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Interrelation between the Chemical Structure and Antioxidant Properties of N-Substituted Amides of Salicylic Acid

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Abstract—The kinetics of the initiated oxidation of a model lipid (methyl oleate has been investigated in the presence of a group of new "hybrid" structures, namely, N-substituted amides of salicylic acid whose structure contains an amide residue conjugated with, or separated by a bridging fragment (three methylene groups) from, an N-phenolic substituent. The compounds also differ in the degree of screening of the OH groups. The process was initiated by thermal decomposition of azobisisobutyronitrile at 60°C (initiation rate of $w_i = 4.2 \times 10^{-8}$ mol L^{-1} s^{-1}) or by UV irradiation (λ = 313–365 nm, $w_i = 0.6 \times 10^{-8}$ mol L^{-1} s^{-1}). The compounds examined exhibit antiradical activity owing to the presence of the phenolic hydroxyl groups. N-substituted salicylamides efficiently inhibit the overall methyl oleate oxidation process and are comparable in activity with dibunolum and α-tocopherol or are superior to them. The structures in which the residues of salicylamide and sterically hindered phenol are separated by the bridging fragment are particularly efficient. The advantages of the salicylamides absorbing at 300–365 nm manifest themselves in UV-initiated oxidation. The peroxidase activity of the N-substituted salicyl acid derivatives is determined by the structure of the amide moiety. The compounds examined here are new, promising, effective antioxidants, whose particular structural fragments act via different mechanisms in oxidation.

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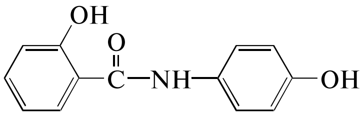
In recent years, medicine and pharmacy have been showing keen interest in derivatives of salicylic acid, because it has been discovered that this acid is biosynthesizable and executes a number of regulatory functions [1]. New salicylic acid derivatives exhibiting anti-inflammatory, antipyretic, and fibrinolytic properties are being studied [2]. It has been demonstrated that the salicylic acid residue makes compounds capable of absorbing ultraviolet radiation, including in the 300–305 nm range, which is the most dangerous from the standpoint of melanoma development [3, 4]. These properties make the salicylic acid derivatives promising for the prophylaxis of skin cancer and photodegradation. As a rule, new-generation antioxidants (AOs) contain several characteristic groups that synergically enhance their effect during oxidation [5–8]. Therefore, phenolic derivatives of salicylic acid can be of interest as oxidation inhibitors and polymer photostabilizers.

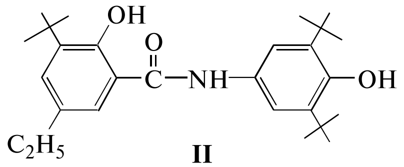
Here, we report the properties of a group of new "hybrid" structures synthesized from N-substituted salicylamides and compare them with the known synthetic AO dibunolum and with the natural oxidation inhibitor α-tocopherol.

The directed synthesis of potential AOs was carried out at the Vorozhtsov Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences. The structures examined differ in the degree of conjugation of electron density and in the number of screened phenol groups.



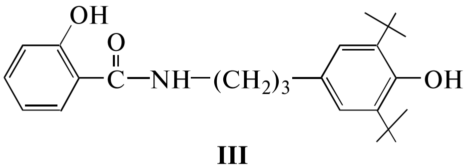
I

N-(4'-hydroxyphenyl)amido-2-hydroxybenzoic acid



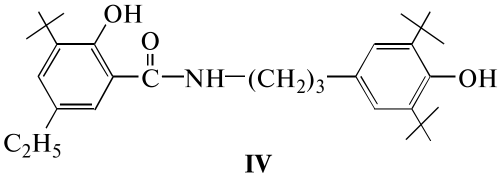
II

N-(4'-hydroxy-3',5'-di-*tert*-butylphenyl)amido-2-hydroxybenzoic acid



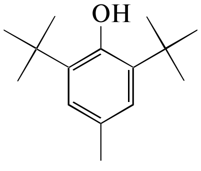
III

N-[(4'-hydroxy-3',5'-di-*tert*-butylphenyl)trimethyleno] amido-2-hydroxybenzoic acid



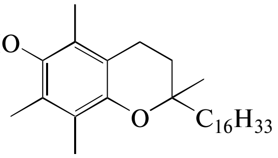
IV

N-[(4'-hydroxy-3',5'-di-*tert*-butylphenyl)trimethyleno] amido-2-hydroxy-3-*tert*-butyl-5-ethylbenzoic acid



V

2,6-di-*tert*-butyl-4-methylphenol



VI

α-tocopherol.

In structures **I** and **II**, all groups of atoms are involved in the common conjugation system. In compounds **III** and **IV**, the salicylamide residue and the phenol moiety are separated by three methylene groups (bridging fragment). Compound **I** (osalmid) is a sterically unhindered phenol. In the structure of amide **III**, the OH group in the salicylic acid residue is not screened. In compounds **II** and **IV**, all phenolic hydroxyl groups are sterically hindered because of the presence of the *ortho*-*tert*-butyl substituents.

EXPERIMENTAL

The antiradical activity of N-substituted salicylamides was evaluated in terms of the constant k_7 using the chemiluminescence method for the initiated oxidation of ethylbenzene [9]. The following equation was used to determine the rate constant for the reaction of AO with peroxyl radicals, k_7:

$$\sqrt{J_0/J} = 1 + (1.1 \pm 0.1)k_7[\mathrm{InH}]\big/\sqrt{k_6 w_\mathrm{i}}, \qquad (1)$$

where J_0 and J are the experimentally determined chemiluminescence intensities in the absence and in the presence of an inhibitor, respectively; w_i is the initiation rate; and k_6 is the rate constant of chain termination in the known scheme of free-radical chain oxidation. The dependence of the luminescence intensity on the AO concentration was studied. To rule out the influence of the products of inhibitor conversion and the possible nonstationarity of the process, $[\mathrm{d}t(J/J_0)/\mathrm{d}t]_\mathrm{max}$ was extrapolated to the zero concentration of AO. This made it possible to determine k_7 using the equation

$$[\mathrm{d}t(J/J_0)/\mathrm{d}t]_\mathrm{max} = (0.22 \pm 0.02)k_7\sqrt{w_\mathrm{i}}\big/\sqrt{k_6} \qquad (2)$$

at known values of k_6 and initiation rate w_i [9].

The kinetics of oxygen uptake in the oxidation of methyl oleate (MO) at a concentration of 0.67 mol/L was studied by a volumetric method in an inert solvent (chlorobenzene) using a Warburg manometer apparatus. The reaction was carried out at 60 ± 0.2°C. The process was initiated by thermal decomposition of azobisisobutyronitrile (AIBN) (1×10^{-3} mol/L) or by irradiation of the substrate with a DRSh-250-3 mercury lamp ($\lambda = 313$–365 nm) for 20 min at room temperature. The initial rate was estimated by the inhibitor method using Dibunolum as the reference AO [10].

The UV spectra of the amides were recorded on an IR Prestige-21 (model 206-72010) spectrophotometer (Shimadzu) and on a Specord-75IR spectrophotometer. Deuteration was carried out by dissolving a compound in methanol CD_3OD followed by evaporation of methanol at 40–50°C.

A laser flash photolysis technique based on an Nd:YAG neodymium laser (355 nm) was used (pulse duration of 5 ns, exposed surface area of 0.03 cm^2, pulse energy of 2 mJ (66 $\mathrm{mJ/cm}^2$)). The photolysis setup was essentially similar to the one described in [11]. For steady-state photolysis, solutions of the salicylamides in CCl_4 were irradiated with the mercury lamp using a KF window with a slit width of 0.43 cm. The radiation power was measured by a standard procedure [12] using potassium ferrioxalate as a chemical actinometer.

The accumulation kinetics of hydroperoxides (ROOH) was studied under autooxidation conditions using iodometric back titration in a nonaqueous medium. A sample of lipids (0.1–0.2 g) was dissolved in a mixture (10 mL) of anhydrous acetic acid and chloroform (1 : 1). The mixture was purged with carbon dioxide for 5 min, and a saturated methanolic solution of potassium iodide (5 mL) was then added. The sample was kept in the dark at room temperature for 18 h, water (50 mL) was then added, and the sample was titrated with a solution of sodium thiosulfate (0.01 mol/L). A blank experiment was carried out in parallel. The amount of iodine, which was proportional to the amount of ROOH (peroxide number), was calculated using the equation

$$[\mathrm{ROOH}] = 0.1269(a - b)/d,$$

where a and b are the volume of sodium thiosulfate consumed in the titration of the examined and blank samples, respectively, and d is the weight of the lipid sample. The peroxide number ((g I_2)/(100 g lipids)) was determined at 5-min intervals. The ROOH accumulation rate was estimated in (g I_2)/(100 g lipids) × 10^{-4} s^{-1} units.

Amides were used as received. The solvent was chlorobenzene (reagent grade). Spectra were recorded using spectroscopically pure heptane and CCl_4.

Table 1. Numerical values of the constant k_7 for the reactions of the N-substituted salicylamides with the peroxyl radicals

Compound	$k_7 \times 10^4$, L mol^{-1} s^{-1}	f
I	6.86	2.4
II	1.69	2.6
III	0.52	3.3
IV	0.85	3.6
V	1.40	2.0
VI	360.00	2.0

Note: $w_i = 2.3 \times 10^{-8}$ mol L^{-1} s^{-1}, AO concentration of 1×10^{-3} mol/L, 60°C.

RESULTS AND DISCUSSION

It was demonstrated by the chemiluminescence method that all of the compounds examined here efficiently quench luminescence induced by the initiated oxidation of the model compound (ethylbenzene). The variation of the chemiluminescence intensity did not obey the Stern–Volmer equation, indicating that the observed quenching is chemical in nature, caused by the interaction of the compounds with free radicals ($RO_2^{\bullet}$). The k_7 values are given in Table 1. These data demonstrate that the highest activity is exhibited by compound **I**, which has two sterically unhindered phenolic OH groups and π–ρ conjugated electron densities of two phenol rings and an amide group. Due to the three *ortho-tert*-butyl substituents in the structure of compound **II**, the constant k_7 for this compound is smaller by a factor of 4 at the same degree of electron density delocalization. Thus, an increase in the degree of screening of the OH group decreases the efficiency of the AO in its reaction with $RO_2^{\bullet}$. This is in agreement with the data indicating that sterically unhindered phenols show a higher antiradical activity [10].

The constant k_7 for N-substituted amide **II** is comparable with the corresponding value for compound **V** (Dibunolum) (Table 1). The antioxidant activity of compounds **III** and **IV**, whose structures include a salicylamide residue and a phenolic residue separated by a bridging fragment, is lower. A comparison between compounds **II** and **IV**, which contain the same substituents, shows that the separation of the two conjugated fragments by the bridge consisting of three methylene groups reduces the value of k_7 almost by half. Therefore, the degree of conjugation of electron density and the presence of screening substituents are the factors that determine the antiradical activity of the N-substituted salicylic acid derivatives. The natural AO α-tocopherol has a considerably higher activity than Dibinolum or the N-substituted salicylamides.

The stoichiometric inhibition factor f, which is equal to the number of radicals decaying on one AO molecule, is 2 only for Dibunolum and α-tocopherol. For the amides examined, which are diatomic phenols, $f < 4$. The largest values of f (3.3 and 3.6) are observed for amides **III** and **IV**, in which the phenol groups act independently due to their isolated positions. For phenols **I** and **II**, whose structures contain phenolic OH groups involved in the common conjugation system of electron density, f only slightly exceeds 2 (Table 1). Therefore, some OH groups in these compounds do not participate in the reaction with the free radicals. This can be due to the fact that the salicylamides form complexes with intra- and intermolecular hydrogen bonds due to the presence of the phenolic OH groups. The possibility of formation of monomers and H-bonded dimers of acetylsalicylic acid and methyl salicylate was demonstrated in an earlier study [13]. Therefore, it seems necessary to investigate the supramolecular organization of the salicylamides.

The formation of supramolecular structures in solutions was studied by IR spectroscopy for amide **II** as an example. The results are presented in Fig. 1. The IR spectrum exhibits ν(OH) (3644 cm^{-1}) and ν(NH) (3450 cm^{-1}) bands due to stretching vibrations of the phenol and amide groups, respectively [14]. The spectrum of amide **II** also contains a band at 3529 cm^{-1}, which arises from composite vibrations of the benzene rings. The position of these bands reflects the electronic effects of the π–π- and π–ρ conjugations.

The broad complex absorption band at 2300–3400 cm^{-1} is due to the phenolic OH group involved in the formation of intra- and intermolecular hydrogen bonds [13, 14]. It is difficult to identify the hydrogen bonds, because strong absorption due to the =C–H and –C–H bonds is observed in the 2800–3100 cm^{-1} range.

To obtain additional proofs for the existence of hydrogen bonds in the structure of amide **II**, this compound was deuterated. A comparative analysis showed that the absorption bands of the nonbonded OH (3644 cm^{-1}) and NH (3454 cm^{-1}) groups do not change their positions upon deuteration, but their intensity decreases (Fig. 1). The spectra of the deuterated molecules show bands due to O–D and N–D bonds uninvolved in hydrogen bonding, whose frequencies are 2686 and 2561 cm^{-1}, respectively. A new broad doublet with maxima at 2250 and 2175 cm^{-1} is observed in the low-frequency spectral range. The appearance of this band indicates the presence of O–D hydrogen bonds, which is due to the Fermi resonance interaction of frequencies and, summarily, to the difference transitions involving the low-frequency vibrations of the D bond [15]. The position of the band of the OH group involved in the formation of hydrogen-bonded structures and the position of the band of the OD group in a similar complex are known to be related by the formula $\nu(OH) = \sqrt{2\nu(OD)}$. Calculations show that, in the initial undeuterated structure, the hydrogen bond absorbs at 3045 and 3150 cm^{-1}. Two maxima on

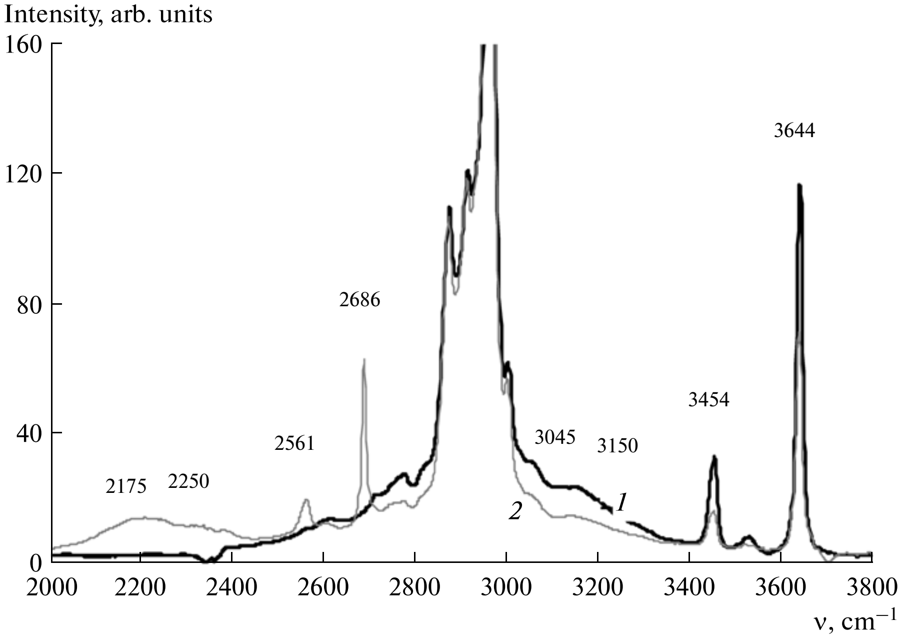
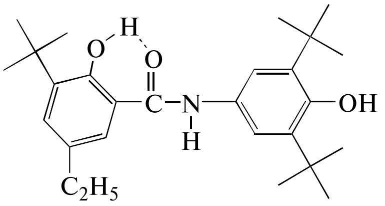
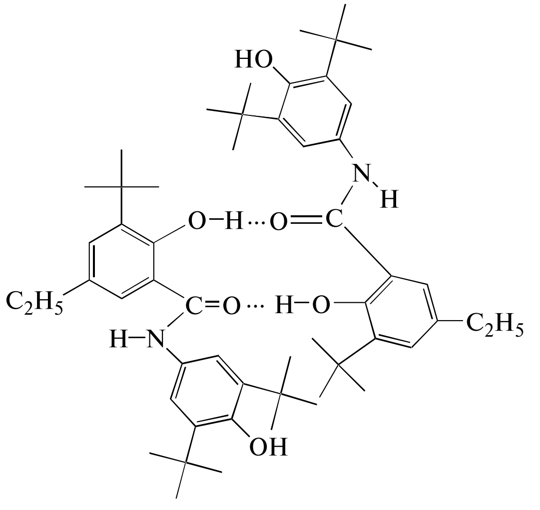


Fig. 1. IR spectra of amide **II** (10^{-2} mol/L) in CCl_4: (*1*) initial compound and (*2*) the same compound partially deuterated at the OH and NH groups.

the shoulder of the intense absorption of the =C–H and –C–H groups are indeed observed just in this range. The intensity of this doublet decreases as a result of deuteration, which additionally confirms the presence of hydrogen bonds. Thus, the phenol groups of the salicylamides participate in the formation of complexes with intra- and intermolecular hydrogen bonds. The presumable structures of these complexes are presented below.





The probability of the formation of complexes with intermolecular hydrogen bonds for the salicylamides decreases with a decreasing salicylamide concentration and with increasing solution temperature.

It follows from the above observations that, in aprotic solvents, such as ethylbenzene, some phenolic OH groups of the amide derivatives of salicylic acid are not involved in the reaction with peroxyl radicals, which explains the decrease in the stoichiometric inhibition factor *f*.

The antioxidant effects of the amides examined and Dibunolum as a reference were compared by determining the values of the induction period (τ_{ind}) in the oxidation of the model substrate in the presence and in the absence of inhibitors. The value of τ_{ind} reflects the complexity and multistep character of the process and characterizes the overall inhibiting effect of the AO under certain reaction conditions. The induction period was determined as the segment on the time axis cut by the perpendicular dropped to the abscissa from the intersection point of the tangents to the kinetic curve at its inflection points.

The process was initiated by the thermal decomposition of AIBN. The resulting radicals $r^{\bullet}$ were replaced by radicals $RO_2^{\bullet}$ of the substrate, which led the oxidation process:

$$r^{\bullet} \xrightarrow{O_2} rO_2^{\bullet} \xrightarrow{RH} R^{\bullet} + rOOH \xrightarrow{O_2} RO_2^{\bullet}.$$

Figure 2 shows that all of the compounds at comparable concentrations inhibit the oxidation of MO. The highest efficiency is displayed by compounds **III** and **IV**, which are sterically hindered phenols with conjugated fragments separated by three methylene groups.

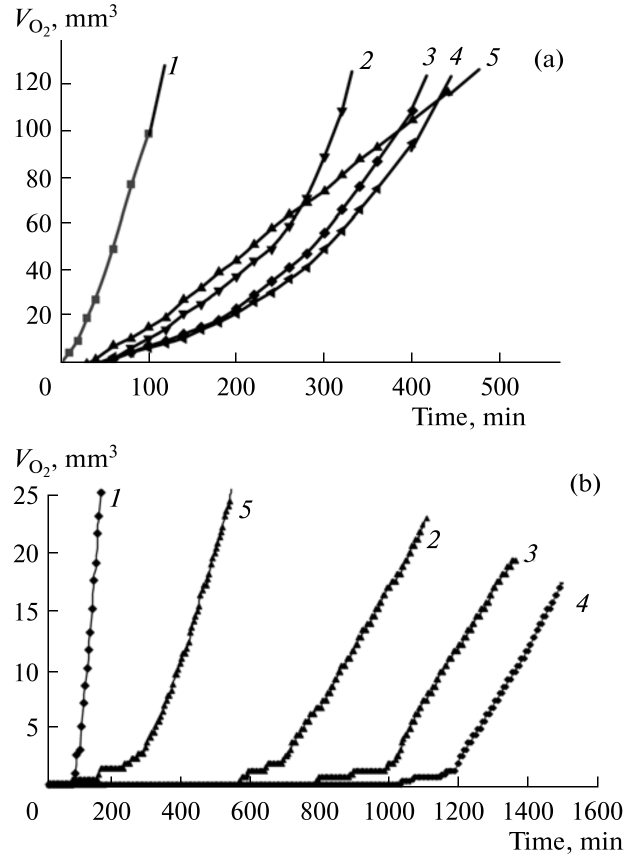


Fig. 2. Kinetics of oxygen uptake by MO in chlorobenzene upon the initiation of the reaction with (a) AIBN (w_i = 4.2 × 10^{-8} mol L^{-1} s^{-1}) and (b) UV irradiation (w_i = 0.6 × 10^{-8} mol L^{-1} s^{-1}): (*1*) MO (without AO), (*2*) MO + amide **II**, (*3*) MO + amide **III**, (*4*) MO + amide **IV**, and (*5*) MO + amide **I**. The AO concentration is 2 × 10^{-4} mol/L, 60°C.

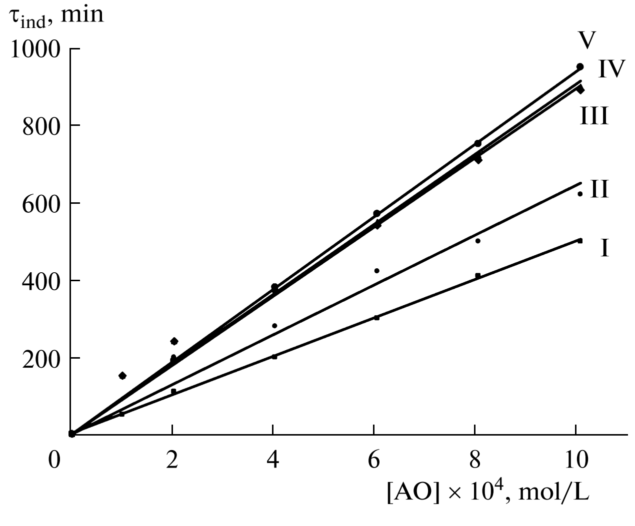


Fig. 3. Dependences of the induction period on the concentration of amides **I**–**IV** and **V** for AIBN-initiated oxidation; w_i = 4.2 × 10^{-8} mol L^{-1} s^{-1}, 60°C.

The inhibiting effect of each salicylamide was studied in a wide range of concentrations (from 5 × 10^{-5} to 1 × 10^{-3} mol/L). The plots of the induction period versus AO concentration are shown in Fig. 3. Compounds **III** and **IV**, which are sterically hindered diatomic phenols, are comparable in efficiency with the monoatomic phenol Dibunolum. In spite of the presence of two phenol groups, amides **I** and **II**, with the highest degree of electron density conjugation, are substantially inferior to Dibunolum and compounds **III** and **IV**.

Thus, among the N-substituted amides of salicylic acid, diatomic phenols produce the highest overall inhibiting effect. In these phenols, the OH groups are screened by the *ortho-tert*-butyl substituents and the salicylamide and phenol residues are separated by the bridging fragment consisting of three methylene groups.

In order to elucidate the effect of the amides on the peroxide accumulation kinetics, we studied how [ROOH] changes upon the introduction of an AO into partially oxidized linoleic acid. The experiments were carried out at room temperature. The results are presented in Fig. 4. The effects of all amides were approximately the same: after the inhibitor was introduced, the ROOH concentration in the system decreased almost to the initial level and did not increase at the later stages of the process. In the blank experiment (without AO), peroxides continued to accumulate. The hydroperoxides ROOH decomposed in the presence of the AOs at comparable rates (Table 2). It can be assumed that the decomposition does not proceed via a radical route, because no further accumulation of the primary oxidation products was observed. The ability of the N-substituted salicylamides to decompose ROOH is probably due to the presence of the amide group. Thus, the amides can inhibit the oxidation process due to both the efficient scavenging of $RO_2^{\bullet}$ radicals and the decomposition of the hydroperoxides via a molecular mechanism. The antiradical activity of the inhibitors is due to the presence of the phenolic hydroxyl group in their chemical structure, and their capability to decompose ROOH is due to the presence of the amide group.

Salicylic acid and its derivatives can absorb ultraviolet radiation. Some researchers believe that these compounds can inhibit UV-initiated oxidation by absorbing part of the UV radiation. It is assumed that these properties of the salicylamides can make them more efficient than other phenols under conditions of UV-initiated oxidation. To verify this hypothesis, we studied the UV absorption spectra of the compounds examined here versus the absorption spectrum of dibunolum (Fig. 5). The salicylamides actually absorb light between 300 and 365 nm, including the 301–305 range, which is the most dangerous in respect of melanoma development. The absorption maxima in the spectra of amides **I** and **II** are shifted to longer wavelengths (340 and 325 nm, respectively) relative to the same maxima for amides **III** and **IV** (311 and 316 nm, respectively). The bathochromic shift of the absorption maxima qualitatively distinguishes the most conjugated structures **I** and **II** from structures **III** and **IV**, in which the conjugated fragments of the molecules are separated by three methylene groups. Figure 5a demonstrates that Dibunolum is practically nonabsorbing in this spectral range.

In connection with the above observations, we studied the overall inhibiting effect of the AOs under conditions of UV-initiated oxidation. The radiation of the mercury lamp fitted well the absorption range of the salicylamides (313–365 nm).

The generation of free radicals under UV irradiation is due to the transfer of the energy of a light quantum to an O_2 molecule in the ground, triplet state, which yields active singlet oxygen O_2^*, whose electrons have opposite spins and lie on one ($^1\Delta g$) or different ($^1\Delta g^+$) 2ρ–ρ* orbitals [16]. Oxygen O_2^* adds to the double bond of unsaturated lipids to form dioxyethane derivatives, which then isomerize to hydroperoxides. The latter decompose photochemically to yield hydroxyl and alkoxyl radicals, which are exchanged by reacting with the substrate in an oxygen atmosphere for peroxide radicals $RO_2^\bullet$ carrying the oxidation chains [17].

The oxygen uptake curves of for the steady-state UV-initiated oxidation of a solution of the substrate and salicylic acid derivatives with a total volume of 2.0 cm^3 are shown in Fig. 2b. The initiation rate w_i was estimated by the inhibitor method using dibunolum as the reference AO. This value was determined to be 0.6×10^{-8} mol L^{-1} s^{-1}, smaller than for the process initiated by AIBN ($w_i = 4.2 \times 10^{-8}$ mol L^{-1} s^{-1}). The results of the comparative study of the concentration dependences of the inhibiting effects of dibunolum and salicylamides under the UV initiation conditions are presented in Fig. 6. Compound **IV** exhibits the highest efficiency, and the inhibition periods in the presence of amide **III** and Dibunolum at comparable concentrations almost coincide. As for the AIBN-initiated oxidation, under the UV-irradiation conditions amides **I** and **II** are substantially inferior in inhibiting effect to the compounds whose structures contain the conjugated molecular fragments separated from each other.

Thus, under different oxidation conditions, the separation of the salicylamide and phenol residues in the molecule by the bridge of three methylene groups provides a nearly twice higher efficiency than is observed for the compounds in which these fragments are conjugated. Regardless of the initiation method, sterically hindered phenols exhibit a stronger inhibiting effect, which is explained by the low activity of the resulting phenoxyl radicals in side chain propagation reactions [18].

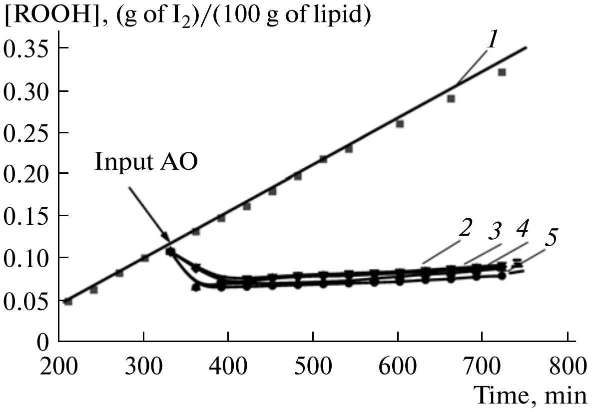


Fig. 4. Kinetics of hydroperoxide accumulation in the autooxidation of linoleic acid in the presence of the salicylamides: (*1*) blank experiment (in the absence of AO) and (*2–5*) amides **I**, **II**, **III**, and **IV**, respectively. The AO concentration is 2 × 10^{-4} mol/L, 60°C.

Knowing the initiation rate, induction period, and factor *f* determined by the chemiluminescence method (Table 1), one can estimate the concentration [InH] at which the efficient inhibition of the oxidation process is attained (effective concentration) using the equation $f[\mathrm{InH}] = \tau_{\mathrm{ind}} w_i$ [10]. This concentration may differ from the actual AO concentration and depends on the structural features of the AO, on the possibility of its interaction with other components of the mixture to produce synergistic or antagonistic effects, and on the oxidation conditions. It was shown above that some of the salicylamides cannot participate in inhibition because of intra- and intermolecular bond formation. For this reason, it was of interest to confirm or reject this hypothesis by investigating the kinetics of inhibited oxidation. For this purpose, we compared [InH] found from the kinetic data and the actual concentration of the AO. The data in Table 3 show that, for the AIBN-initiated oxidation, the calculated values of [InH] for all N-substituted salicylamides is somewhat smaller than, and those for dibunolum and α-tocopherol are comparable with, the inhibitor concentration that was actually used in the inhibition of

Table 2. Kinetics of hydroperoxide accumulation in the autooxidation of linoleic acid in the presence of AO

AO	Rate of ROOH decomposition × 10^{-4}, (g I$_2$)/(100 g lipid) s^{-1}	Degree of decomposition of ROOH in 7 h, %
Without AO	5.52	–
I	3.81	72.9
II	3.33	71.7
III	3.42	71.9
IV	3.48	72.2

Note: AO concentration of 2 × 10^{-4} mol/L, 60°C.

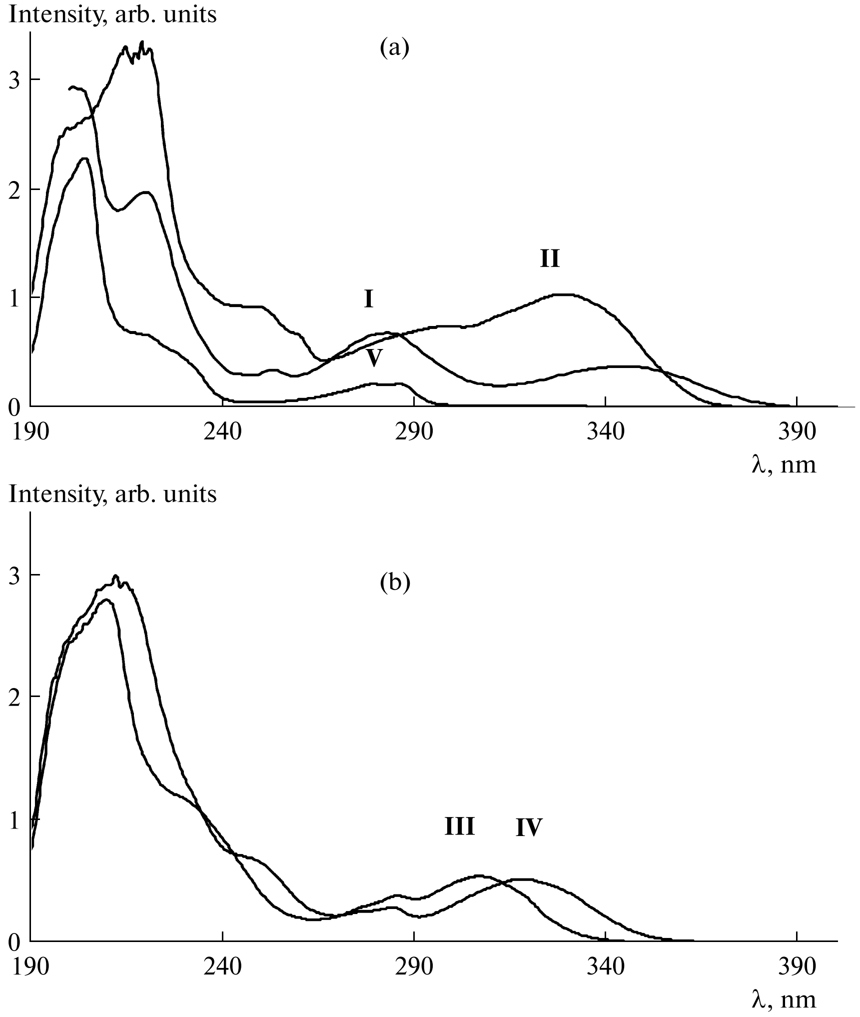


Fig. 5. UV spectra of the amide derivatives of salicylic acid: (a) **I**, **II**, and **V**; and (b) **III** and **IV** (heptane as the solvent, AO concentration of 5×10^{-4} mol/L).

the process (2×10^{-4} mol/L). Evidently, this is due to the presence of intra- and intermolecular hydrogen bonds in the amide molecules. The possibility of formation of these bonds in CCl_4 and heptane at relatively low temperatures was noted above. The kinetics of inhibited MO oxidation was studied at 60°C and relatively low AO concentrations. Under these conditions, the complexes with intermolecular hydrogen bonds are usually unstable, unlike the complexes with intramolecular hydrogen bonds.

The differences between the actual value of [InH] and the calculated concentration for the AIBN-initiated oxidation can be due to the specific features of the supramolecular organization of solutions of the compounds in MO. It was earlier shown that phenolic AOs form complexes with a hydrogen bond between the OH group of phenol and a basic site in the MO molecule, namely, –C=O (carbonyl) and $-OCH_3$ (alkoxyl) groups [19]. The MO–α-tocopherol association constant is rather low: at 20 and 60°C, it is 2.58 and 1.20 L/mol, respectively [19]. The hydroperoxides resulting from oxidation can also interact with phenol [19, 20]. Under our experimental conditions, the ratio of the initial AO and substrate (MO) concentrations was 1 : 3300; hence, theoretically, a certain part of the AO molecules could be in the form of AO–substrate association species and in the form of complexes having intramolecular hydrogen bonds. The data presented in Table 3 show that the reactions of α-tocopherol and Dibunolum with the substrate under the chosen oxidation conditions practically does not affect the efficiency of the AO. Therefore, the formation of intramolecular hydrogen bonds discovered for the N-substituted salicylamides by IR and UV spectroscopy exerts an effect on the kinetics of inhibited oxidation, decreasing the efficiency of AO.

For UV-initiated oxidation, the calculated value of [InH] is smaller than the actual concentration by a factor of 2–4 (Table 3). Obviously, these significant discrepancies are due to the photolysis of phenols that occur under irradiation.

We studied the photochemistry of the N-substituted salicylamides. Figure 7 shows the IR spectra of amide **II** recorded before irradiation and after the AO solution was irradiated over different periods of times through the slit of the KF window, which was separated by a distance of 10 cm from the radiation source. It can be seen that irradiation-induced changes are mainly observed for the absorption bands of the nonbonded OH group (3644 cm^{-1}) and amidic NH group (3454 cm^{-1}). The absorption at $\nu = 3454$ cm^{-1} remains unchanged during the UV irradiation of the studied salicylamides, because it arises from composite vibrations of the benzene rings. The UV irradiation of the solutions of amide **II** gives rise a band at 3424 cm^{-1}, which is due to photolysis products of presumably quinoid structure, and the intensity of this band increases during the process.

One of the intermediate products of the photoionization of phenols (ROH) is the phenoxyl radical $RO^{\bullet}$ [21, 22]. The flash photolysis of amide **II** yields a long-lived intermediate, namely, phenoxyl radical, which was detected by UV spectroscopy. Its optical spectrum consists of two absorption bands at 480 and 380 nm (Fig. 8a). The phenoxyl radicals are known to disappear mainly via recombination [10, 21, 22]. The kinetic curve describing the decline of absorbance at 380 nm is shown in Fig. 8b. The disppearance of the phenoxyl radicals obeys a second-order law. The phenoxyl recombination rate constant for amide **II** is $2k_{rec} \approx 4.6 \times 10^8$ L mol^{-1} s^{-1}, which is equal to the recombination rate constants of a number of sterically hindered phenoxyls forming unstable dimers [10]. Thus, both the substrate and the phenolic AOs undergo photoconversion under UV irradiation. Therefore, the AO concentration that actually participates in the inhibition of the process decreases substantially upon UV-initiated oxidation.

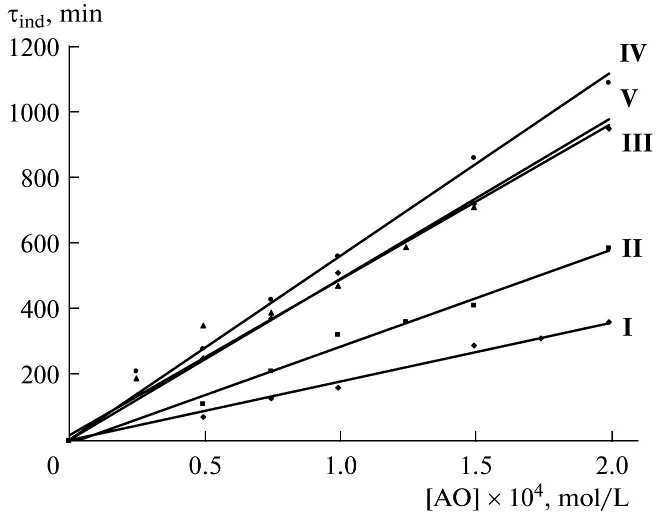


Fig. 6. Dependence of the induction period on the concentration of amides **I–IV** for the UV-initiated oxidation of MO ($w_i = 0.6 \times 10^{-8}$ mol L^{-1} s^{-1}).

The above results show that the N-substituted salicylic acid derivatives exhibit antiradical and antioxidant activities and can decompose hydroperoxides. Their inhibiting effect depends substantially on their chemical structure. The sterically hindered phenols in which the salicylic acid residue and the N-substituent are separated by three methylene groups (amides **III** and **IV**) exhibit the highest activity. These compounds are comparable with dibunolum in their inhibiting effect. Due to the specific features of their chemical structure, the N-substituted salicylamides in aprotic solvents exist in part as supramolecular complexes,

Table 3. Kinetic characteristics of the antioxidant effect of compounds **I–VI**

Compound	Initiator					
	AIBN ($w_i = 4.2 \times 10^{-8}$ mol L^{-1} s^{-1})			UV radiation ($w_i = 0.6 \times 10^{-8}$ mol L^{-1} s^{-1})		
	τ_{ind}, min	f[InH] × 10^4, mol/L	[InH] × 10^4, mol/L	τ_{ind}, min	f[InH] × 10^4, mol/L	[InH] × 10^4, mol/L
I	110	2.8	1.15	360	1.3	0.5
II	220	5.5	2.10	585	2.1	0.8
III	240	6.0	1.80	950	3.4	1.0
IV	240	6.0	1.68	1090	3.9	1.0
V	190	4.2	2.1	960	3.5	1.7
VI	160	4.0	2.0	550	2.0	1.0

Note: AO concentration of 2 × 10^{-4} mol/L, 60°C.

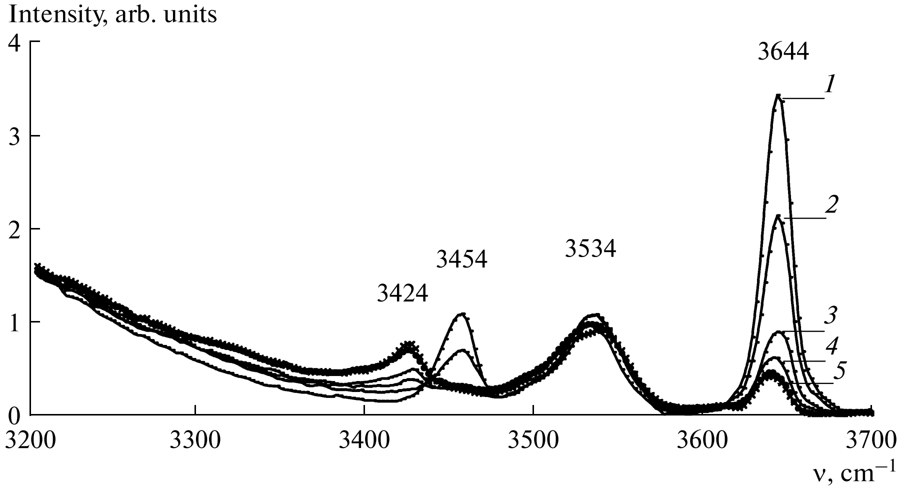


Fig. 7. IR spectra recorded under conditions of the steady-state photolysis of amide **II** (5×10^{-3} mol/L) in CCl_4 1, 2, 3, 4, and 5 min after the beginning of irradiation (*1–5*, respectively).

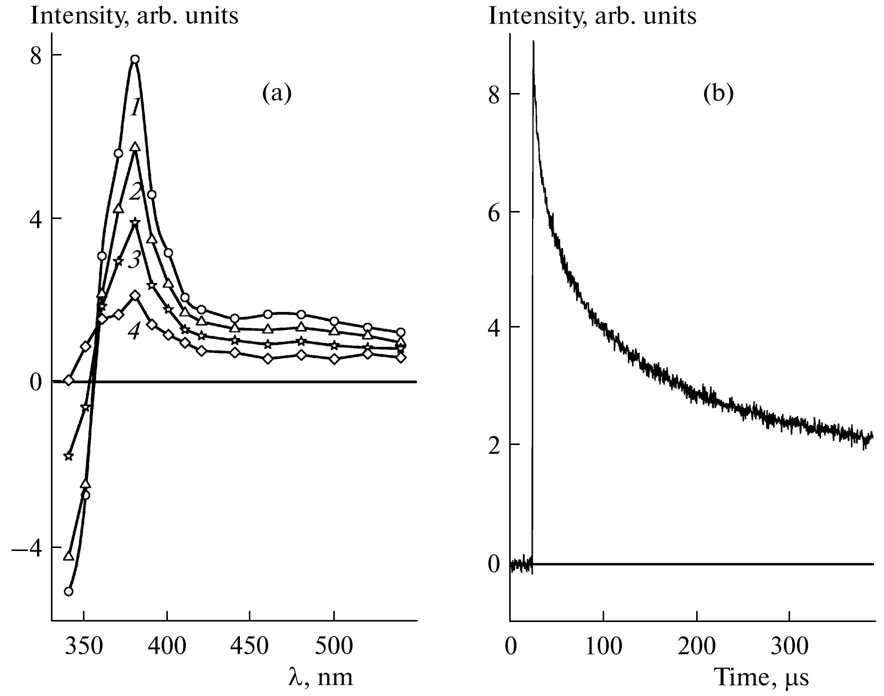


Fig. 8. (a) Absorption spectra of the intermediate resulting from the flash photolysis of amide **II** (3.45×10^{-4} mol/L) in heptane at an oxygen concentration of 3×10^{-3} mol/L in the solution. Laser pulse duration: (*1*) 3, (*2*) 12, (*3*) 90, and (*4*) 380 μs. (b) Kinetics of the disappearance of the photolysis products absorbing at 380 nm.

specifically, monomers with intramolecular hydrogen bonds and dimers with intermolecular hydrogen bonds. Their formation involves the OH group of the salicylic acid residue, which cannot interact, for this reason, with free radicals. As a consequence, the inhibition factor *f* for these compounds is smaller than for the diatomic phenols. Therefore, it would be pertinent to carry out the directed synthesis of N-substituted amides based on *para*-hydroxy- or *para*-aminobenzoic acids, which form no complexes having intramolecular hydrogen bonds.

Upon photoinitiation, some phenols undergo photolysis to form phenoxyl radicals decaying via a second-order reaction. The photolysis of the N-substituted salicylamides yields stable products with the quinoid structure.

The high efficiency of the N-substituted salicylamides having a bridging fragment (three methylene groups) between the salicylic acid residues and the sterically hindered phenol makes them promising inhibitors for the oxidation of various lipids.

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