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Antioxidant activity and redox properties of *cis*-2,4,5-tris(hydroxyaryl)imidazolines

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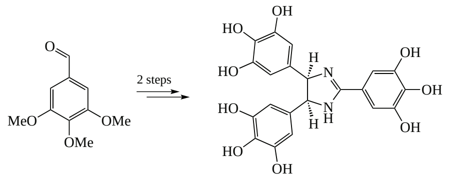
New effective antioxidants of *cis*-2,4,5-tris(hydroxyaryl)-imidazoline type were assembled from aromatic aldehydes and ammonia. Their antioxidant activity was measured against hydroxyl radical and superoxide radical anion in physiological media, and oxidation potentials were measured by cyclic voltammetry. The lead compound bearing 3,4,5-hydroxyphenyl moieties showed activity 3.5 times higher compared to Trolox.

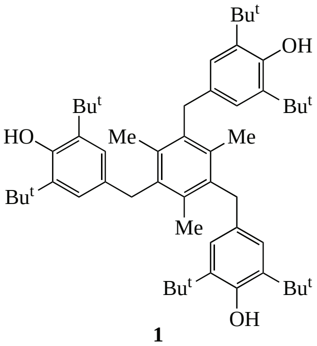


Antioxidant activity:
3.5 higher than that of Trolox under physiological conditions
3.8 higher than that of Trolox in DPPH test

Keywords: phenolic antioxidants, *cis*-imidazolines, polyphenolic compounds, quinonoid oxidation, propyl gallate, superoxide anion, ionol analogues.

Natural antioxidants and their synthetic analogues are used in food chemistry[1–5] (ascorbic acid, tocopherol), polymer chemistry[6–10] (ionol derivatives), as fuel additives[11–14] (ionol, *p*-hydroxydiphenylamine). The antioxidant properties of compounds are usually studied together with biological activity, since many pathologies of living systems are accompanied by a violation of redox processes.[15–18] Phenol derivatives represent an important class of antioxidants due to their high efficiency, low toxicity, and availability. The mechanism of the antioxidant radical activity of phenols is associated with the high stability of phenoxy radicals, especially with substituents located *ortho* to the hydroxy group.[1]

An approach to the design of polyphenolic antioxidants by combining several functional fragments is quite successful.[19,20] Compounds with several phenolic fragments combined into a symmetrical structure are actively used in practice. Compounds **1** and **2** are used as polymer stabilizers. In food and cosmetic industry, a well-known stabilizer containing three hydroxy groups is propyl gallate **3**, additive E310. Propyl gallate **3** contains no bulky alkyl substituents near hydroxyl groups, however, its antioxidant activity is due to the quantity of hydroxy groups.



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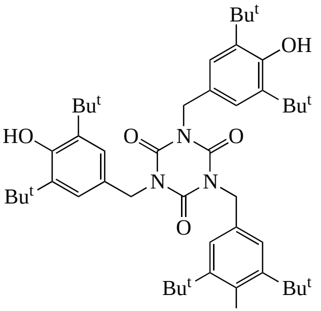

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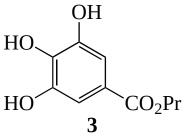

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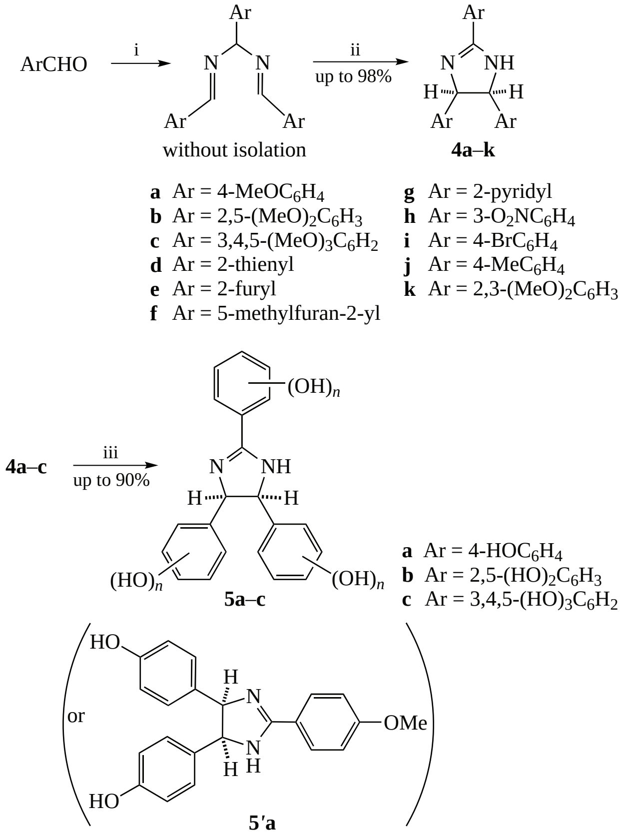
Another known functional unit possessing antioxidant activity is imidazoline heterocycle.[21] However, compounds containing both polyphenol and imidazoline moieties in one molecule have not been studied yet. Therefore, obtaining substances of this type is an interesting and urgent problem.

In previous works, we synthesized compounds based on the *cis*-imidazoline core containing two or more phenolic fragments and showed the possible routes for their modification[22–24] suitable for scaling.[25,26] According to previous study, hydroxyphenyl derivatives are non-toxic,[22] which allows them to be considered as antioxidants in biological systems. In this work, we represent a synthetic route to propyl gallate analogue containing three polyphenolic fragments combined with imidazoline ring (Scheme 1). As propyl gallate **3** is widely used in cosmetics and food chemistry, we also studied antioxidant activity of these analogues under physiological conditions using a method based on the chemiluminescent model of free-radical oxidation of luminol initiated by a mixture of hemoglobin–hydrogen peroxide (Hb–H_2O_2–Lm) in an aqueous medium. This method allows one to estimate antioxidant activity against two reactive oxygen species playing the key role in inflammation: hydroxyl radical and superoxide radical anion.[27] A spectrophotometric DPPH test and electrochemical studies were performed for confirmation of activity. Results were expressed in Trolox equivalent antioxidant capacity (TEAC).

For the synthesis of compound **5c**, propyl gallate analogue, 3,4,5-trimethoxybenzaldehyde, was used, and it was obtained in two steps in total yield of 80%. It is worth noting that the synthesis of hydroxyarylated imidazolines **5a–c** directly from the corresponding hydroxy aldehydes was not possible, since the



a Ar = 4-MeOC$_6$H$_4$
b Ar = 2,5-(MeO)$_2$C$_6$H$_3$
c Ar = 3,4,5-(MeO)$_3$C$_6$H$_2$
d Ar = 2-thienyl
e Ar = 2-furyl
f Ar = 5-methylfuran-2-yl
g Ar = 2-pyridyl
h Ar = 3-O$_2$NC$_6$H$_4$
i Ar = 4-BrC$_6$H$_4$
j Ar = 4-MeC$_6$H$_4$
k Ar = 2,3-(MeO)$_2$C$_6$H$_3$

a Ar = 4-HOC$_6$H$_4$
b Ar = 2,5-(HO)$_2$C$_6$H$_3$
c Ar = 3,4,5-(HO)$_3$C$_6$H$_2$

Scheme 1 *Reagents and conditions*: i, NH$_3$ (aq. or THF), room temperature, 24 h; ii, Bu^{t}OK, THF, room temperature, 3 min, then H$_2$O; iii, BBr$_3$, CH$_2$Cl$_2$, 0 °C, 24 h (for **5a**–**c**), 4 h (for **5′a**), then MeOH (see ref. 22).

reaction of electrocyclic ring closure (see Scheme 1, stage ii) requires the absence of acidic protons in the reagent. The subsequent mild demethylation of methoxy groups in precursors **4a**–**c** was performed with boron tribromide. The rest compounds of this series **4d**–**k** were synthesized according to the previously described procedures[22] and were used to study the structure–property relationship.

Antioxidant activity against hydroxyl radical and superoxide radical anion in the hemoglobin–hydrogen peroxide–luminol system was exhibited only by hydroxy derivatives **5b**,**c** with TEAC values of 1.4 and 3.5, respectively (Table 1). Compounds **5a** and **5′a** containing only one hydroxy group in aryl moiety showed no antioxidant activity, which is in accordance with the common structural requirements for antioxidants. To confirm the activity of compounds **5b**,**c**, a spectrophotometric DPPH test was performed, in which these compounds showed a 2.5 and 3.8 times higher activity than the standard Trolox. The results obtained were in good agreement with those of the fluorescence method. The studied compounds **5b**,**c** possess good antioxidant properties in comparison with the nearest analogues, propyl gallate **3** and gallic acid, for which the range of TEAC is 1.85–4.2 depending on the measurement method.[28]

Table 1 Antioxidant activity of synthesized compounds.

Compound	Antioxidant activity		
	Hydroxyl radical (Hb–H$_2$O$_2$–Lm)/TEAC^a	Superoxide radical anion (Hb–H$_2$O$_2$–Lm)/μM	Radical (DPPH)/TEAC^a
4a–**k**	<0.1	>500	–^{b}
5a	<0.1	>500	<0.1
5′a	<0.1	>500	<0.1
5b	1.4	110	2.5
5c	3.5	100	3.8

^{a}TEAC shows how many times the concentration of Trolox should be greater than the concentration of substances under investigation under the same conditions to maintain the antioxidant capacity. ^{b}Not measured.

Table 2 Electrochemical potentials of compounds **5a**–**c** and Trolox.^{a}

Compound	E_{a1}/V	E_{a2}/V	E_{c1}/V	E_{c2}/V
5a	1.05	1.37	–	–
5′a	0.96	1.25	–0.85	–
5b	0.90/0.41^b	1.33/0.79^b	–1.65	–2.03
5c	0.76	–	–1.02	–
Trolox	1.02/0.74^b	–	–	–

^{a}0.5 M Bu$_4$NBF$_4$ in MeCN, GC electrode, Ag/AgCl, C = 1 mM, 200 mV s^{-1}. ^{b}On the reverse scan.

The redox properties of compounds **5a**–**c** were explored by cyclic voltammetry (CV) in MeCN using glassy carbon (GC) electrode (Table 2). Compounds **5a**, **5′a** and **5c** are characterized by the presence of two one-electron irreversible anodic peaks, obviously corresponding to consecutive oxidation of phenolic moieties. On the other hand, in the case of compound **5b** two diffusion-controlled peaks of the two-electron oxidation appeared in anodic range, and corresponding reduction peaks were observed on the reverse scan (Figure 1). The CV curves irreversibility of the compounds under study indicates that the oxidation proceeds according to the EC mechanism, *i.e.*, the electron transfer is followed by a fast chemical reaction, most probably, deprotonation. The voltammogram character of **5b** can be explained as consecutive oxidation of phenolic fragments to quinonoid structures according to the way which corresponds to the known scheme of hydroquinone oxidation[29] (Scheme 2). It should be mentioned that the first anodic peaks in case of **5b**,**c** are observed at less positive potentials compared to compounds **5a** and **5′a**. Thus, the redox behavior correlates well with the antioxidant activity data: the most easily oxidized substances **5b**, **5c** demonstrate the highest activity (see Tables 1 and 2). It is also remarkable that the first oxidation peak of **5a**–**c** is shifted significantly towards cathodic potentials as compared to hydroquinone (E_a = 1.56 V). Therefore, it can be assumed that the presence of imidazoline cycle leads to the rise of generated radical cations stability (see Scheme 2), which results in first and

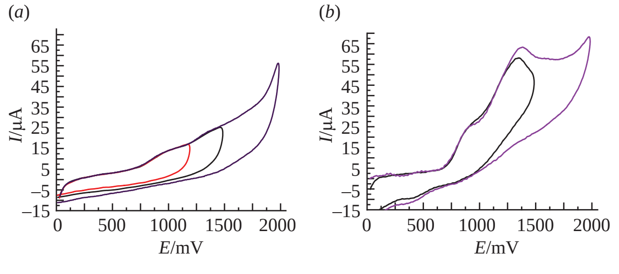
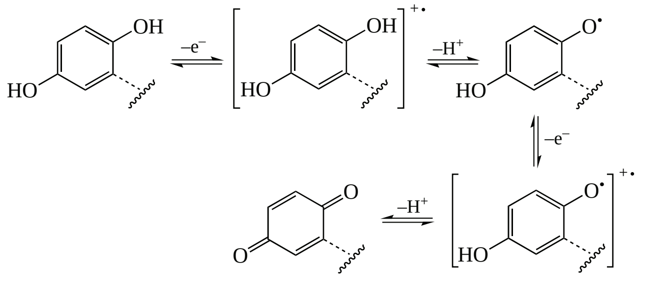


Figure 1 Cyclic voltammograms of (*a*) compound **5a** and (*b*) compound **5b** in MeCN, GC electrode, 200 mV s^{-1}, C = 1 mM.



Scheme 2 Proposed mechanism of electrochemical oxidation of compound **5b**.

second oxidation peaks separation (see Figure 1). It may point out that imidazoline cycle participates in the total spin density delocalization.

Summing up, we have synthesized new polyphenolic compound **5c** based on the imidazoline core with TEAC value of 3.5 in a physiological system against two reactive oxygen species playing the key role in inflammation.[30] The results of antiradical activity were confirmed by the DPPH test. The obtained data are in the range of antioxidant properties of the known analogues propyl gallate and gallic acid (1.95–4.20 TEAC[28]). The electrochemical behaviour of phenolic substances was examined, electrochemical potentials were measured and a mechanism for the oxidation of studied compounds was proposed.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.038.

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