Generation of hydroxyl radicals by the intramolecular oxidation of tricyclic artemisinin analogs and their antimalarial activity

E. T. Denisov and T. G. Denisova*

Institute of Problems of Chemical Physics, Russian Academy of Sciences, 1 prosp. Akad. Semenova, 142432 Chernogolovka, Moscow Region, Russian Federation. E-mail: det@icp.ac.ru

The kinetic schemes were constructed for the intramolecular oxidation of four tricyclic artemisinin derivatives differed in number and arrangement of the methyl groups. Each step of the scheme was characterized by the enthalpy. The activation energies and rate constants were calculated by using the intersecting parabolas model. Three of the four tricyclic derivatives were found to undergo intramolecular oxidation, and the hydroperoxide groups formed generate free radicals. Owing to this, the compounds possess antimalarial activity. The fourth compound is not substantially oxidized due to certain specific features of its structure and exhibits no antimalarial activity. The latter correlates with the number of hydroxyl radicals generated by the compound (n_{OH}). The dep endence of the IC_{50} index on n_{OH} is nonlinear. Three elementary reactions leading to the generation of reactive hydroxyl radicals were identified.

Key words: antimalarial activity, intramolecular radical reaction, hydroxyl radicals, DNA, kinetic scheme, rate constant, intersecting parabolas model, oxidation, 3,4-secoartemisinin, activation energy, enthalpy of reaction.

Artemisinin (**1**) is a unique antimalarial drug, which kills malaria plasmodium by the generation of free radicals.[1—6] The radicals are formed *via* the redox reaction[7]

$$ROOR + Fe^{2+} \longrightarrow RO^- + Fe^{3+} + RO^{\cdot}.$$

The high medical efficiency of artemisinin is due, first of all, to the fact that the content of Fe^{II} in malaria plasmodium is by two orders of magnitude higher than that in a human organism.[4—6] If the medical activity of compound **1** is due only to its ability to react with iron ions and complexes with the formation of free radicals, a correlation between the rate constant of the reaction of peroxide radicals with Fe^{II} ions and their medical activity should be expected. The latter is characterized by the IC_{50} index (IC_{50} is the dose of a drug (in ng mL^{-1}) that decreases the parasite concentration by 50%). The literature[8] values of $IC_{50}(\mathbf{1})/IC_{50}$(compound) and rate constant of the reaction of the peroxide group of the compound with Fe^{II} (k_d) are compared in Fig. 1.

It is seen that there is no correlation between IC_{50} and k_d for the compounds. Certain of the studied compounds, being analogs of **1**, are characterized by different rate constants of the reactions with Fe^{II} but have the same antimalarial activity (similar values of IC_{50}). On the contrary, there are compounds for which the rate constants of the reactions with Fe^{II} are similar, but antimalarial activities are different. Therefore, the presence of the peroxide group is a necessary, but insufficient condition, and other important factors affect the medical action of these peroxide compounds along with their ability to react with Fe^{II} ions.

The kinetics of the radical transformation of compound **1** in the presence of oxygen has recently[9—11] been analyzed using the parabolic model. This analysis is very important to understand the mechanism of action of compound **1**, because malaria plasmodium lives in red haematocytes of an organism, which are oxygen carriers, and the medium of plasmodium inhabitancy is saturated with oxygen. It has been shown[9—11] for the first time that the cleavage of the peroxide bridge in compound **1** is followed

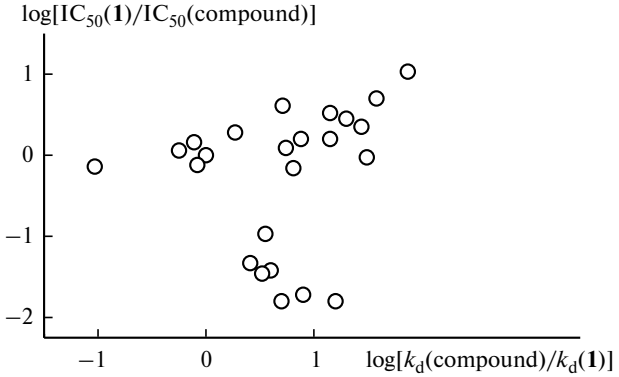

Fig. 1. Comparison of the relative antimalarial activity of the compounds ($IC_{50}(\mathbf{1})/IC_{50}$(compound)) with the rate constant of radical generation by the reaction with iron ions (k_d) ($FeSO_4$ in H_2O—MeCN (1 : 1), 310 K) in the logarithmic coordinates.

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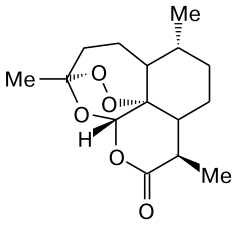
by a cascade of intramolecular radical reactions, which results in polyatomic peroxide. In turn, the polyhydroperoxide formed generates in succession a series of new radicals by the reaction with Fe^{II}. The processes of formation and decomposition of hydroperoxide groups are assumed to determine unique antimalarial properties of compound **1**. However, this hypothesis ought to answer the following questions.

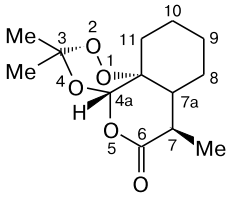
First, does the compound having the peroxide group but resistant to intramolecular oxidation retain its antimalarial activity?

Second, radicals of different structure and reactivity are formed by the oxidation and destruction of compound **1**.[11] Are they equivalent in their antimalarial activity? Does the antimalarial activity depend on the total number of radicals formed or on the number of radicals of a certain kind?

The purpose of the present work is to address these questions and to further develop the kinetic approach to testing of antimalarial drugs. Artemisinin analogs **2**—**5**, being methyl derivatives of 3,4-secoartemisinin, were chosen as objects of the study.



1



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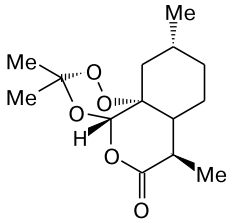

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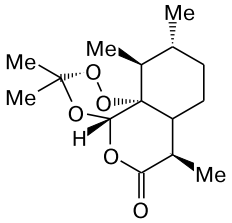

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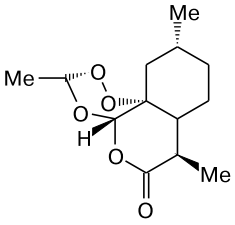


5

These compounds are characterized by different antimalarial activities (IC_{50} index), while one of them (**5**) is inactive.[12] At the same time, these derivatives differ insignificantly in the number and stereoorientation of the methyl groups and the rate constants of their reactions with Fe^{II} are similar.[8]

Calculation procedure

The intramolecular mechanism of oxidation of compound **1** was discovered owing to a kinetic analysis of its radical transformations.[9—11] This approach makes it possible to take into account stereochemical features of a molecule, accessibility or inaccessibility of C—H bonds for the attack by the alkoxyl or peroxyl radical, and the energy of each step; to perform a quantitative analysis of the competition of parallel reactions; and to construct a substantiated scheme of the main routes of oxidation and destruction of the molecule. To estimate the main route of intramolecular oxidation, we used the intersecting parabolas model,[13—15] which makes it possible to calculate the activation energy of the reaction from its enthalpy with an inaccuracy of 1.5 kJ mol^{-1}.

For the radical abstraction reactions

$$XO^{\cdot} + RH \longrightarrow XOH + R^{\cdot}$$

the enthalpy of the reaction (ΔH) was estimated by the R—H and O—H bond dissociation energies

$$\Delta H = D_{R-H} - D_{O-H}, \qquad (1)$$

and ΔH of the decyclization reactions were estimated through the group increments by the Benson method[16] (examples for this calculation are published[11]).

The activation energy was calculated by the equation

$$\sqrt{E_e} = B\left\{1 - \alpha\sqrt{1 - \frac{\Delta H_e}{Bbr_e}}\right\}, \qquad (2)$$

where $B = br_e/(1 - \alpha^2)$, $b = b_{R-H}$ is the force constant of the attacked bond to the one-half power, $\alpha = b_{R-H}/b_{O-H}$, r_e is the elongation of the reacting bonds in the transition state, and ΔH_e is the classical enthalpy ($\Delta H_e = \Delta H + 0.5hN_A(\nu_{R-H} - \nu_{O-H})$, where h and N_A are Planck´s constant and Avogadro´s number, respectively; ν_{R-H} and ν_{O-H} are the stretching vibration frequencies of the corresponding bonds).

The classical activation energy is as follows:

$$E_e = E + 0.5hN_A - 0.5RT.$$

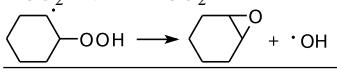
For the decyclization reactions, E and $k = A\exp(-E/RT)$ were calculated similarly. The values of α, br_e, and other kinetic characteristics for reactions of various classes, as well as the pre-exponential factor A for each class of reactions, are listed in Table 1.

To calculate the enthalpy of the reaction of the chosen compounds, the C—H and O—H bond dissociation energies in the model compounds[10] were used (Table 2).

In order to choose the fastest step among a series of parallel reactions of one class, their enthalpies were calculated and compared. For instance, the peroxyl radical C(7a)OO$^{\cdot}$ from compound **4** can attack three C—H bonds in the β-position: C(4a)—H, C(9)—H, and C(11)—H. The enthalpies, activation energies, and rate constants of these reactions are given below.

Reaction	ΔH	E	k_{310K}/s^{-1}	Predomination (%)
	kJ mol^{-1}			
C(7a)OO$^{\cdot}$ → C(4a)$^{\cdot}$	19.7	44.4	$1.82 \cdot 10^5$	96.2
C(7a)OO$^{\cdot}$ → C(9)$^{\cdot}$	50.2	59.9	$4.44 \cdot 10^2$	0.2
C(7a)OO$^{\cdot}$ → C(11)$^{\cdot}$	36.9	52.9	$6.71 \cdot 10^3$	3.6

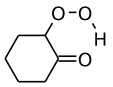
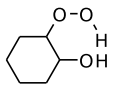
Table 1. Kinetic parameters of reactions of various classes occurring upon oxidation of compounds **2**—**5** (see Refs 17 and 18)

Class of reactions	α	br_e /kJ$^{1/2}$ mol$^{-1/2}$	$0.5hN_A\nu_i$ kJ mol^{-1}	$0.5hN_A(\nu_i - \nu_f)$ kJ mol^{-1}	log(A/s^{-1})
RO· → R·	0.796	13.13	17.4	−4.3	12.6
RO· → Decyclization	0.748	9.84	6.2	−2.1	13.0
RO· + LSH	0.707	11.67	15.1	−6.6	7.3*
RO_2· → R· (n = 6)**	0.814	13.23	17.4	−3.8	12.74
RO_2· → R· (n = 7)**	0.814	13.43	17.4	−3.8	12.74
R_iO_2· → R_jO_2·	1.000	13.13	21.2	0.0	11.54
RO_2· + LSH	0.722	11.94	15.1	−6.1	7.3*
RCO_2· → R· + CO_2	0.548	10.40	8.2	−5.8	13.5
	0.826	15.13	5.1	−1.6	11.6

* For this reaction $A = A_0$[LSH].
** n is the number of atoms in the cyclic transition state.

The enthalpies of these reactions differ substantially, and the first reaction predominates (96%). The calculation shows that, for the difference in the reaction rate constants equal to e times, the difference in their activation energies (ΔE) is 2.5 kJ mol^{-1} and the difference in enthalpies ($\Delta\Delta H$) is 5.0 kJ mol^{-1}. Thus, predominance of one of the parallel reactions can be deduced from the difference in enthalpies of these reactions. L-Cysteine (LSH), which enters into the composition of proteins,[10] is most reactive among the substrates reacting with radicals RO· and RO_2·. The rate constant of the intramolecular reaction at [LSH] = 0.05 mol L^{-1} was compared with this reaction.

Table 2. Dissociation energies of C—H bonds (D_{C-H}/kJ mol^{-1}) and O—H bonds (D_{O-H}/kJ mol^{-1}) in compounds **2**—**5** and in hydroperoxides formed from them[10,19—21]

Bond	D_{C-H}	Bond	D_{O-H}
C(4a)—H	378.3	O(1)—H	434.8
C(7)—H	385.3	O(2)—H	438.5
C(7a)—H	387.6	C(4a)OO—H	357.6
C(8)—H,	408.8	C(7)OO—H	362.9
C(9)—H		C(7a)OO—H	358.6
C(10)—H (**2**)	408.8	C(8)OO—H	365.5
C(10)—H (**3**—**5**)	395.5	C(9)OO—H	365.5
C(11)—H	408.8	C(10)OO—H (**2**)	365.5
(**2**, **3**, **5**)		C(11)OO—H (**2**)	365.5
C(11)—H (**4**)	395.5	C(10)OO—H (**3**, **4**)	358.6
C(3)—H (**5**)	378.3	C(11)OO—H (**3**)	365.5
>C—H(OH)	388.4	C(11)OO—H (**4**)	358.6
C—H(OOH)	375.8		369.8
	394.1		362.1

Results and Discussion

The kinetic schemes for the oxidation reactions of compounds **2**—**4** are shown in Schemes 1—3. It can be expected that iron ions predominantly form a complex with the terminal oxygen atom O(1) because of steric hindrances. Therefore, the alkoxyl radical RO^{2}· is mainly formed due to the electron transfer from this complex. Each stage of the kinetic scheme incudes two consecutive elementary acts

$$R_i\cdot + O_2 \longrightarrow R_iO_2\cdot,$$

$$R_iO_2\cdot \longrightarrow R_j\cdot.$$

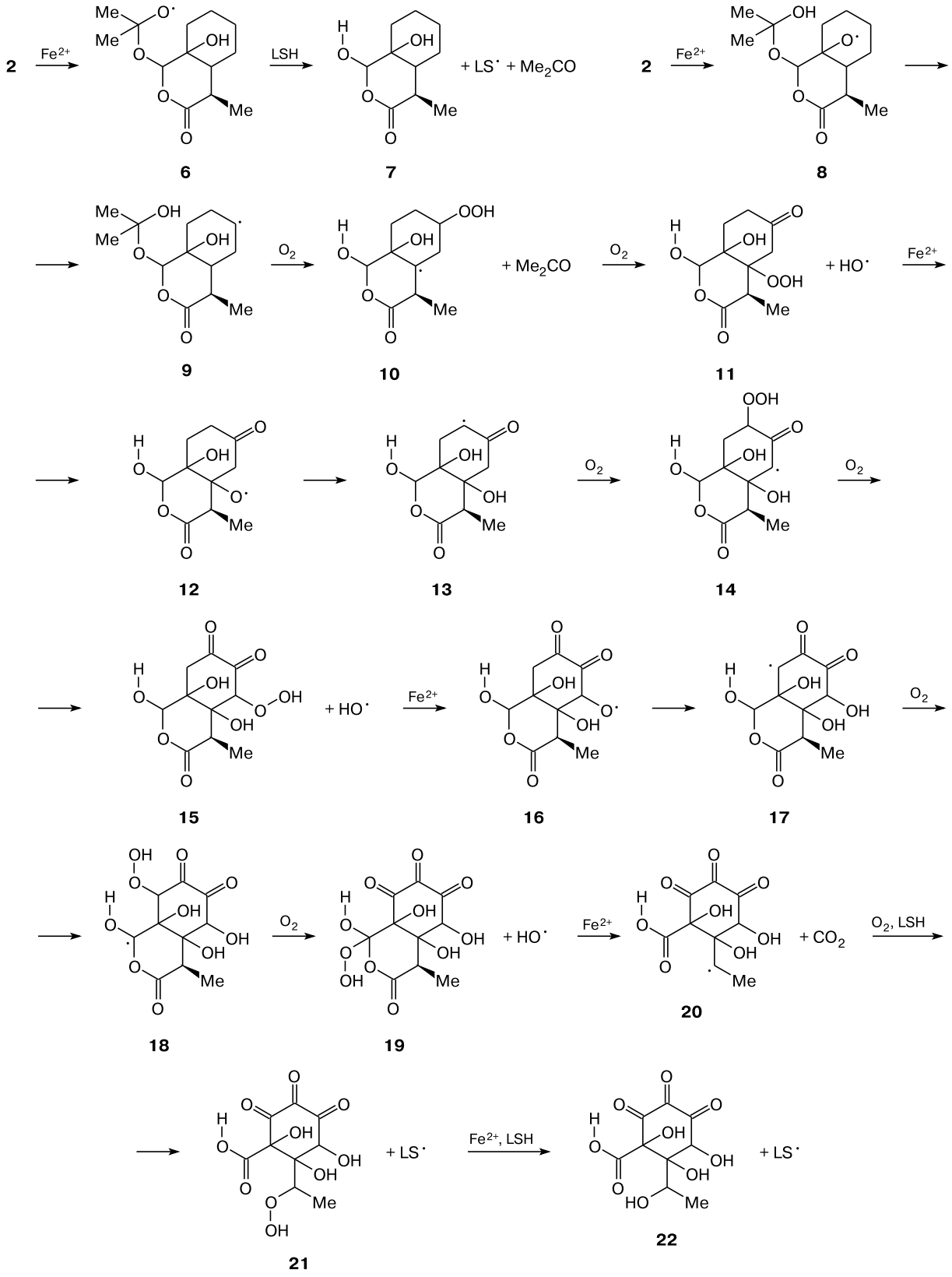
The addition of O_2 occurs very rapidly without activation energy within ~10^{-6} s and it is not a rate-determining process.[10] The fastest reaction was chosen among parallel reactions of RO_2· isomerization with H atom transfer. Radicals RO· predominantly abstract the H atom from the γ-position or react with the thio groups of the L-cysteine residue of protein *via* the exothermic reaction.[10,11] Radicals RO_2· are either isomerized to form alkyl radicals with H atom abstraction from the β- or γ-C—H bond to form hydroperoxide or react with L-cysteine.[10,11] The kinetic scheme of oxidation reactions of compound **1** was presented earlier.[11]

Five radicals, *viz.*, three hydroxyls and two thiyl radicals, are formed from one molecule of compound **2** due to the oxidation transformations (Scheme 1).

The oxidation transformations of molecule **3** give 3.3 hydroxyl radicals and one thiyl radical with allowance for the competition of reactions **35** → **36** and **35** → **41** (Scheme 2).

The intramolecular oxidation of each molecule of peroxide **4** generates three hydroxyl and three thiyl radicals (Scheme 3). The kinetic characteristics of the rate-

Scheme 1


2
Fe2+
LSH
+ LS· + Me2CO
O2
+ HO·
OOH
+ CO2
O2, LSH
Fe2+, LSH
6
7
8
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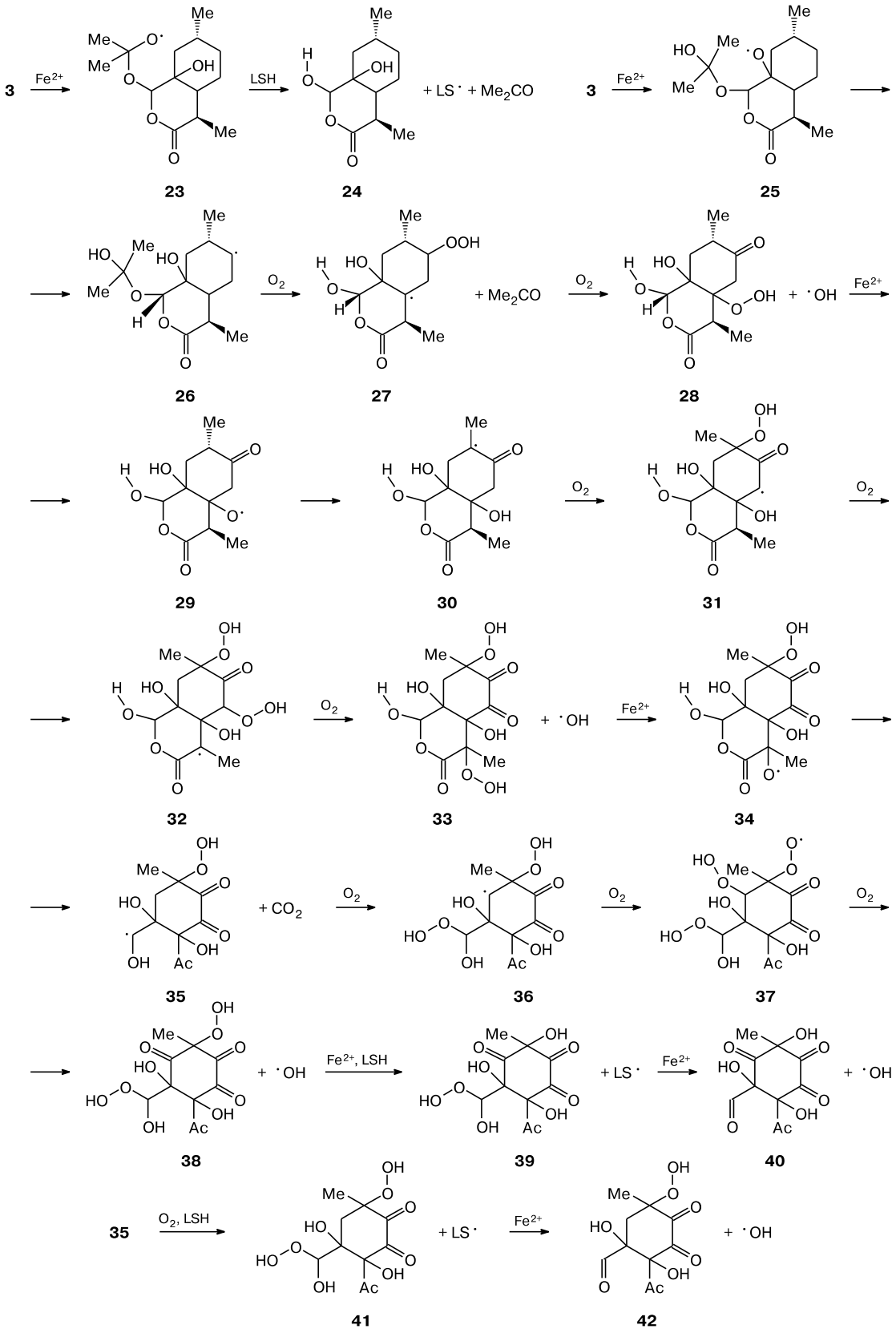
22

Scheme 2


3
Fe2+
LSH
+ LS· + Me2CO
O2
+ ·OH
+ CO2
O2, LSH
Fe2+, LSH
23
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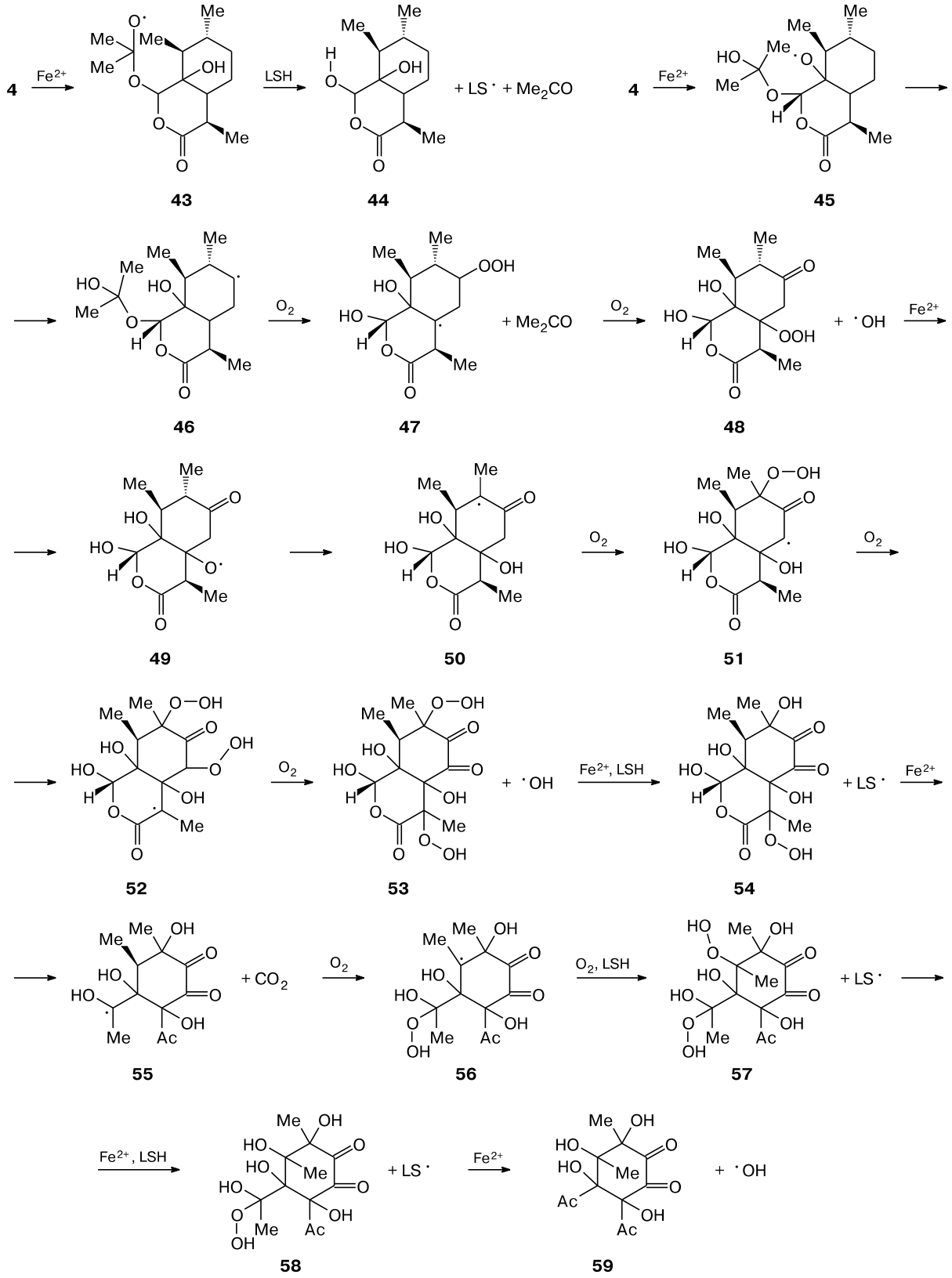
Scheme 3


4
Fe2+
LSH
+ LS· + Me2CO
4
Fe2+
O2
+ Me2CO
O2
+ ·OH
Fe2+
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O2
O2
Fe2+, LSH
+ LS·
Fe2+
+ CO2
O2
O2, LSH
+ LS·
Fe2+, LSH
+ LS·
Fe2+
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43
44
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52
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58
59

determining steps presented in Schemes 1—3 are given in Table 3.

An unexpected result was obtained by analysis of the oxidation transformations of compound **5**, which differs from compound **3** by the absence of only one methyl group in position 3. This minor structural distinction, as it turned out, changes dramatically the mechanism of radical oxidation of compound **5**. In this compound, the C(3)—H bond is weakened because of the influence of two adjacent oxygen atoms (D_{C-H} = 378.3 kJ mol^{-1})[19] and represents a unique trap for radical **62** (Scheme 4). The alkoxyl radical RO^{2}· formed by the cleavage of the O(1)—O(2) bond attacks the weakest bond C(3)—H and leaves the stronger bond C(9)—H of the cyclohexane ring (D_{C-H} = 408.8 kJ mol^{-1}) intact.[19] As a result, the decalin ring is not subjected to oxidative destruction with the formation of new radicals, as it occurs in the case of compounds **1**—**4**. The hydroxyalkyl radical >C·(OH) adds oxygen, and the hydroxyperoxyl radical formed rapidly interacts with the thio group of L-cysteine converting into hydrogen peroxide, which decomposes rapidly by Fe^{II}. As a result, one molecule **5** generates only one hydroxyl radical (see Scheme 4).

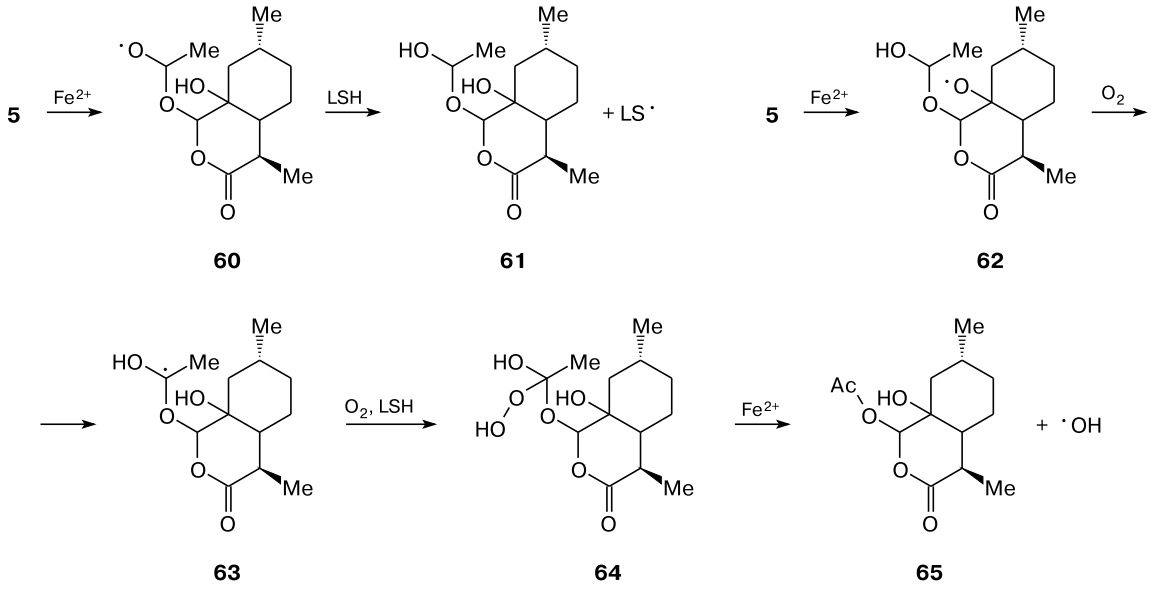
It seems reasonable to compare the initiating ability of compounds **1**—**5** with their antimalarial activity. The therapeutical activity of these compounds was studied[12] for two clones of parasites *Plasmodium falciparum* abundant in Indo-China (W-2) and Sierra Leone (D-6). The activity of compound **1** was accepted to be 100%, whereas the activity of other compounds is presented as the ratio [IC_{50}(compound)/IC_{50}(**1**)] · 100. The results of this comparison are given in Table 4.

The example of compound **5** which does not undergo noticeable intramolecular oxidation and exhibits no antimalarial activity, confirms the significance of intramolecular oxidation as an important factor of the activity. A comparison of the antimalarial activity with the total number of radicals generated by the compound due to oxidation (n_Σ) reveals that there is no correlation between

Table 3. Kinetic characteristics of different steps of oxidation of peroxides **2**—**5**

Step	ΔH	E	k_{310K} /s^{-1}
	kJ mol^{-1}		
6 → **7**, **23** → **24**, **43** → **44**	−74.9	6.7	$1.49 \cdot 10^6$
8 → **9**, **12** → **13**, **25** → **26**, **45** → **46**	−29.7	24.5	$2.96 \cdot 10^8$
9 → **10**, **26** → **27**, **46** → **47**	22.1	45.7	$1.10 \cdot 10^5$
10 → **11**, **27** → **28**, **37** → **38**, **47** → **48**	17.2	43.2	$2.89 \cdot 10^5$
13 → **14**	24.3	46.7	$7.43 \cdot 10^4$
14 → **15**	10.3	41.6	$5.35 \cdot 10^5$
16 → **17**	−44.4	18.2	$3.43 \cdot 10^9$
17 → **18**	12.8	41.2	$6.27 \cdot 10^5$
18 → **19**	3.5	37.0	$3.21 \cdot 10^6$
20 → **21**, **60** → **61**	−5.5	29.5	$2.14 \cdot 10^2$
21 → **22**	−71.9	6.1	$1.90 \cdot 10^6$
29 → **30**, **49** → **50**	−43.0	18.9	$2.61 \cdot 10^9$
30 → **31**, **50** → **51**	35.5	52.2	$8.81 \cdot 10^3$
31 → **32**, **51** → **52**	15.5	44.1	$2.03 \cdot 10^5$
32 → **33**, **52** → **53**	−1.8	34.6	$8.12 \cdot 10^6$
35 → **36**	46.7	58.1	$5.68 \cdot 10$
36 → **37**	3.1	24.8	$6.00 \cdot 10^5$
38 → **39**, **53** → **54**, **57** → **58**	−78.5	5.8	$2.11 \cdot 10^6$
35 → **41**, **63** → **64**	−2.1	30.9	$1.24 \cdot 10^2$
55 → **56**	33.4	51.2	$8.26 \cdot 10^2$
56 → **57**	1.4	32.3	$7.14 \cdot 10$
62 → **63**	−60.2	12.6	$2.64 \cdot 10^9$

Scheme 4



these two values (see Table 4, *cf.* n_Σ for **1** and **2**, **2** and **3**, and **3** and **4**). However, analysis of the results presented in Table 4 suggests that hydroxyl radicals formed from the compounds are biologically most active. This follows from the fact that the therapeutical activity of the compound and the number of hydroxyl radicals formed from it by the oxidative destruction (n_{OH}) correlate. Most likely, the formation of thiyl radicals is not so significant as the generation of very reactive hydroxyl radicals.

An important role of hydroxyl radicals agrees with the hypothesis about the decay of the malaria parasite due to the damage of its DNA with radicals.[1,22,23] The red haematocytes, where the malaria parasite settles, contains no DNA of warm-blooded animals and includes only DNA of the parasite,[1] so that the DNA of malaria plasmodium is the target, which is attacked by hydroxyl radicals formed from the drug. The destruction of DNA under the action of hydroxyl radicals was proved in experiments with Fenton´s reagent.[23]

In connection with the aforesaid, it seems reasonable to consider in more detail the reactions of generation of hydroxyl radicals. The latter are very reactive, since the energy of the HO—H bond formed upon H atom abstraction is high and close to 498 kJ mol^{-1}.[24] Based on kinetic Schemes 1—3, one can distinguish three sources of these radicals.

1. The oxidation of the methylene group gives rise to the >CHOOH group in which the C—H bond is weakened, because the radical >C$^\cdot$OOH formed from this group is stabilized due to the interaction of an unpaired electron of the C atoms with *p*-electrons of the oxygen bridge. This C—H bond is attacked by the peroxyl radical from the β- or γ-position,[17] and the unstable α-hydroperoxyalkyl radical formed decomposes rapidly to the carbonyl compound and hydroxyl (see Schemes 1—3, steps **10** → **11**, **14** → **15**, **27** → **28**, **37** → **38**, **47** → **48**, and **52** → **53**)

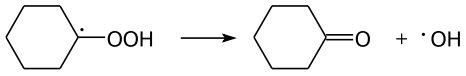
$$>C^\cdot OOH \longrightarrow >C{=}O + O^\cdot H.$$

Table 4. Comparison of the initiating ability of compounds **1**—**5** with their antimalarial activity to clones W-2 and D-6 of *Plasmodium falciparum* (the activity of compound **1** was accepted as 100%)

Compound	$[IC_{50}(compound)/IC_{50}(\mathbf{1})]\cdot 10^2$ (%)		n_{OH}	n_{LS}	n_Σ
	W-2	D-6			
1	100	100	3.5	0.2	3.7
2	6	20	3.0	2.0	5.0
3	75	108	3.3	1.0	4.3
4	14	7	3.0	3.0	6.0
5	0	0	0.5	0.5	1.0

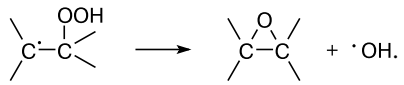
Note. n_{OH}, n_{LS}, and n_Σ are the number of hydroxyl and thiyl radicals, and the total number of radicals generated by the compound by the oxidation, respectively.

This decomposition reaction is strongly exothermic and proceeds very rapidly.[25] For instance, the enthalpy of the decomposition reaction

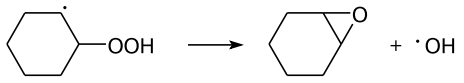


is −164.2 kJ mol^{-1}.

2. The decomposition reactions of the α-hydroperoxyalkyl radical (>C$^\cdot$C(OOH)<) can be a source of the hydroxyl radical[17,26]



The decomposition of the α-hydroperoxycyclohexyl radical



is characterized by the enthalpy $\Delta H = -64.2$ kJ mol^{-1}, activation energy $E = 38.8$ kJ mol^{-1}, and $k = 1.15\cdot 10^5$ s^{-1} ($T = 310$ K).[17] If oxygen adds more rapidly than this radical decays with the formation of oxide, the decomposition of the α-hydroperoxyalkoxyl radical prevails; if not, the decomposition of the α-hydroperoxyalkyl radical predominates. It is significant that the peroxyl radical is generated in the both parallel reactions.

3. One more source of hydroxyl radicals is hydroxyhydroperoxide >C(OH)OOH. It converts into the unstable hydroxyalkoxyl radical by the reaction with Fe^{II} ions. The radical decomposes to form the carbonyl compound and hydroxyl radical (see Schemes 2—4, steps **39** → **40**, **58** → **59**, and **64** → **65**)

$$>C(OH)OOH + Fe^{2+} \longrightarrow >C(OH)O^\cdot + Fe^{3+} + OH^-,$$

$$>C(OH)O^\cdot \longrightarrow >C(O) + HO^\cdot.$$

A comparison of the IC_{50} values with the yield of hydroxyl radicals n_{OH} per molecule reveals the absence of a linear dependence between these parameters. As can be seen from Fig. 2, this dependence is described by the equation

$$[IC_{50}(\mathbf{1})/IC_{50}(compound)] = (-0.15\pm0.10) + (5.65\pm1.08)\cdot 10^{-4} n_{OH}{}^6. \qquad (3)$$

It is most likely that a nonlinear character of this correlation hints that there is a protection mechanism from radical attacks in the organism of malaria plasmodium. A cumulative action of hydroxyl radicals is needed to surmount the protection mechanism. This is achieved by the formation of a series of radicals from polyatomic hydroperoxide.

Thus, the complete kinetic scheme was constructed using the intersecting parabolas method for the oxidation

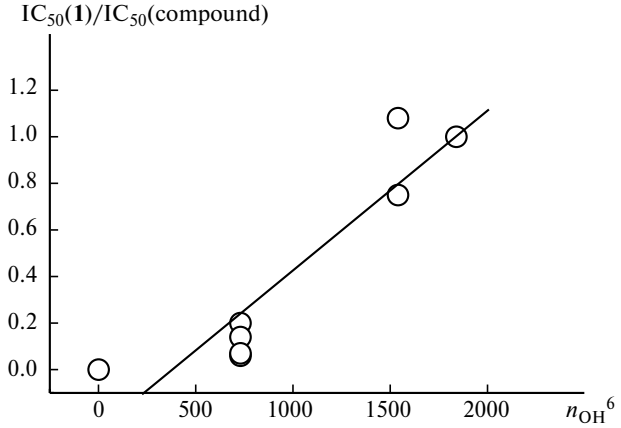


Fig. 2. Correlation between parameter IC_{50} and the number of hydroxyl radicals generated by the compound by oxidative destruction (n_{OH}).

of artemisinin derivatives and the number and structure of free radicals formed were estimated. Using four derivatives of artemisinin **1** (compounds **2**—**5**) as examples, we established that the kinetics of intramolecular oxidation of such compounds and, hence, the number of radicals formed due to oxidative destruction depend on the structure. It was shown for compound **5** that an insignificant change in the structure (elimination of one methyl group) dramatically changes the oxidation mechanism and the number of generated radicals. The comparison of the antimalarial activity of the compounds with the number of generated radicals showed a nonlinear correlation between the parameter IC_{50} and the number of hydroxyl radicals formed from these compounds (see Fig. 2). Among the radicals formed, hydroxyl radicals are the main agents inducing the decay of the malaria parasite. Probably, their major target is DNA of the parasite.

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