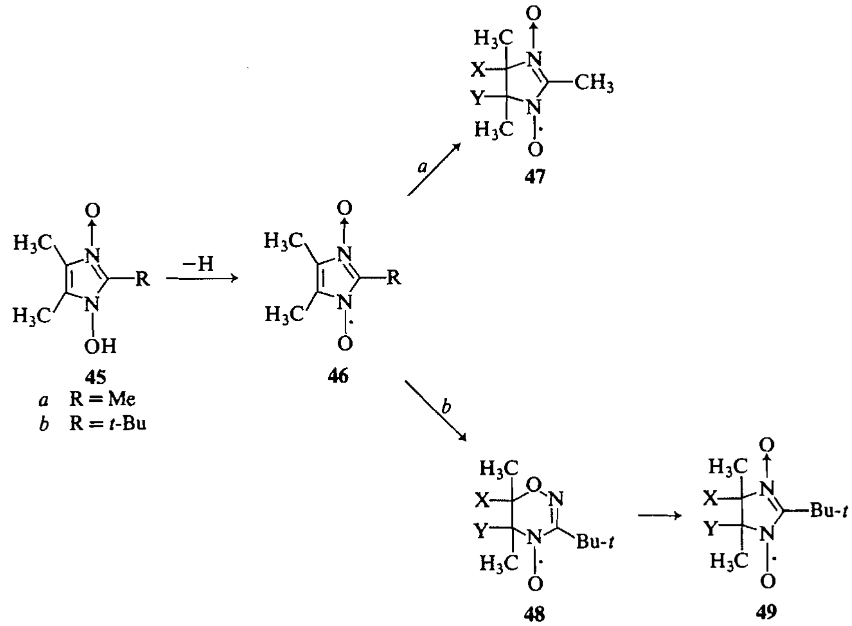
Obviously, the easy conversion of **46***a* and **46***b* reveals the particular reactivity of the vinyl group which is conjugated with a nitroxide group. The difference in the reactivity of **46***a* and **46***b* suggests that an attack at the 2-position of **46** or its precursor **45** is involved in the reaction sequence forming the derived radicals.

From this it seems possible that the conversion begins with bond formation between the vinylic carbon atom of **46** and the 2-position of the precursor molecule **45** to afford again a vinyl nitroxide moiety which then undergoes further intramolecular reactions, e.g. spin trapping.

---

[5] H. G. Aurich and J. Schmock, unpublished results.

[12]



45
a R = Me
b R = *t*-Bu

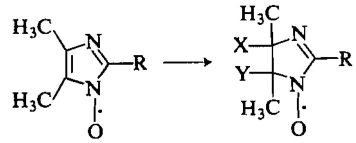
46

47

48

49

[13]



50

51

The conversion of the imidazolyl-1-oxides **50** into the imidazolinyl-1-oxides **51** is thought to occur in a similar way. Since the esr spectrum of **50***a*, in contrast to that of **50***b*, could never be observed, it must be concluded that this radical is even more reactive than the corresponding radical **46***a*.

Acknowledgements

I would like to thank my co-workers for their cooperation. This work was supported by the Fonds der Chemischen Industrie.

1. E. G. Rozantsev. Free nitroxyl radicals. Plenum Press, New York, London. 1970. p. 125.
2. L. R. Mahoney, G. D. Mendenhall, and K. U. Ingold. J. Am. Chem. Soc. **95**, 8611 (1973).
3. (*a*) E. G. Janzen. Acc. Chem. Res. **4**, 31 (1971); (*b*) M. J. Perkins. Essays on free radical chemistry. *Edited by* R. O. C. Norman. Chem. Soc. Spec. Publication No. 24, 1970. p. 97.
4. P. Schmid and K. U. Ingold. J. Am. Chem. Soc. **100**, 2493 (1978).
5. D. F. Bowman, T. Gillan, and K. U. Ingold. J. Am. Chem. Soc. **93**, 6555 (1971).
6. R. Briere and A. Rassat. Tetrahedron, **32**, 2891 (1976).
7. H. G. Aurich, K. Hahn, and K. Stork. Chem. Ber. **112**, 2776 (1979).
8. (*a*) A. R. Forrester and R. H. Thomson. Nature, **203**, 74 (1964); (*b*) K. U. Ingold. Acc. Chem. Res. **9**, 13 (1976).
9. H. G. Aurich and K. Hahn. Chem. Ber. **112**, 2769 (1979).
10. F. De Sarlo and G. Renzi. J. Chem. Soc. Perkin Trans. I, 1113 (1978).
11. J. Thesing, A. Müller, and G. Michel. Chem. Ber. **88**, 1027 (1955).
12. H. G. Aurich and J. Trösken. Chem. Ber. **106**, 3483 (1973).
13. (*a*) H. Meerwein. J. Prakt. Chem. [2], **97**, 225 (1918); (*b*) J. L. Huntington and D. G. Davis. J. Magn. Reson. **3**, 456 (1970).
14. (*a*) W. Dersch. Diss. Univ. Marburg, 1974; (*b*) C. Lagercrantz and M. Setaka. Acta Chem. Scand. B, **28**, 619 (1974).
15. H. G. Aurich and W. Dersch. Z. Naturforsch. Teil B, **28**, 525 (1973).
16. R. W. Layer. Tetrahedron Lett. 4413 (1970).
17. H. G. Aurich, J.-M. Heinrich, and G. Waßmuth. J. Chem. Res. (S), 222 (1980); (M), 3046 (1980).
18. H. G. Aurich, J.-M. Heinrich, and G. Waßmuth. J. Chem. Res. (S), 224 (1980); (M), 3062 (1980).
19. H. G. Aurich and W. Weiss. Top. Curr. Chem. **59**, 65 (1975).
20. H. G. Aurich, S. K. Duggal, P. Höhlein, H.-G. Klingelhöfer, and W. Weiss. Chem. Ber. **114**, 2440 (1981).
21. G. Zinner and U. Dybowski. Arch. Pharm. Weinheim, **304**, 877 (1971).
22. K. Volkamer and H. W. Zimmermann. Chem. Ber. **102**, 4177 (1969).
23. (*a*) H. G. Aurich and W. Weiss. Chem. Ber. **106**, 2408 (1973); (*b*) H. G. Aurich and K. Stork. Chem. Ber. **108**, 2764 (1975).
24. D. G. B. Boocock, R. Darcy, and E. F. Ullman. J. Am. Chem. Soc. **90**, 5945 (1968).