5-Aryl-2-(3,5-dialkyl-4-hydroxyphenyl)-4,4-dimethyl-4H-imidazole 3-Oxides and Their Redox Species: How Antioxidant Activity of 1-Hydroxy-2,5-dihydro-1H-imidazoles Correlates with the Stability of Hybrid Phenoxyl–Nitroxides

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Abstract: Cyclic nitrones of the imidazole series, containing a sterically hindered phenol group, are promising objects for studying antioxidant activity; on the other hand, they can form persistent hybrid phenoxyl–nitroxyl radicals (HPNs) upon oxidation. Here, a series of 5-aryl-4,4-dimethyl-4H-imidazole 3-oxides was obtained by condensation of aromatic 2-hydroxylaminoketones with 4-formyl-2,6-dialkylphenols followed by oxidation of the initially formed N-hydroxy derivatives. It was shown that the antioxidant activity of both 1-hydroxy-2,5-dihydroimidazoles and 4H-imidazole 3-oxides increases with a decrease in steric volume of the alkyl substituent in the phenol group, while the stability of the corresponding HPNs generated from 4H-imidazole 3-oxides reveals the opposite tendency.

Keywords: cyclic hydroxylamines; 4H-imidazole 3-oxides; sterically hindered phenols; antioxidants; hybrid phenoxyl–nitroxides; electron paramagnetic resonance

1. Introduction

Nitrones constitute a rapidly emerging class of functional substances whose high reactivity not only serves as a starting point for the synthesis of biologically important nitrogen compounds [1,2] but also perfectly correlates with the manifestation of a wide range of bioactivities by them [3–5]. Nitrones are unique free-radical scavengers acting as spin traps of very cytotoxic reactive oxygen species (ROS) accumulating in tissues at high concentrations under oxidative stress.

High antioxidant activity of nitrones bearing aliphatic, aromatic, heterocyclic, or heteroatom substituents allows the consideration of them as effective therapeutic agents against oxidative stress that occurs under critical pathological conditions in the human body, e.g., myocardial infarction or stroke [6]. One of the first nitrones to be used as a neuroprotector reducing ischemic hippocampal damage in animals was N-tert-butyl-α-phenylnitrone (PBN) 1a [7]. Furthermore, a series of 1a derivatives has been synthesized and applied as (i) hydrophilic spin traps for different types of organic radicals (e.g., 4-POBN 1b for OH•, CO2•−) [8] and (ii) spin traps for the hydroxymethyl radical and promising agents for...
neuroprotection yielding good results in an in vitro model of cellular injury of cortical neurons (N-aryl and C-alkyl modified nitrones 3a,b) [9]. Water-soluble disulfonyl PBN derivative 1c (NXO-059) [10] has reached AstraZeneca Phase IIIb/III clinical trials for the treatment of acute stroke, and although it eventually failed at the efficacy assessment when compared with a placebo, at the same time, this compound turned out to be a promising novel anticancer agent (OKN-007) [11]. Lipophilic bis-nitroene of the azulene series 2 (STAZN), possessing an improved level of blood-brain barrier penetration, has shown impressive results in terms of both outstanding antioxidant activity [12] and prospects for its application as a lead compound for stroke treatment [13] (Scheme 1).

![Scheme 1. Chemical structures of nitrones with a lateral or exocyclic C=N=O− group.](image)

The chemical and pharmacological properties of nitrones depend mainly on the bioavailability as well as the nature and position of the substituents in the nitroene group. During the last decade, Marco-Contelles at al. have synthesized and tested a large series of acyclic nitrones that hold promise for the treatment of neurodegenerative diseases: (a) PBN analogs containing isovanillin moieties (RP-6) 1d [14], (b) 3- and 4-nitronylquinolines 5 (RP-19 and QN-23) [15,16] and 6 (QN-6) [17], and (c) heteroatomic C-phosphoryl derivative 3c [18] (Scheme 1). Moreover, very recently, a new cholesterol derivative containing exocyclic nitroene function 4 (ISQ-201) was obtained by the same group of researchers [19]. Detailed study of two spatial isomers of this lipophilic molecule has revealed that only the (E)-isomer significantly decreases ischemia-induced neuronal death and apoptosis, in a dose-dependent manner. This compound manifested its therapeutic effect when administered before 6 h after postischemic reperfusion onset: effects that persisted for 3 months after the ischemic episode [20]. In addition, other heterocyclic nitrones of pyrazine 7 (TBN) [21] and triazole 8 [22] series have shown noticeable anti-inflammatory and anticarcinogenic properties.

Among cyclic nitrones, derivatives of pyrroline-N-oxide 9 are best known as spin traps of free radicals, such as 5,5-dimethyl-1-pyrroline N-oxide (DMPO) [23] (to date, over 3000 papers on DMPO have been published) and its functional derivatives, ethoxycarbonyl (EMPO) [24], the more lipophilic t-butoxycarbonyl (BMPO) [25], and 5-diethoxyphosphoryl-5-methyl-1-pyrroline 1-oxide (DEPMPO) [26], which have contributed substantially to the understanding of free-radical-mediated processes in biochemical systems. Some cyclic nitrones can trap different short-lived radical species, forming more stable spin adducts than PBN or DMPO. These include compounds of the imidazole series 10 [27,28] and 14 [29], isoindoline 12 [30], and isoquinoline 13 [31] derivatives. Screening of recently synthesized 3H-indol-3-one 1-oxides revealed that 2-alkylisatogens 11 are novel ROS scavengers.
 capable of inhibiting cellular necroptosis [32], whereas 2-aryl derivatives possess very promising antiplasmoidal activity [33] (Scheme 2).

Although a wide range of nitrones has been obtained, and their biological activity in various models has been proven, the question of the correlation between their ability to capture short-lived radicals and their neuroprotective activity is still open. As recently noted, “the mode of action of nitrone has been subject to debate over the past three decades and the exact mechanism of neuroprotection is not fully known. There is strong evidence that nitrones may affect genomic regulation and stimulate anti-inflammatory reactions as well as antioxidant properties and action on important membrane enzymes. However, so far there is no clear link between the chemical structure, the chemical reactivity and the potency of nitrone in preventing cell death.” [9]. Therefore, the search for new biologically active functional nitrones is still a relevant and important task.

As part of our ongoing research on the properties and applications of π-conjugated planar stable hybrid phenoxy–nitroxides (HPNs) based on the 4H-imidazole 3-oxide frame [34,35], we turned our attention to the possible application of diamagnetic HPN precursors: 2,4-diarylimidazole derivatives bearing either hydroxylamine or nitrone functions—along with the sterically hindered phenolic group—as promising antioxidants containing two antiradical moieties. Although only a limited number of compounds possessing a structure of similar type (compounds 15–19) is described in the literature, they have proven to be “dual” traps of free radicals (15 [36–38] and 16 [39])—in addition to having remarkable properties—and as unique agents with a wide spectrum of biological activities, in particular, antioxidant, anti-inflammatory, and neuroprotective properties (15, 17, 18) (Scheme 3) [40–44]. Hybrid molecules 19 (R = t-Bu, cyclopropyl), combining a vitamin E moiety and a spin trap part, as it has turned out, are comparable to Trolox in scavenging free radicals and outperform nitrone-type reference compounds, for example, PBN or NXY-059 [45].

Scheme 2. Examples of cyclic nitrones with an endocyclic C=\(\text{N}^+\text{O}^-\) group.

Scheme 3. Examples of spin traps, antioxidants, and neuroprotectors containing \(\alpha,\alpha'\)-dialkyl–substituted phenolic or nitrone groups.
2. Results

2.1. Preparation of Key Compounds

2.1.1. Synthesis of 4-formylphenols 23 and Their Condensation with p-X-Ar-substituted 2-hydroxylamino Ketones 25

4-Formyl-2,6-dialkylphenols 23a–e required for the further condensation with 2-hydroxylamino ketones were obtained with high yields via the Duff reaction of α,α′-dialkyl–substituted phenols 24a–e with an excess of hexamethylenetetramine, during heating in glacial acetic acid (Scheme 4).

![Scheme 4. Synthesis of initial 4-formylphenols 23.](image)

To synthesize the main synthetic blocks (2-hydroxylamino ketones 25), α-bromo derivatives of p-aryl–substituted isobutyrophenones 26 were reacted with nitrogen nucleophiles in two ways outlined in Scheme 5. Following the first method, bromoketone 26d containing a deactivated phenolic hydroxyl group was introduced into the reaction with an excess of a sodium salt of Z-benzaldoxime (cf. [49]) and the obtained nitrone 27 was subsequently treated with 1 equiv of NH₂OH-HCl. After extraction of the reaction mixture and separation of waste benzaldoxime, the aqueous solution was carefully neutralized by ammonia to quantitatively precipitate hydroxylamino ketone 25. According to the second method, when reactive bromoketones 26a–c were introduced into the reaction with a large excess of hydroxylamine, intermediate 2-hydroxylamino oximes 28a–c were obtained with a high yield. Boiling of the latter in concentrated hydrochloric acid led to the desired 2-hydroxylamino ketone 25a–c, as their corresponding hydrochlorides (Scheme 5).
we noticed that overexposure of the mixture in an open flask leads to its darkening and decreases the
properties were purified by crystallization from an appropriate solvent (Supplementary Materials).

Condensation reactions of resultant hydroxylamino ketones 25a–c (as hydrochlorides) or as free
bases (25d) with 4-formylphenols 23a–e were carried out in the presence of a large excess (6–10 equiv)
of ammonium acetate to minimize the formation of the side products of the reaction, ketonitrones 29,
and therefore to increase the yield of the desired 1-hydroxy-2,5-dihydroimidazoles 20a–s (Scheme 5,
Table 1). Although this reaction takes place at ambient temperature and usually finishes in 6–12 h,
we noticed that overexposure of the mixture in an open flask leads to its darkening and decreases the
yields of imidazolines 20a–s owing to oxidative processes. Precipitated cyclic hydroxylamines 20 were
pure enough to use them for the next synthetic step; the samples designed to investigate their antioxidant
properties were purified by crystallization from an appropriate solvent (Supplementary Materials).

Table 1. The library of new compounds prepared in this study.

| Compound(s) | R<sup>3</sup> | R<sup>1</sup> | R<sup>2</sup> | Yield of 20, % | Yield of 21, % |
|-------------|--------------|--------------|--------------|---------------|---------------|
| 20–22a      | H            | Me           | Me           | 87            | 87            |
| 20–22b      | H            | Me           | i-Pr         | 87            | 81            |
| 20–22c      | H            | i-Pr         | i-Pr         | 75            | 87            |
| 20–22d      | H            | Cy           | Cy           | 91            | 93            |
| 20–22e      | H            | t-Bu         | t-Bu         | 78            | 97            |
| 20–22f      | F            | Me           | Me           | 87            | 86            |
| 20–22g      | F            | Me           | Cy           | 91            | 86            |
| 20–22h      | F            | i-Pr         | i-Pr         | 85            | 96            |
| 20–22i      | F            | Cy           | Cy           | 82            | 96            |
| 20–22j      | F            | t-Bu         | t-Bu         | 76            | 90            |
| 20–22k      | Br           | Me           | Me           | 98            | 91            |
| 20–22l      | Br           | Me           | Cy           | 93            | 94            |
| 20–22m      | Br           | i-Pr         | i-Pr         | 78            | 97            |
| 20–22n      | Br           | Cy           | Cy           | 89            | 100           |
| 20–22o      | Br           | t-Bu         | t-Bu         | 88            | 93            |

Scheme 5. Synthesis of key compounds: 2,4-diaryl-1-hydroxy-2,5-dihydroimidazoles 20, 2,5-diaryl-4H-
imidazole 3-oxides 21, and HPNs 22. Reagents and conditions: (i) R<sup>3</sup> = OH: (Z)-PhCH=NOH, EtONa
(2 equiv), EtOH<sub>abs</sub>, 0 °C → 20 °C, 72 h, 65%; (ii) R<sup>3</sup> = H, F, Br: NH<sub>2</sub>OH·HCl (5 equiv), MeONa
(4 equiv), MeOH, rt→Δ (6–8 h), 60–85%; (iii) R<sup>3</sup> = OH: NH<sub>2</sub>OH·HCl, EtOH, rt, 48 h, then 25% aq NH<sub>3</sub>,
80%; (iv) R<sup>3</sup> = H, F, Br: HCl<sub>conco</sub>, Δ, 25–50 min, 75–85%; (v) R<sup>3</sup> = H, F, Br, OH: NH<sub>4</sub>OAc (6–10 equiv),
4-formylphenol 23, MeOH (or EtOH<sub>abs</sub>), rt, 6–12 h, then 0 °C, 12 h, 68–98%; (vi) R<sup>3</sup> = H, F, Br, OH:
Cu(OAc)<sub>2</sub>·3H<sub>2</sub>O (20 mol%), 16% aq NH<sub>3</sub>, O<sub>2</sub>, MeOH, rt, 1–6 h, 81–100%; (vii) R<sup>3</sup> = H, F, Br: CHCl<sub>3</sub>, PbO<sub>2</sub>,
296 K, 1 min, then dilution with PhMe, argon, 75–85% for 22e,j,o.
2.1.2. Oxidation of 2,5-dihydroimidazoles 20 to 4H-imidazole 3-Oxides 21

4H-Imidazole 3-oxides 21a–s were prepared with a high yield via oxidation of cyclic hydroxylamines 20a–s by air oxygen using a mild homogeneous catalytic system: a copper(II) ammine complex in aqueous methanol (Scheme 5, Table 1). Attempts to apply various oxidants (heterogeneous MnO$_2$, PbO$_2$, or homogeneous aqueous solutions of sodium periodate or alkaline potassium hexacyanoferrate) to this reaction led to a lower product yield and significant resinification of the reaction mixture owing to side oxidation of the phenolic hydroxyl group. 4H-Imidazole 3-oxide derivatives 21a–s are bright yellow or orange high-melting-point crystalline compounds, poorly soluble in polar and aprotic solvents and moderately soluble in halogenated hydrocarbons.

2.2. Antiradical Activity of the 1-Hydroxy-2,5-Dihydroimidazole 20 and 2,5-Diaryl-4H-Imidazole 3-Oxide 21 Derivatives

Comparative analysis of antiradical activity (ARA) of the 27 synthesized imidazole derivatives 20–21 was carried out in the model system of azobisisobutyronitrile (AIBN)-initiated cumene oxidation at 60 °C. The oxidation of aliphatic and aromatic hydrocarbon derivatives, polymers, and lipids by molecular oxygen is a radical chain process proceeding according to the hydroperoxide mechanism, which can be described by means of reactions (0)–(6) (Supplementary Materials, Scheme S2). Interaction of the phenolic antioxidants with peroxide radicals of an oxidizable substrate (Scheme S2 Equation (1)) is the principal step determining the ability of phenolic compounds (ArO-H) to inhibit the chain oxidation process. Unlike the peroxide radical RO$_2$•, phenoxyl radical ArO• formed in reaction (7) is inactive in the chain extension process; therefore, the presence of ArO-H significantly decelerates the substrate oxidation. Thus, the rate constant ($k_7$) of the reaction between the antioxidant (AO) and peroxide radicals is one of the main characteristics of the effectiveness of an inhibitor. Therefore, $k_7$ as well as stoichiometric inhibition coefficients $f$, numerically equal to the average number of oxidation chains terminated per phenoxyl group of the inhibitor, were chosen as the quantitative ARA characteristics.

According to the obtained data (Table 2), all the investigated compounds had a pronounced inhibitory activity against the oxidation of cumene. Moreover, different groups of compounds showed different inhibition coefficient values $f$ and the rate constants $k_7$ as well.

Thus, for 2,5-dihydroimidazoles 20, inhibition coefficient $f$ was 2.8 to 4.8, but 4H-imidazole 3-oxides 21 were characterized by lower values of $f$ (1.9 to 2.5) under the same experimental conditions.

It is known that an $f$-value experimentally determined under conditions of initiated oxidation is close to 2 for most of 2,4,6-trialkylphenols [50], which corresponds to quantitative transformation of phenols (ArO-H) to phenoxyls (ArO•) via Equation (1) (Scheme S2), followed by conversion of the latter into the molecular products by Equation (2) (Scheme S2):

$$\text{ArO-H} + \text{RO}_2^• \rightarrow \text{ROOH} + \text{ArO} \quad (1)$$

$$\text{ArO}^• + \text{RO}_2^• \rightarrow \text{molecular products} \quad (2)$$
It is noteworthy that a clear dependence of the experimentally determined f-value on the nature of the ortho-substituents in the hydroxyaryl part of 2,5-dihydroimidazoles 20 was observed. Indeed, compounds 20e,j,o with di-tert-butyl ortho-substituents near phenolic hydroxyl, were characterized by lower f-values (2.8 to 3.2) than their analogs bearing methyl, isopropyl, and cyclohexyl as ortho-substituents, featuring f-values of 3.9 to 4.9 (Table 2).

Table 2. Quantitative ARA characteristics of imidazole derivatives 20 and 21 in initiated cumene oxidation (60 °C) *

| Compound | R<sup>3</sup> | R<sup>1</sup> | R<sup>2</sup> | f  | k<sub>f</sub> \( \times 10^{-4} \), M<sup>-1</sup>s<sup>-1</sup> |
|----------|--------------|--------------|--------------|----|-----------------|
| 20a      | H            | Me           | Me           | 3.9 ± 0.3 | 5.1 ± 0.8       |
| 20b      | H            | Me           | Cy           | 4.5 ± 0.5 | 5.0 ± 1.2       |
| 20c      | H            | i-Pr         | i-Pr         | 4.0 ± 0.1 | 4.5 ± 0.1       |
| 20d      | H            | Cy           | Cy           | 4.4 ± 0.1 | 5.0 ± 0.8       |
| 20e      | H            | t-Bu         | t-Bu         | 3.2 ± 0.3 | 4.0 ± 0.3       |
| 20f      | F            | Me           | Me           | 4.1 ± 0.1 | 4.9 ± 0.4       |
| 20g      | F            | Me           | Cy           | 4.7 ± 0.2 | 5.6 ± 0.6       |
| 20h      | F            | i-Pr         | i-Pr         | 4.5 ± 0.1 | 4.5 ± 0.3       |
| 20j      | F            | t-Bu         | t-Bu         | 2.8 ± 0.3 | 4.7 ± 0.8       |
| 20k      | Br           | Me           | Me           | 4.44 ± 0.02 | 6.4 ± 0.1     |
| 20l      | Br           | Me           | Cy           | 4.83 ± 0.02 | 4.1 ± 0.5     |
| 20m      | Br           | i-Pr         | i-Pr         | 4.5 ± 0.1 | 3.7 ± 0.1       |
| 20n      | Br           | Cy           | Cy           | 4.7 ± 0.2 | 5.1 ± 0.9       |
| 20o      | Br           | t-Bu         | t-Bu         | 3.2 ± 0.2 | 4.0 ± 0.2       |
| 21a      | H            | Me           | Me           | 2.1 ± 0.1 | 6.0 ± 0.6       |
| 21b      | H            | Me           | Cy           | 2.05 ± 0.02 | 6.0 ± 0.6     |
| 21c      | H            | i-Pr         | i-Pr         | 2.1 ± 0.1 | 5.1 ± 0.5       |
| 21e      | H            | t-Bu         | t-Bu         | 1.9 ± 0.2 | 4.1 ± 0.7       |
| 21f      | F            | Me           | Me           | 2.11 ± 0.04 | 4.9 ± 0.2     |
| 21g      | F            | Me           | Cy           | 2.1 ± 0.1 | 6.6 ± 0.9       |
| 21h      | F            | i-Pr         | i-Pr         | 2.1 ± 0.1 | 5.5 ± 0.7       |
| 21j      | F            | t-Bu         | t-Bu         | 1.9 ± 0.2 | 3.9 ± 0.3       |
| 21k      | Br           | Me           | Me           | 2.4 ± 0.1 | 5.5 ± 0.4       |
| 21l      | Br           | Me           | CyH          | 2.3 ± 0.1 | 5.2 ± 0.4       |
| 21m      | Br           | i-Pr         | i-Pr         | 2.34 ± 0.04 | 4.3 ± 0.4     |
| 21n      | Br           | Cy           | Cy           | 2.5 ± 0.1 | 5.9 ± 0.9       |
| 21o      | Br           | t-Bu         | t-Bu         | 2.0 ± 0.2 | 3.8 ± 0.1       |

* For comparison, the k<sub>f</sub> constant for 3,5-diisobutyl-4-hydroxytoluene (BHT) in this model system is 3.1 × 10<sup>4</sup> M<sup>-1</sup>s<sup>-1</sup>.

Because the f-values of compounds 20a,f,k with the least bulky methyl ortho-substituents did not exceed those of isopropyl and cyclohexyl-substituted analogs, it can be assumed that for the manifestation of high f-values in the series of 2,5-dihydroimidazoles, the presence of ortho-alkyl substituents with benzylic hydrogen atoms is crucial. In other words, in the case of tert-butyl-substituted 20e,j,o the oxidation of the hydroxyaryl moiety was stopped at the stage of phenoxyl radical formation, whereas for methyl-, isopropyl-, and cyclohexyl-substituted derivatives, the interaction with peroxide radicals was more profound, leading to the formation of substituted ortho-methylenequinones. Moreover, 1-hydroxy-2,5-dihydroimidazoles 20 can break the oxidation chains via a reaction involving the N-hydroxy groups. The formed nitroxyl apparently does not have an inhibitory activity. This assumption is supported by the established fact that 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPOL) does not inhibit initiated oxidation of cumene [51]. Finally, one more antiradical center in 20 is obviously the hydrogen atom at the C-2 position of the imidazole ring. The easiness of the cleavage of the corresponding C-H bond is due to the stability of the forming C-centered radical, containing a prolonged conjugated system covering both aryl substituents of the imidazole ring and providing effective delocalization of the spin density of an unpaired electron. Recombination of the
peroxide radical with the C-centered radical breaks another oxidation chain and leads to the final product. Accordingly, in the reaction with peroxide radicals one 2,5-dihydroimidazole molecule 20 can interrupt at most five oxidation chains, turning presumably into 3-imidazoline 1-oxyl 30 (Scheme 6).

![Scheme 6](image)

Scheme 6. Possible oxidative transformations of 1-hydroxy-2,5-dihydroimidazoles under the action of peroxide radicals as exemplified by disopropyl substituted derivative 20h. Colored circles indicate the sites where the predominant attack of the peroxide radical occurs.

The experimentally obtained $f$-values for 2,5-dihydroimidazoles 20g,1,n amounted to 4.7–4.8, respectively, and were in good agreement with the above-mentioned reasoning. The most likely final products of the oxidation of compounds 20e,j,o are corresponding stable HPNs 22, bearing a quinone methide–conjugated moiety. Conversion from 20e to 22e corresponds to breakage of 3 oxidation chains, in good agreement with the obtained $f$-values for 20e, 20j, and 20o (2.8 ± 0.3 to 3.2 ± 0.3).

The use of 4H-imidazole 3-oxide derivatives 21 as AOs in comparison with 2,5-dihydroimidazoles 20 under the same experimental conditions caused less prolonged inhibition of cumene oxidation. Indeed, the $f$-values of 21 were within the range 1.9 to 2.5, wherein, similarly to compounds 20, derivatives 21e, 21j, and 21o with a di-tert-butyl-substituted hydroxyaryl part were characterized by lower $f$-values equal to 1.9–2.0. At the same time, the methyl-, isopropyl-, and cyclohexyl-substituted analogs had $f$-values of 2.05 to 2.5.

Molecules of 4H-imidazole 3-oxide 21 contain two antiradical centers: a hydroxyaryl part and a nitro group, respectively. It might be suggested that the hydroxyaryl group in 21 bearing ortho-substituents with benzylic hydrogen atoms can undergo transformations similar to those for 2,5-dihydroimidazoles 20, interrupting two oxidation chains and, consistently turning into the corresponding phenoxyl radicals and then into ortho-methylenquinones. On the other hand, nitrones are also able to break oxidation chains via the addition of active radicals to a double bond with the formation of stable nitroxide radicals [52], which in the case of 21 leads to analogous paramagnetic product 30. Therefore, it is expected that 4H-imidazole 3-oxides 21 bearing partially shielded hydroxyaryl substituents can interrupt three oxidation chains at most. This notion is in good agreement with the experimentally obtained data for this series of compounds 21k–n: the $f$-coefficient reached 2.5, which is close to 3.0.

Compounds 20 and 21 contain several reaction centers able to interact with cumene peroxide radicals, but only one of them—the 3,5-dialkyl-4-hydroxyphenyl moiety—is common for both types of molecules. Because significant differences in $k_7$-values, characterizing the corresponding pairs of compounds, 2,5-dihydroimidazole 20 and 4H-imidazole 3-oxide 21 series, were not observed, we assumed that the experimentally obtained values of $k_7$ (Table 2) refer to 3,5-dialkyl-4-hydroxyphenyl parts of these compounds.

It is known [50] that the reactivity of ortho-dialkyl–substituted phenols toward active radicals depends, on the one hand, on the steric hindrances created by ortho-substituents for the ArO–H bond attack (that is, upon the effective volume of the ortho-substituents), and, on the other hand, upon the energy of the ArO–H bond, which decreases as the electron-donating ability of ortho-substituents increases. These factors are independent, thus often making quantification of the alkyl substituents’ effect on the $k_7$ value difficult. It has been shown previously that ortho-di-tert-butyl-substituted phenols are inferior in the magnitude of $k_7$ to their analogs containing $n$-alkyl and sec-alkyl ortho-substituents. According to the literature data, $k_7$ values of 2,4,6-trialkyl–substituted phenols are
2.4 × 10^4 to 1.6 × 10^5 M^{-1} \cdot s^{-1} under the conditions of initiated cumene oxidation at 60 °C. Herewith, 2,6-di-tert-butylphenols were characterized by the lowest values of \( k_f \), which were 5–7-fold less than those for their analogs with dimethyl and dicyclohexyl ortho-substitution [53].

The measured \( k_f \) values for imidazole derivatives 20 and 21 under study also changed depending on the nature of the alkyl ortho-substituents; however, the differences in the determined values were much less pronounced. Specifically, for 2,5-dihydroimidazole series 20, the compounds with tert-butyl substituents were characterized by \( k_f \) values equal to (4.0–4.7) × 10^4 M^{-1} \cdot s^{-1}, and the highest \( k_f \) values were detected for dimethyl-substituted derivatives 20a, 20f, and 20k: 4.9 × 10^4 to 6.4 × 10^4 M^{-1} \cdot s^{-1}. A similar trend was also observed for 4H-imidazoles 21 (Table 2). In this way, the presence of the 3,5-dialkyl-4-hydroxyphenyl moiety at the C-2 atom of the imidazole ring in 20 and 21 causes leveling of differences in \( k_f \) values characterizing the ARA of ArO-H with ortho-substituents of different nature. The presence or absence of the halogen atom at the 4(5)-position of the heterocycle did not affect the experimentally determined values of the \( k_f \) constant, most likely owing to the significant remoteness of the functional group from the active center of the phenolic part.

2.3. Generation and EPR Study of New Hybrid Phenoxy–Nitrooxides 22

Recently, we published a detailed study on intra- and intermolecular magnetic properties of HPNs bearing an aliphatic, aromatic, and heteroaromatic substituent at the C-4(5) carbon atom of the heterocyclic ring to show their usefulness as new building blocks for molecular magnetic materials [35]. To continue the detailed analysis of magnetic properties of this new class of organic radicals for their further potential application in magnetochemistry, we investigated in the present study how structural features of the molecule, in particular, the nature of the substituents adjacent to the phenolic group, can affect the stability and electronic properties of persistent HPNs 22 (Figure 1) by means of X-band continuous-wave (CW) EPR spectroscopy and density-functional theory (DFT) calculations.

HPNs 22a–o were generated via oxidation of 4H-imidazole 3-oxide derivatives 21a–o by lead dioxide in diluted toluene solutions (see the Experimental section for details). The corresponding EPR spectra were recorded after the oxidant filtration and subsequent deoxygenation of the obtained radical solutions. The spectra of 22a–d and 22e,j,o are presented in Figures 2 and 3, respectively; all the other spectra can be found in Supplementary Materials. The observed spectra represent complex patterns at \( g_{iso} = 2.0049 \) to 2.0063, which can be well reproduced taking into account hyperfine splitting (hfs) constants of two nonequivalent nitrogen nuclei (N^1 and N^3), two slightly different phenoxy protons (H^2 and H^6), and the protons of alkyl substituents at \( \alpha,\alpha' \)-carbon atoms of the phenoxy group. The simulation parameters are listed in Table 3. The observed hfs constants varied within the following limits: \( A_{N1} = 0.343–0.550 \) mT, \( A_{N3} = 0.042–0.064 \) mT, \( A_{H2,H6} = 0.066–0.312 \) mT, and \( A_{H-R1R2} = 0.150–0.767 \) mT, in line with the quantum chemical calculations presented below.
The obtained data are well consistent with the theoretical calculations described below. Consequently, the main part of the spin density in hybrid radicals 22a phenoxyl moiety significantly influences the spin density distribution within the phenoxyl-nitroxide part (blue in Figure 1). Nevertheless, a comparison of 22e constants of the fluorine nucleus for radical 22j, 22o and two nonequivalent protons H2,6. This is due to the presence of several conformational isomers of these radicals with different spin density distributions, which exist in equilibrium in their diluted solutions, and therefore the observed spectra are a superposition of the spectra of these conformers.

Due to the absence of protons at α,α′-carbon atoms, radicals bearing tert-butyl substituents R1 and R2 (compounds 22e,j,o) have hfs constants of only two nonequivalent nitrogen nuclei of the heterocycle and two nonequivalent protons H2,6 (Figure 3). In addition, it was possible to estimate a small hfs constant of the fluorine nucleus for radical 22j. Moreover, slight differences in the chemical structures of 22e,j,o led to changes of their EPR spectra and thus allowed to analyze how the R3 substituent (H, F, Br) influences the spin density distribution within the side part of the molecules. Nevertheless, a comparison of hfs constants of these radicals showed that in general, the spin density distribution map changed only insignificantly. Thus, hfs constants of 22e, j, o vary within the following limits: A_{N1} = 0.548–0.552 mT, A_{N3} = 0.061–0.063 mT, A_{H2} = 0.163–0.166 mT, and A_{H6} = 0.152–0.158 mT. The obtained data are well consistent with the theoretical calculations described below.

**Figure 2.** EPR spectra recorded for diluted and oxygen-free toluene solutions of HPNs at 295 K: (a) 22a, (b) 22b, (c) 22c, and (d) 22d. Black curve: experimental spectra; red curve: simulated spectra with the parameters listed in Table 3.
Figure 3. EPR spectra acquired for diluted and oxygen-free toluene solutions of HPNs at 295 K: (a) 22e, (b) 22j, and (c) 22o.

Table 3. EPR parameters used for 22a–o spectral simulations. [R₂h]/[R₂o]: a relative proportion of HPNs that survived after keeping the solution of the radical for 2 h in an argon atmosphere.

| HPNs | βiso | AₐISO | AₐN₁ | AₐN₂ | AₐH₂ | AₐH₆ | AₐH₀(Me) | AₐH[CY] | AₐH(i-Pr) | AₐF | [R₂h]/[R₂o] |
|------|------|-------|------|------|------|------|----------|--------|----------|------|----------|
| 22a  | 2.0049 | 0.343 | 0.045 | 0.216 | 0.100 | 0.767 | -        | -      | -        | 0.85 |          |
| 22b  | 2.0059 | 0.437 | 0.042 | 0.150 | 0.132 | 0.534 | 0.256    | -      | -        | 0.46 |          |
| 22c  | 2.0063 | 0.539 | 0.066 | 0.265 | 0.265 | -     | -        | 0.150  | -        | 0.77 |          |
| 22d  | 2.0063 | 0.536 | 0.062 | 0.247 | 0.247 | -     | 0.163    | 0.163  | -        | 0.75 |          |
| 22e  | 2.0059 | 0.550 | 0.062 | 0.163 | 0.155 | -     | -        | -      | -        | 1    |          |
| 22f  | 2.0049 | 0.377 | 0.051 | 0.312 | 0.100 | 0.775 | 0.620    | -      | -        | 0.83 |          |
| 22g  | 2.0059 | 0.439 | 0.042 | 0.160 | 0.130 | 0.529 | 0.258    | -      | -        | 0.51 |          |
| 22h  | 2.0063 | 0.541 | 0.064 | 0.267 | 0.267 | -     | -        | 0.155  | 0.155    | 0.81 |          |
| 22i  | 2.0063 | 0.539 | 0.060 | 0.249 | 0.249 | -     | 0.161    | 0.161  | -        | 0.79 |          |
| 22j  | 2.0059 | 0.552 | 0.061 | 0.166 | 0.152 | -     | -        | -      | 0.043    | 1    |          |
| 22k  | 2.0049 | 0.358 | 0.049 | 0.225 | 0.066 | 0.747 | 0.656    | -      | -        | 0.81 |          |
| 22l  | 2.0059 | 0.439 | 0.042 | 0.155 | 0.133 | 0.529 | 0.260    | -      | -        | 0.43 |          |
| 22m  | 2.0064 | 0.538 | 0.065 | 0.263 | 0.263 | -     | -        | 0.156  | 0.156    | 0.67 |          |
| 22n  | 2.0063 | 0.541 | 0.071 | 0.258 | 0.258 | -     | 0.162    | 0.162  | -        | 0.68 |          |
| 22o  | 2.0059 | 0.548 | 0.063 | 0.163 | 0.158 | -     | -        | -      | -        | 1    |          |

To additionally confirm our interpretation of the EPR spectra of HPNs 22a–e,j,o, we calculated their hfs constants by the DFT/UB3LYP/6-31G(d) method. The conductor-like polarizable continuum
model (CPCM) (solvent: toluene) was employed to take into account a solvent effect. The calculation results are listed in Table 4 and presented in Supplementary Materials (Figures S1–S5). In general, the calculation data qualitatively correlated with the data obtained by the experimental spectra simulations. As shown in Figure S1, there are hfs constants of only two protons of methyl groups at α,α′-carbon atoms of the phenoxyl part, which are located outside the plane of the aromatic ring. It is clear that in solution, due to the free rotation of this group, an average value of these constants will be observed. This value, calculated as the arithmetic mean of the constants of three protons, is given in Table 4. Similar patterns were observed for HPNs 22b,c,d containing cyclohexyl and isopropyl groups (Figures S2–S4) and existing in solutions as equilibria of conformational isomers (rotamers). For those conformers, where the methine proton in the cyclohexane or isopropyl moiety is located in the plane of the phenoxyl ring, its hfs constant is significantly less than that when the proton is located out of the plane. The calculation method used in this work does not allow estimation of the molar ratio of the conformers exist in the mixture; therefore, the hfs constants listed in Table 4 were calculated assuming that the conformers exist in the mixture in the equimolar ratio.

| HPN | AN1, mT | AN3, mT | AH2, mT | AH6, mT | AH(Mel), mT | AH(Cy), mT | AH(i-Pr), mT | HF, mT |
|-----|---------|---------|--------|--------|-------------|-------------|---------------|-------|
| 22a | 0.526   | 0.110   | 0.249  | 0.232  | 0.425       | -           | -             | -     |
| 22b | 0.523   | 0.110   | 0.231  | 0.247  | 0.459       | 0.243       | -             | -     |
| 22c | 0.519   | 0.110   | 0.233  | 0.250  | -           | -           | 0.125         | 0.134 |
| 22d | 0.522   | 0.110   | 0.231  | 0.247  | -           | 0.179       | -             | -     |
| 22e | 0.525   | 0.109   | 0.228  | 0.246  | -           | -           | -             | -     |
| 22j | 0.526   | 0.110   | 0.228  | 0.246  | -           | -           | -             | −0.122|
| 22o | 0.522   | 0.113   | 0.232  | 0.249  | -           | -           | -             | -     |

As mentioned above, EPR spectra of 22e,j,o are slightly different. Appropriate quantum chemical calculations were performed to investigate how the R3 substituent (H, F, Br) influences the spin density distribution in the side part of the molecule of HPN. Mulliken atomic spin populations for 22e, j, o are presented in Figure 4. It was confirmed by the calculations that the origin of the substituent does not significantly influence the spin density distribution, in agreement with the data obtained by the analysis of their EPR spectra. The calculated spin densities on the aromatic ring vary within the range −0.023 to −0.025 for ortho- and para-carbons and 0.012−0.013 for meta-carbons, respectively; however, the sign of the hfs constant changes when a hydrogen atom is replaced by a halogen atom. The latter can be important for studies on the magnetic properties of these compounds in crystal, because at a certain mutual orientation of the molecules, the sign of the corresponding intermolecular magnetic interaction may change.

![Figure 4](image-url)
Thermodynamic stability of organic radicals (from persistence in solution to high robustness in a crystal state) is an important parameter for their any applications in the chemistry of magnetic and electroactive materials; therefore, we conducted its comparative assessment for a series of HPNs 22. EPR spectra of the diluted toluene solutions of phenoxy–nitroxides 22a–o were recorded just after the formation of the corresponding radical and after keeping the solution for 1 h at 295 K in an Ar atmosphere. It was revealed that compounds 22a–d, f–i, k–n containing similar primary or tertiary substituents at C-3(5) atoms on the phenoxy ring are persistent and exist in solution for several hours. The least stable were radicals 22b, g, l bearing asymmetric substituents: methyl and cyclohexyl groups. Indeed, after incubation of their solution for 1 h, only half of the initial amount of the radical remained. Surprisingly, phenoxy–nitroxides 22a, f, k with two methyl groups in the phenoxy moiety were comparable in stability with 22c, d, h, i, m, n containing isopropyl and cyclohexyl substituents at the same positions. Nonetheless, measurement of the decomposition kinetics for these compounds was challenging, because the EPR spectra of these compounds represent a superposition of two spectra: the spectrum of HPN (22a, f, k) and the spectrum of the paramagnetic product of its decompositions: a nitroxide radical of unknown structure, whose contribution is quite substantial (Figure 5). The ratio of intensities of these two spectra is time-dependent because the unknown radical gradually turns into diamagnetic products. In the case of HPNs 22a, d, h, i, m, n, the contribution of the paramagnetic impurity is small and can be ignored in the analysis of their decomposition kinetics.

Accordingly, the spectra of diluted toluene solutions of 22c, d were recorded every 10 min during 4 h. Double integrals of these spectra were computed to estimate concentrations of the paramagnetic compounds in solutions. The obtained kinetic curves are presented in Figure 6. Readers can see that the radicals decompose via first-order kinetics at approximately the same rate: the rate constants were found to be 1.2 × 10⁻⁴ s⁻¹. Radicals 22e, j, k with quaternary substituents in the phenoxy moiety are quite stable compounds. They can be isolated as solids and stored for a long time under ambient conditions without changes.

Attempts to oxidize 4H-imidazole 3-oxides 21p–s containing a para-hydroxy group in the aryl substituent at the C-5 atom (R³ = OH) did not lead to the formation of corresponding persistent HPNs 22p–s. The reason is possibly the fast reduction of the formed paramagnetic center as a result of its intermolecular interaction with a labile phenolic group.
1. General Information

The UV-Vis spectra were obtained for EtOH solutions of radicals' decomposition rates, the corresponding EPR spectra were recorded every 10 min for 1–4 h at 60 °C. The intensity of oxidative processes was monitored by means of the rate of oxygen uptake, C. The intensity of oxidative processes was monitored by means of the rate of oxygen uptake, Oxidation at 60 °C. The intensity of oxidative processes was monitored by means of the rate of oxygen uptake, AIBN: 5.3 × 10−1 M, AO: 5 × 10−5 M, O2 pressure in the system: 1 atm, and sample volume: 4 mL.

Initiation rate \( W_i \) was calculated according Equation (3) from a known AIBN concentration in a sample:

\[
W_i = ek_p[AIBN] \tag{3}
\]

\( e \): radicals' yield relative to one decaying initiator molecule, \( k_p \): an initiator decay rate constant; for cumene at 60 °C: \( e = 1.13, k_p = 1.01 \times 10^{-5} \text{ s}^{-1}, W_i = 6.09 \times 10^{-8} \text{ M s}^{-1} \).

Absolute values of \( k_y \) were calculated taking into account that chain continuation rate constant \( k_2 \) was 1.75 M\(^{-1}\) s\(^{-1}\) under the model conditions of oxidation in question [55]. 2,6-Di-tert-butyl-4-methylphenol (BHT) served as a reference standard.

EPR spectra of phenoxy-21-nitroxides 22 were acquired by means of X-band CW EPR spectrometer Bruker Elexys E540 at 295 K for diluted (10⁻⁴–10⁻⁵ M) and oxygen-free radical solutions. Experimental settings were as follows: microwave power, 0.8 mW; modulation frequency, 100 kHz; modulation amplitude, 0.02 mT; number of points, 1024; and the number of scans, 10. For determining radicals' decomposition rates, the corresponding EPR spectra were recorded every 10 min for 1–4 h.

Figure 6. Kinetics of decomposition of HPNs 22c and 22d in diluted and oxygen-free toluene solutions.

3. Materials and Methods

3.1. General Information

Fourier transform infrared spectra (FT-IR) were acquired in KBr pellets on a Bruker Vector-22. The UV-Vis spectra were obtained for EtOH solutions of 4H-imidazole 3-oxides 21 using a Hewlett-Packard HP 8453 spectrophotometer. \(^1\)H nuclear magnetic resonance (NMR) and \(^13\)C NMR spectra were recorded on Bruker AV-300, AV-400, and DRX-500 spectrometers at 300/400/500 and 75/100/125 MHz, respectively, for 3–10% solutions of compounds in CDCl\(_3\) and DMSO-\(_d_6\); the positions of signals were determined relative to residual proton signals [DMSO-\(_d_6\) (2.50 ppm), CDCl\(_3\) (7.24 ppm)] or carbon signals [DMSO-\(_d_6\) (39.4 ppm), CDCl\(_3\) (76.9 ppm), for \(^13\)C spectra] of the deuterium solvent. The assignment of signals of carbon atoms in the \(^13\)C NMR spectra of compounds 20, 21 was made on the basis of a previous spectral work on the spectra of cyclic nitrones of the 4H-imidazole series [54]. Elemental analyses were performed on an automatic CHNS analyzer Euro EA 3000. The melting points were determined by means of an FP 81 HT instrument, Mettler Toledo. Column chromatography and thin-layer chromatography (TLC) were performed using Acros silica gel 60A series [54]. Elemental analyses were performed on an automatic CHNS analyzer Euro EA 3000. The working concentrations of the components in a sample (60 °C) were as follows; RH: 6.9 M, AIBN: 5.3 × 10⁻³ M, AO: 5 × 10⁻⁵ M, O₂ pressure in the system: 1 atm, and sample volume: 4 mL.

Initiation rate \( W_i \) was calculated according Equation (3) from a known AIBN concentration in a sample:

\[
W_i = ek_p[AIBN] \tag{3}
\]

\( e \): radicals' yield relative to one decaying initiator molecule, \( k_p \): an initiator decay rate constant; for cumene at 60 °C: \( e = 1.13, k_p = 1.01 \times 10^{-5} \text{ s}^{-1}, W_i = 6.09 \times 10^{-8} \text{ M s}^{-1} \).

Absolute values of \( k_y \) were calculated taking into account that chain continuation rate constant \( k_2 \) was 1.75 M\(^{-1}\) s\(^{-1}\) under the model conditions of oxidation in question [55]. 2,6-Di-tert-butyl-4-methylphenol (BHT) served as a reference standard.

EPR spectra of phenoxy-21-nitroxides 22 were acquired by means of X-band CW EPR spectrometer Bruker Elexys E540 at 295 K for diluted (10⁻⁴–10⁻⁵ M) and oxygen-free radical solutions. Experimental settings were as follows: microwave power, 0.8 mW; modulation frequency, 100 kHz; modulation amplitude, 0.02 mT; number of points, 1024; and the number of scans, 10. For determining radicals' decomposition rates, the corresponding EPR spectra were recorded every 10 min for 1–4 h.
at the following experimental settings: microwave power, 2.0 mW; modulation frequency, 100 kHz; modulation amplitude 0.02 mT; the number of points, 1024; and the number of scans, 10. To determine the value of isotropic g-factors (g_{iso}), X-band CW EPR spectra of a mixture of an analyzed radical with Finland trityl [56] were recorded. Then, the known g_{iso} of Finland trityl was used for the spectrum simulation, and the target g_{iso} value was excluded. The simulations of the solution EPR lines were carried out using the software package Easy Spin which is available at www.easyspin.org.

Geometry optimization and spin density calculation for 22a–o were performed by means of Gaussian 09 software package at the UB3LYP/6-31G(d) level of theory.

3.2. Synthesis

3.2.1. General Procedure for Formylation of 2,6-dialkylphenols 24a–e Using the Synthesis of 4-hydroxy-3-cyclohexyl-5-methylbenzaldehyde (23b) as an Example.

A mixture of 2-cyclohexyl-6-methylphenol [57] (9.51 g, 50 mmol), hexamethylenetetramine (14.1 g, 100 mmol), 50 mL of glacial acetic acid, and 10 mL of water was placed into a 2-necked round-bottomed flask equipped with a thermometer and a Dean–Stark trap. The reaction mixture was stirred at 105–110 °C until 11 mL of water collected in the receiver, then the mixture was refluxed at 118–120 °C for 6 h. After cooling to ambient temperature, the solution was diluted with the equal volume of water, the formed precipitate was filtered off, washed with ice water (2 × 20 mL), air dried, and twice crystallized: first from benzene and then from EtOH.

Pale yellow crystals, isolated yield 10.21 g (94%), m.p. 131–133 °C (EtOH). Elemental analysis: found: C, 77.05; H, 8.53; calcd. for C_{14}H_{12}O_{2}: C, 77.03; H, 8.31%. UV (EtOH), λ_{max} nm, (lg ε): 230 (4.21), 293 (4.17). 1H NMR (400 MHz, CDCl$_3$), δ, ppm (J, Hz): 1.19–1.31 (1H, m, C$_6$H$_{11}$); 1.35–1.48 (4H, m, C$_6$H$_{11}$); 1.70–1.79 (1H, m, C$_6$H$_{11}$); 1.79–1.91 (4H, m, C$_6$H$_{11}$); 2.30 (3H, s, CH$_3$); 2.76–2.89 (1H, m, CH$_2$-(CH$_2$)$_3$); 5.99 (1H, br. s, OH); 7.51 (1H, d, J = 1.8, H-6); 7.59 (1H, d, J = 1.8, H-2); 9.79 (1H, s, CHO). 13C NMR (100 MHz, CDCl$_3$), δ, ppm: 16.0 (CH$_3$); 26.0, 26.7, 32.9 (3 CH$_2$); 37.0 (CH-C=C); 123.8 (C-5); 127.1 (C-2); 129.2 (C-1); 130.5 (C-6); 133.6 (C-3); 157.2 (C-4); 191.7 (CHO).

4-Hydroxybenzaldehydes 23a, c–e were obtained in a similar way. Their spectral characteristics and melting points were in accordance with those described in the literature (see Supplementary Materials).

3.2.2. General Synthetic Procedure for 2-(3,5-dialkyl-4-hydroxyphenyl)-4-aryl-1-hydroxy-4,4-dimethyl-2,5-dihydro-1H-imidazoles 20a–s.

Ammonium acetate (2.78 g, 36 mmol) and corresponding 3,5-dialkyl-4-hydroxybenzaldehyde 23 (6.2 mmol) were successively added to a solution of 2-hydroxylamino ketone 25a–c [58] as hydrochloride or its free base 25d [59] (6 mmol) in methanol (5 mL) (or in absolute EtOH in the case of the synthesis of 20p–s). The reaction mixture was diluted with 5 mL of the corresponding alcohol and stirred for 6–12 h until the full conversion of 2-hydroxylamino ketone (TLC control). The resultant suspension was kept for 12 h at 20 °C and 3 h at 0 °C; the formed precipitate was filtered off; washed with cold alcohol (2 × 4 mL), water (10 mL), and again cold alcohol (3 mL); and air dried at rt. In the case of 20r, a combined alcohol filtrate was evaporated; the residue was mixed with 25 mL of water and kept for 48 h at 0 °C. The formed precipitate was filtered off and air dried at rt, thereby giving an additional amount of 20r. To obtain 20q from the reaction mixture, the solution was evaporated, and the residue was mixed with water (40 mL) and incubated for 24 h at 0 °C. The formed precipitate was filtered off, washed with water, and air dried until constant weight. To prepare an analytical sample, the dried precipitate was washed thoroughly with 20 mL of CHCl$_3$ to remove traces of starting benzaldehyde and 4H-imidazole 3-oxide and dried finally at 80 °C.

3.2.3. General Synthetic Procedure for 5-aryl-2-(3,5-dialkyl-4-hydroxyphenyl)-4,4-dimethyl-4H-imidazole 3-oxides 21a–s

To a suspension of 2,5-dihydro-1H-imidazole 20 (5 mmol) in 30 mL of MeOH, a solution of copper(II) acetate hydrate (199 mg, 1 mmol) in 16% aq ammonia (2 mL) was added, and the mixture
was stirred with bubbling by a slow stream of air at 20 °C during 1–6 h until the full substrate conversion. The formed yellow precipitate of 21 was filtered off, washed with 5% aq hydrochloric acid and water, and dried at 60–70 °C. An additional amount of 4H-imidazole 3-oxide (in the case of 21a, c, e, f, h, m, q) was obtained by evaporation of the methanolic filtrate, followed by extraction of the residue with CHCl₃, washing of the organic layer with 5% aq HCl, drying over MgSO₄, evaporation, and trituration of the residue with hexane. In the case of isolation of imidazoles 21p, r, s, the reaction mixture was evaporated, and the residue was dissolved in 30 mL of CHCl₃, washed with 5 mL of 5% aq HCl, dried, and evaporated. The residue was purified by column chromatography (SiO₂, eluent CHCl₃: MeOH, 20:1), the bright yellow fraction was collected, and after evaporation and trituration of the residue with hexane, a precipitate of 4H-imidazole 3-oxide 21p, r, s was filtered off.

3.2.4. Preparation of Hybrid Phenoxyl–Nitroxides 22a–o

Formation of HPNs 22a–o was accomplished in the following way: PbO₂ (5 mg) was added to a solution of diamagnetic precursor 21a–o (~3 mg) in CHCl₃ (2 mL), and the mixture was stirred for 1 min at 295 K. An inorganic precipitate was filtered off, and 5 µL of the filtrate were taken, diluted with 1 mL of toluene, and bubbled with argon.

4. Conclusions

In summary, a large set of cyclic hydroxylamines of the 2,5-dihydroimidazole series was obtained via condensation of para-formyl–substituted 2,6-dialkylphenols with different aromatic 2-hydroxylamino ketones containing donor and acceptor substituents of the benzene ring. Their mild oxidation allowed to obtain the corresponding 4H-imidazole 3-oxides capable of generating persistent hybrid phenoxyl-nitroxide radicals under the conditions of heterogenic oxidation. It was shown that the antioxidant activity of the investigated imidazole derivatives strongly depends on i) the number of active centers in a molecule able to react with ROS; ii) the structure and effective volume of alkyl substituents in the phenolic moiety, making 1-hydroxy-2-(3,5-dialkyl-4-hydroxyphenyl)-2,5-dihydroimidazole derivatives more active than the widely known BHT. On the other hand, it was established that steric shielding of the phenoxyl moiety influences the hybrid radical stability more strongly than the nature of the substituent at the para-position of the aryl substituent at position C-5 of the heterocycle.

Considering that stable phenoxyl radicals and their diamagnetic precursors have a high potential in modern applications of materials chemistry (as electroactive elements [60], additives for the prevention of destruction of perovskite-derived solar cells [61], and effective hydrogen acceptors in ammonia fuel cells, where electricity is generated through oxidation of NH₃ to dinitrogen [62]), we suppose that hybrid phenoxyl–nitroxides and their precursors can be considered in the future as promising compounds for new technologies of energy storage and processing.

Supplementary Materials: The following are available online at http://www.mdpi.com/1420-3049/25/14/3118/s1.

- Synthesis of 2-hydroxylamino ketone 25c, spectral and analytical data for all 2,5-dihydroimidazoles 20 and 4H-imidazole 3-oxides 21.
- EPR spectra and calculations of geometry and hfs constants for all generated phenoxyl-nitroxides 22.
- Figures S1–S5. Molecular geometry and hfs constants for HPNs 22a–e,j,o calculated at UB3LYP/6-31G(d) level of theory, solvent effect was taken into account using CPCM model (solvent – toluene).
- Scheme S1. Preparation of 2-hydroxylamino ketone hydrochloride 25cHCl. Scheme S2. Typical reactions occurring at inhibited and non-inhibited hydrocarbon oxidation.

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References
1. Grigor’ev, I.A. Nitrones: Novel strategies in synthesis. In Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, 2nd ed.; Feuer, H., Ed.; John Wiley@Sons Inc.: Hoboken, NJ, USA, 2007; pp. 129–434. [CrossRef]
2. Murahashi, S.-I.; Imada, Y. Synthesis and transformations of nitrones for organic synthesis. Chem. Rev. 2019, 119, 4684–4716. [CrossRef]
3. Towner, R.A.; Floyd, R.A. Nitrones as potent anticancer therapeutics. In Redox-Active Therapeutics, Oxidative Stress in Applied Basic Research and Clinical Practice; Batinić-Haberle, I., Rebouças, J.S., Spasojević, I., Eds.; Springer International Publishing: Cham, Switzerland, 2016; pp. 245–264. [CrossRef]
4. Rosselin, M.; Poeggeler, B.; Durand, G. Nitrone derivatives as therapeutics: From chemical modification to specific-targeting. Curr. Topics Med. Chem. 2017, 17, 2006–2022. [CrossRef] [PubMed]
5. Oliveira, C.; Benfeito, S.; Fernandes, C.; Cagide, F.; Silva, T.; Borges, F. NO and HNO donors, nitrones, and nitroxides: Past, present, and future. Med. Res. Rev. 2018, 38, 1159–1187. [CrossRef] [PubMed]
6. Escobar-Peso, A.; Chioua, M.; Frezza, V.; Martínez-Alonso, E.; Marco-Contelles, J.; Alcázar, A. Nitrones, old fellows for new therapies in ischemic stroke. In Neuroprotective Therapy for Stroke and Ischemic Disease; Lapchak, P.A., Zhang, J.H., Eds.; Springer International Publishing: Cham, Switzerland, 2017; pp. 251–283. [CrossRef]
7. Phillis, J.W.; Clough-Helfman, C. Protection from cerebral ischemic injury in gerbils with the spin trap agent N-tert-butyl-α-phenylnitrone (PBN). Neurosci. Lett. 1990, 116, 315–319. [CrossRef]
8. Dikalova, A.E.; Kadiiska, M.B.; Mason, R.P. An in vivo ESR spin-trapping study: Free radical generation in rats from formate intoxication-role of the Fenton reaction. Proc. Natl. Acad. Sci. USA 2001, 98, 13549–13553. [CrossRef]
9. Deletraz, A.; Zéamari, K.; Hua, K.; Combes, M.; Villamena, F.A.; Tuccio, B.; Callizot, N.; Durand, G. Substituted α-Phenyl and α-Naphthyl-N-tert-butyl Nitrones: Synthesis, Spin-Trapping and Neuroprotection Evaluation. J. Org. Chem. 2020, 85, 6073–6085. [CrossRef] [PubMed]
10. Kuroda, S.; Tsuchidate, R.; Smith, M.-L.; Maples, K.R.; Siesjo, B.K. Neuroprotective effects of a novel nitrone, NXY-059, after transient focal cerebral ischemia in the rat. J. Cereb. Blood Flow Metab. 1999, 19, 778–787. [CrossRef] [PubMed]
11. Battiste, J.D.; Ikeguchi, A.; Woo, S.; Sharan, S.; Zhao, Y.D.; Cohoon, A.; Sung, S.; Wright, D.; Teague, A.M.; Jensen, R.L.; et al. Phase I clinical trial of OKN-007 in recurrent malignant glioma. J. Clin. Oncol. 2020, 38, 2538. [CrossRef]
12. Becker, D.A.; Ley, J.J.; Echegoyen, L.; Alvarado, R. Stilbazulenyl Nitrone (STAZN): A Nitronyl-substituted hydrocarbon with the potency of classical phenolic chain-breaking antioxidants. J. Amer.Chem. Soc. 2002, 124, 4678–4684. [CrossRef] [PubMed]
13. Lapchak, P.A.; Schubert, D.R.; Maher, P.A. De-Risking of Stilbazulenyl Nitrone (STAZN), a lipopholic nitrone to treat stroke using a unique panel of in vitro assays. Transl. Stroke Res. 2011, 2, 209–217. [CrossRef] [PubMed]
14. Arce, C.; Díaz-Castroverde, S.; Canales, M.J.; Marco-Contelles, J.; Samadi, A.; Oset-Gasque, M.J.; González, M.P. Drugs for stroke: Action of nitrone (Z)-N-(2-bromo-5-hydroxy-4-methoxybenzylidene)-2-methylpropan-2-amino oxide on rat cortical neurons in culture subjected to oxygen-glucose-deprivation. Eur. J. Med. Chem. 2012, 55, 475–479. [CrossRef] [PubMed]
15. Ayuso, M.I.; Martínez-Alonso, E.; Chioua, M.; Escobar-Peso, A.; Gonzalo-Gobernado, R.; Montaner, J.; Marco-Contelles, J.; Alcázar, A. Quinolinyl Nitrone RP19 induces neuroprotection after transient brain ischemia. ACS Chem. Neurosci. 2017, 8, 2202–2213. [CrossRef] [PubMed]
16. Chioua, M.; Martínez-Alonso, E.; Gonzalo-Gobernado, R.; Ayuso, M.I.; Escobar-Peso, A.; Infantes, L.; Hadjipavlou-Litina, D.J.; Montoya, J.J.; Montaner, J.; Alcazar, A.; et al. New quinolynitrones for stroke therapy: Antioxidant and neuroprotective (Z)-N-tert-Butyl-1-(2-chloro-6-methoxyquinolin-3-yl)methanimine Oxide as a new lead-compound for ischemic stroke treatment. J. Med. Chem. 2019, 62, 2184–2201. [CrossRef] [PubMed]
17. Chioua, M.; Salgado-Ramos, M.; Diez-Iriepa, D.; Escobar-Peso, A.; Iriepa, I.; Hadijipavlou-Litina, D.; Martínez-Alonso, E.; Alcázar, A.; Marco-Contelles, J. Novel quinolynitrone derivatives combining neuroprotective and antioxidant properties. ACS Chem. Neurosci. 2019, 10, 2703–2706. [CrossRef] [PubMed]

18. Piotrowska, D.G.; Mediavilla, L.; Cuarental, L.; Glowacka, I.E.; Marco-Contelles, J.; Hadijipavlou-Litina, D.; Lópe-Muñoz, F.; Oset-Gasque, M.J. Synthesis and neuroprotective properties of N-Substituted C-Dialkoxophosphorylated nitrones. ACS Omega 2019, 4, 8581–8587. [CrossRef] [PubMed]

19. Ayuso, M.I.; Chioua, M.; Martínez-Alonso, E.; Soriano, E.; Montaner, J.; Masjuan, J.; Hadijipavlou-Litina, D.J.; Marco-Contelles, J.; Alcázar, A. Cholesterol-Nitrone for stroke. J. Med. Chem. 2015, 58, 6704–6709. [CrossRef]

20. Martínez-Alonso, E.; Escobar-Peso, A.; Ayuso, M.I.; Gonzalo-Gobendro, R.; Chioua, M.; Montoya, J.J.; Montaner, J.; Fernández, I.; Marco-Contelles, J.; Alcázar, A. Characterization of a Cholesterol-Nitrone (ISQ-201), a novel drug candidate for the treatment of ischemic stroke. Antioxidants 2020, 9, 291. [CrossRef]

21. Sun, Y.; Yu, P.; Zhang, G.; Wang, L.; Zhong, H.; Zhai, Z.; Wang, L.; Wang, Y. Therapeutic effects of tetramethylpyrazine nitrone in rat ischemic stroke models. J. Neurosci. Res. 2012, 90, 1662–1669. [CrossRef]

22. Rao, P.S.; Kurumurthy, C.; Veeraswamy, B.; Kumar, G.S.; Poornachandra, Y.; Kumar, C.G.; Vasamsetti, S.B.; Kotamraju, S.; Narsaiah, S. Synthesis of novel 1,2,3-triazole substituted-N-alkylaryl nitrones derivatives, their anti-inflammatory and anticancer activity. Eur. J. Med. Chem. 2014, 80, 184–191. [CrossRef]

23. Finkelstein, E.; Rosen, G.M.; Rauckman, E.J. Spin trapping. Kinetics of the reaction of superoxide and hydroxyl radicals with nitrones. J. Amer. Chem. Soc. 1980, 102, 4994–4999. [CrossRef]

24. Olive, G.; Mercier, A.; Le Moigne, F.; Rockenbauer, A.; Tordo, P. 2-Ethoxycarbonyl-2-methyl-3,4-dihydro-2H-pyrrole-1-oxide: Evaluation of the spin trapping properties. Free Rad. Bio. Med. 2000, 28, 403–408. [CrossRef]

25. Zhao, H.; Joseph, J.; Zhang, H.; Karoui, H.; Kalyanaraman, B. Synthesis and biochemical applications of a solid cyclic nitrone spin trap: A relatively superior trap for detecting superoxide anions and glutathyl radicals. Free Rad. Biol. Med. 2001, 31, 599–606. [CrossRef]

26. Frejaville, C.; Karoui, H.; Tuccio, B.; Le Moigne, F.; Culcasi, M.; Pietri, S.; Lauricella, R.; Tordo, P. 5-(Diethoxyphosphoryl)-5-methyl-1-pyrroline-1-oxide (DMPO) and 2H-imidazole-1-oxides. Biochem. Biophys. Res. Commun. 1996, 218, 616–622. [CrossRef] [PubMed]

27. Dikalov, S.; Kirilyuk, I.; Grigor’ev, I. Spin trapping of O-, C-, and S-centered radicals and peroxyxinitryle by 2H-imidazole-1-oxides. Biochem. Biophys. Res. Commun. 1996, 228, 616–622. [CrossRef] [PubMed]

28. Krainev, A.G.; Williams, T.D.; Bigelow, D.J. Oxygen-centered spin adducts of 5,5-dimethyl-1-pyrroline-1-oxide: Evaluation of the spin trapping properties. Free Rad. Biol. Med. 2000, 28, 403–408. [CrossRef]

29. Ranieri, K.; Conradi, M.; Chavant, P.-Y.; Blandin, V.; Barner-Kowollik, C.; Junkers, T. Enhanced Spin-capturing polymerization and radical coupling mediated by cyclic nitrones. Austr. J. Chem. 2012, 65, 1110–1116. [CrossRef]

30. Hatano, B.; Miyoshi, K.; Sato, H.; Ito, T.; Ogata, T.; Kijima, T. Synthesis and spin trapping properties of 1,1-dimethyl-3-(trifluoromethyl)-1H-isoinoide N-oxide. Tetrahedron Lett. 2010, 51, 5399–5401. [CrossRef]

31. Bernotas, R.C.; Thomas, C.E.; Carr, A.A.; Nieduzak, T.R.; Adams, G.; Ohlweiler, D.F.; Hay, D.A. Synthesis and radical scavenging activity of 3,3-Dialkyl-3,4-Dihydro-isoquinoline 2-Oxides. Biorg. Med. Chem. Lett. 1996, 6, 1105–1110. [CrossRef]

32. Ramana, C.V.; Patel, P.; Vanka, K.; Miao, B.; Degterev, A. A Combined experimental and density functional theory study on the Pd-Mediated Cycloisomerization of o-Alkynylnitrobenzenes—Synthesis of Isatogens and their evaluation as modulators of ROS-Mediated cell death. Eur. J. Org. Chem. 2010, 5955–5966. [CrossRef]

33. Nephveu, F.; Kim, S.; Boyer, J.; Chatriant, O.; Ibrahim, H.; Reybier, K.; Monje, M.-C.; Chevalley, S.; Perio, P.; Lajoie, B.H.; et al. Synthesis and antiplasmodial activity of new indolone N-Oxide derivatives. J. Med. Chem. 2010, 53, 699–714. [CrossRef]

34. Ten, Y.A.; Salnikov, O.G.; Amitina, S.A.; Stass, D.V.; Rybalova, T.V.; Kazantsev, M.S.; Bogomyakov, A.S.; Mostovich, E.A.; Mazhukin, D.G. The Suzuki–Miayaura reaction as a tool for modification of phenoxyl-nitroxyl radicals of the 4H-imidazole N-oxide series. RSC Adv. 2018, 8, 26099–26107. [CrossRef]

35. Zayotseva, E.; Shioni, D.; Ten, Y.; Gatilov, Y.V.; Lomanovich, A.; Stass, D.; Bogomyakov, A.; Yu, A.; Sugisaki, K.; Sato, K.; et al. Magnetic Properties of π-Conjugated hybrid Phenoxyl–Nitroxide radicals with extended n-Spin delocalization. J. Phys. Chem. A 2020, 124, 2416–2426. [CrossRef]

36. Pacífico, J.G.; Browning, H.L., Jr. α-(3,5-Di-tert-butyl-4-hydroxyphenyl)-N-tert-butylnitro. A Novel Probe for Radical Detection and Identification. J. Amer. Chem. Soc. 1970, 92, 5231–5233. [CrossRef]
37. Pryor, W.A.; Terauchi, K.; Davis, W.H., Jr. Electron spin resonance (ESR) study of cigarette smoke by use of spin trapping techniques. *Environ. Health Perspect.* 1976, 16, 161–176. [CrossRef] [PubMed]

38. Yamaji, T.; Noda, Y.; Yamauchi, K.; Terauchi, K.; Davis, W.H., Jr. Multi-Frequency ESR Study of the Polycrystalline Phenoxyl Radical of α-(3,5-Di-tert-butyl-4-hydroxyphenyl)-N-tert-butylnitroso in the Diamagnetic Matrix. *J. Phys. Chem.* A 2006, 110, 1196–1200. [CrossRef]

39. Caldwell, S.T.; Quin, C.; Edge, R.; Hartley, R.C. A Dual sensor spin trap for use with EPR spectroscopy. *Org. Lett.* 2007, 9, 3499–3502. [CrossRef] [PubMed]

40. Porcal, W.; Hernández, P.; Rodriguez, M.; Ferreira, A.; Olea-Azar, C.; Cereccettu, H.; Castro, A. Heteroaryl nitrones as drugs for neurodegenerative diseases: Synthesis, neuroprotective properties, and free radical scavenger properties. *J. Med. Chem.* 2008, 51, 6150–6159. [CrossRef]

41. Chavarria, C.; Perez, D.I.; Perez, C.; Garcia, J.A.M.; Alonso-Gil, S.; Perez-Castillo, A.; Gil, C.; Souza, J.M.; Porcal, W. Microwave-assisted synthesis of hydroxyphenyl nitrones with protective action against oxidative stress. *Eur. J. Med. Chem.* 2012, 58, 44–49. [CrossRef] [PubMed]

42. Chioua, M.; Sucunza, D.; Soriano, E.; Hadjipavlou-Litina, D.; Alcazar, A.; Ayuso, I.; Oset-Gasque, M.J.; Gonzalez, M.P.; Monjas, L.; Rodriguez-Pranco, M.I.; et al. α-Aryl-N-alkyl nitrones, as potential agents for stroke treatment: Synthesis, theoretical calculations, antioxidant, anti-inflammatory, neuroprotective, and brain–blood barrier permeability properties. *Med. Chem.* 2012, 55, 153–168. [CrossRef]

43. Cancela, S.; Cancelini, L.; Mouriglia-Ettlin, G.; Hernández, P.; Merlino, A. Neuroprotective effects of novel nitrones: In vitro and in silico studies. *Eur. J. Pharm.* 2020, 871, 172926. [CrossRef]

44. Vasko, P.; Hurmalainen, J.; Mansikkamäki, A.; Peuronen, A.; Mailman, A.; Tuononen, H. Synthesis of new hybrid 1,4-thiazinyl-1,2,3-dithiazolyl radicals via Smiles rearrangement. *Dalton Trans.* 2011, 40, 868–879. [CrossRef]

45. Winter, S.M.; Balo, A.R.; Robert, R.; Lekin, K.; Assoud, A.; Dube, P.A.; Oakley, R.T. Hybrid dithiazolothiadiazinyl radicals; versatile building blocks for magnetic and conductive materials. *Chem. Commun.* 2013, 49, 1603–1605. [CrossRef]

46. Buehler, E.; Brown, G.B. General Synthesis of N-Hydroxyaminoo Acids. *J. Org. Chem.* 1967, 32, 265–268. [CrossRef]

47. Roginsky, V.A. *Phenolic antioxidants. Reactivity and Efficiency*; Nauka: Moscow, USSR, 1988; pp. 1–247.

48. Oleyenik, A.S.; Trubnikova, Y.N.; Kandalintseva, N.V.; Grigor’ev, I.A. Study of antioxidant properties of nitrones of 3-imidazoline 3-oxide, dihydropyrazine 1,4-dioxide, and 2-imidazole 1-oxide series in reactions with peroxy radicals. *Chem. Sustain. Develop.* 2007, 15, 555–559.

49. Buchachenko, A.L.; Vasserman, A.M. *Stable radicals, Electronic Structure, Reactivity and Application*; Khimiya: Moscow, USSR, 1988; pp. 1–247.

50. Grigor’ev, I.A.; Kirilyuk, I.A.; Volodarskii, L.B. NMR Spectra of Cyclic Nitrones. 4. Synthesis and 13C NMR Spectra of 4H-Imidazole N-Oxides and N,N'-Dioxides. *Chem. Heterocycl. Compd.* 1988, 24, 1355–1362. [CrossRef]

51. Tsepalov, V.F. A Method of Quantitative Analysis of Antioxidants by means of a Model Reaction of Initiated Oxidization. In *Investigation of Synthetic and Natural Antioxidants In Vitro and In Vivo*; Burlakova, E.B., Kruglyakova, K.E., Shishkina, L.N., Eds.; Nauka: Moscow, Russia, 1992; pp. 16–26.

52. Dhimitrinka, I.; Velayutham, M.; Bobko, A.A.; Kramtsov, V.V.; Villamena, F.A.; Hadad, C.M.; Zweier, J.L. Large-scale synthesis of a persistent trityl radical for use in biomedical EPR applications and imaging. *Bioorg. Med. Chem. Lett.* 2007, 17, 6801–6805. [CrossRef]

53. Kozlikovskii, Y.B.; Koshchii, V.A.; Butov, S.A.; Sokolova, A.V. *Ortho* alkylation of α-, m-, and p-cresols with cyclohexene in the presence of aluminum cresolates. *Zh. Org. Khim.* 1987, 23, 1918–1924.
58. Volodarsky, L.B. *Imidazoline Nitroxides: Synthesis and Properties*; CRC Press: Boca Raton, FL, USA, 1988; pp. 1–176.

59. Volodarskii, L.B.; Lapik, A.S.; Russkikh, V.V.; Kobrin, V.S.; Lavretsksaya, E.F.; Volkova, L.I.; Sarkisyan, D.A.; Borisov, M.M. Derivatives of (hydroxylamino) ketone with neurotropic activity. *Chem. Abstr.* **1979**, *91*, 68767.

60. Jähnert, T.; Hager, M.D.; Schubert, U.S. Application of phenolic radicals for antioxidants, as active materials in batteries, magnetic materials and ligands for metal-complexes. *J. Mater. Chem. A* **2014**, *2*, 15234–15251. [CrossRef]

61. Suwa, K.; Suga, T.; Oyaizu, K.; Segawa, H.; Nishide, H. Phenolic antioxidant-incorporated durable perovskite layers and their application for a solar cell. *MRS Commun.* **2020**, [CrossRef]

62. Dunn, P.; Johnson, S.I.; Kaminsky, W.; Bullock, R.M. Diversion of Catalytic C-N Bond Formation to Catalytic Oxidation of NH$_3$ through Modification of the Hydrogen Atom Abstractor. *J. Am. Chem. Soc.* **2020**, *142*, 3361–3365. [CrossRef] [PubMed]

**Sample Availability:** Samples of compounds **20a–s, 21a–s, and 22e,j,o** are available from the authors (D.G.M., Y.A.T., or S.A.A.).

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