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# REDUCTIVE ABILITY OF 1,4-DIHYDROPYRIDINE DERIVATIVES IN RELATION TO IONS OF TRIVALENT IRON

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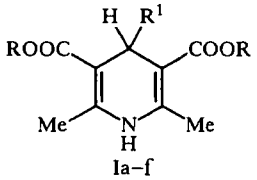
*3,5-Dicarbonyl derivatives of 2,6-dimethyl-1,4-dihydropyridine (1,4-DHP) can reduce $Fe^{3+}$ to $Fe^{2+}$ depending on the nature of the substituents at position 4 and in the 3,5-ester group. This ability is less pronounced for the 1,4-DHP derivatives investigated than for ascorbic acid, but among derivatives possessing antioxidant activity it is less than that of the known antioxidants ionol (BOT) and trolox.*

Iron ions are initiators and accelerators of the peroxide oxidation of lipids [1,2], including fats and oils [3], and also of the degradation of biosubstrates [4]. Antioxidants, natural and synthetic, inhibit these processes, however a large majority of them are also good reducing agents. For successful use of antioxidants it is necessary to know their undesirable ability to reduce ions of trivalent iron, which affect peroxide oxidation less actively, to the significantly more active divalent state, i.e. weaker reducing agents in relation to ions with variable valency are the better antioxidants.

Derivatives of 1,4-dihydropyridine (1,4-DHP) of the type of I, particularly those unsubstituted at position 4, are good hydrogen donors [5], antioxidants [6,7] and are synergists of natural antioxidants [8,9].




Ia–f

Ia R = $C_2H_5$, $R^1$ = H (diludin); b R = $C_4H_9$-*n*, $R^1$ = H; c R = $C_2H_5$, $R^1$ = Me; d R = $C_2H_5$, $R^1$ = COONa; e R = $CH_2COONa$, $R^1$ = H; f R = Me, $R^1$ = $C_6H_4NO_2$-*o* (nifedipine)

The present report is devoted to a study of the ability of compounds Ia-e, possessing antioxidant activity, including the physiologically active derivative of 1,4-dihydroisonicotinic acid (Id), to reduce ions of $Fe^{3+}$ to $Fe^{2+}$. The known cardiovascular preparation nifedipine (If) and the synthetic antioxidants ionol (BOT) and trolox were also investigated for comparison.

The formation of the complex with 1,10-phenanthroline, which has a characteristic absorption maximum at 520 nm, was used to determine the presence of the $Fe^{2+}$ [10].

The results obtained, given in Table 1, show that the 1,4-DHP derivatives investigated, with the exception of nifedipine, can to some extent reduce $Fe^{3+}$ to $Fe^{2+}$. This ability is significantly less for the studied compounds than for the natural reducing agent ascorbic acid which reacts very rapidly. For the latter the optical density reaches a value of 2.0 arbitrary units a few seconds after mixing the reactants.

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TABLE 1. Reduction of $Fe^{3+}$ Ions to $Fe^{2+}$ by Derivatives of 1,4-DHP and Standard Antioxidants

| Compound | Optical density of 1,10-phenanthroline-$Fe^{2+}$ complex | |
|---|---|---|
| | at the time of mixing the solutions | after 30 min |
| Ia (diludin) | 0,12 | 0,16 |
| Ib | 0,09 | 0,14 |
| Ic | 0,11 | 0,12 |
| Id | 0,13 | 0,68 |
| Ie | 0,12 | 0,31 |
| If (nifedipine) | 0,10 | 0,10 |
| Ionol (BOT) | 0,12 | 0,33 |
| Trolox | 0,18 | 0,96 |

Comparison of the reactivity of derivatives Ia-f showed that the effect of substituents was analogous to that on electrochemical oxidation [11]. Thus the presence of a methyl group at the position 4 (compounds Ia, Ic) reduces the reducing ability. However compound Id having a stronger electron-donating substituent in this position (carboxylate anion) is an active reducing agent. The presence of carboxylate anions in the ester substituents at positions 3 and 5 also increases the ability to reduce, but to a lesser extent. Compound Ia (antioxidant diludin) and its homolog Ib display significantly less reducing ability compared to such antioxidants as ionol and trolox.

It may be suggested that reduction of $Fe^{3+}$ to $Fe^{2+}$ with derivatives of I proceeds as a complex multistage process like that described for N-benzyl-1,4-dihydronicotinamide [12].

The results obtained show that from the point of view of the reduction of $Fe^{3+}$ to $Fe^{2+}$, which is undesirable for antioxidants, diludin (Ia) and its n-butyl homolog Ib are more preferable antioxidants that ionol and trolox. Probably the reducing ability must also be considered when interpreting data on the physiological activity of 1,4-DHP derivatives since the compounds investigated may act on redox processes in cells and *in vivo*.

## EXPERIMENTAL

Compounds Ia-f, (purity > 98%), were synthesized as described previously [13]. 1,10-Phenanthroline, BOT, and trolox were purchased from Aldrich, $Fe_2(SO_4)_3 \cdot 6H_2O$ was purchased from Fluka.

The known procedure of [10] was used to determine the reducing ability of compounds Ia-f, ionol, and trolox. Solutions of 1,10-phenanthroline (6 mM) in ethanol, $Fe_2(SO_4)_3 \cdot 6H_2O$ (0.3 mM) in distilled water, and 1,4-DHP derivatives, ionol, and trolox (all 0.3 mM) in 50% ethanol were prepared immediately before the experiment. A current of argon was passed through all solvents for 20 min before use.

**Experimental Procedure.** A mixture of 1,10-phenanthroline (1.5 ml), $Fe_2(SO_4)_3 \cdot 6H_2O$ (1.5 ml), and test substance solution (1.5 ml) was incubated at 37°C in a 1 cm cuvette of a Hitachi UV-vis 557 spectrophotometer, and the optical density at 520 nm was measured immediately after mixing of the solutions and after 30 min. Values given in Table 1 are average of at least 3 experiments. The value, determined for sample Ia (n = 6) is correct to ±5 percent.

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