(h = 15 cm, d = 3 cm). Substantial spontaneous heating was observed in the zone of contact of the solution with aluminum oxide. It was eluted with a 1:3 mixture of ethyl acetate and hexane. As the solution of the substances advanced along the column, heating of the adsorbent was also observed. From the eluent we isolated 0.48 g (~38%) of the dipyridyl (VI), colorless crystals, mp 110-110.5°C (from heptane). PMR spectrum (C_6D_6, 250 MHz): 8.32 (d, 4-H); 9.35 (d, 6-H); 7.04 (d, 4'-H); 7.0 (d, 5'-H); 2.06 (n.s, 3-CH_3); 2.09 (n.s, 3'-CH_3); 7.1-7.3 ppm; (m, 10H, phenyl protons); J: 2.2 (4-H, 6-H); 8.0 (4'-H, 5'-H); 0.8 (4-H, 3-CH_3); 0.7 Hz (4'-H, 3'-CH_3). Found: C 85.8; H 6.0; N 8.3%; M^+ 336. $C_{24}H_{20}N_2$. Calculated: C 85.7; H 6.0; N 8.3%; M 336.

After isolation of the dipyridyl VI, 0.23 g (12%) of the dibromide V was eluted; colorless crystals, which begin to decompose at 180°C. PMR spectrum ($CDCl_3$, 250 MHz): 1.97 (s, NH); 2.37 (s, 3-CH_3); 1.80 (s, 3'-CH_3); 7.72 (d, 4-H); 8.54 (d, 6-H); 4.23 (n.s, 2'H); 4.93 (t, 4'-H); 4.57 (d.d, 6'-H); 2.55 (m, 5'-H_a); 2.22 ppm (m, 5'-H_e); J: 2.7 (4'-H, 5'-H_e); 3.3 (4'-H, 5'-H_a); 2.7 (5'-H_e, 6'-H); 11.5 (5'-H_a, 6'-H); —14.5 Hz (5'-H_a, 5'-H_e). Found: N 5.3; Br 32.2%. $C_{24}H_{24}Br_2N_2$. Calculated: N 5.6; Br 32.0%.

B. We boiled 3 g (8.82 mmoles) of the piperidylpyridine I and 4.5 g (18.44 mmoles) chloranil in 150 ml of benzene with vigorous mixing for 10 h. Then the benzene was distilled off. 15 ml of chloroform was added to the residue, undissolved crystals were filtered off, the mother liquor applied on a chromatographic column with aluminum oxide, (300 g, h = 25 cm, d = 3 cm), and eluted with ether. After the ether was distilled off, the residue (2.3 g) was recrystallized from heptane, yielding 2.1 g (71%) of compound VI, mp 110-110.5°C.

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MECHANISM OF THE ANTIOXIDANT ACTION OF 2,6-DIMETHYL-3,5-DIMETHOXYCARBONYL-4-(2-NITROPHENYL)1,4-DIHYDROPYRIDINE

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A comparison of data on the kinetics of the accumulation of peroxides and the ESR spectra in the case of inhibition of the autooxidation of methyl oleate by 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)1,4-dihydropyridine (I) established that the antioxidant action of the latter is exerted by the formation of a nitroxyl radical. This radical is produced analogously to the well-known scheme from 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrosophenyl)pyridine, which is generated in the reaction medium from I and methyl oleate.

We found [1] that 4-(2'-nitrophenyl)-1,4-dihydropyridines possess antioxidant activity that significantly exceeds the activity of other dihydropyridines and is specifically characteristic only of the o-nitrophenyl derivatives. Such antioxidant activity of these compounds was rather unexpected, since it is usually considered that it is possessed by compounds with extremely pronounced hydrogen donor or electron donor properties or compounds that are stable radicals. Moreover, up to this time it had been observed that the activity of derivatives of 1,4-dihydropyridine, as a rule, was either substantially decreased or disappeared

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TABLE 1. Antioxidant Activity of Compounds in Methyloleate ($c = 7.5 \cdot 10^{-4}$ mole·liter^{-1}, 50°C)

Compound	Name	AOA*
I	2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine	70,0
II	2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrosophenyl)pyridine	85,0
III	2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)pyridine	1,8
IV	2-Nitrosotoluene	38,0

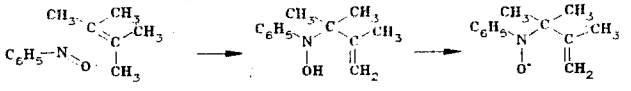
*AOA) relative increase in the induction period of autooxidation of methyl oleate (for the uninhibited reaction the induction period is 3.7 h).

entirely when a substituent, even an electron donor substituent, was introduced into the 4-position, with the exception of derivatives of dihydropyridines possessing weak electron acceptor groups in the 3- and 5-positions.

In testing of the antioxidant activity it was found that a pyridine derivative — 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrosophenyl) pyridine (II, Table 1), produced by photochemical oxidation of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine (nifedipine, phenigidine, I) — possess activity exceeding the activity of the initial compound. At the same time, the pyridine derivative III, produced by chemical oxidation of nifedipine, is active only to a negligible degree. This prompted us to test the antioxidant activity of 2-nitrosotoluene, which can be considered as a component of the molecule of compound II. It was found that 2-nitrosotoluene also possess antioxidant activity in methyl oleate.

The kinetic curve of the accumulation of peroxides in the case of inhibition of autooxidation of methyl oleate by nifedipine (Fig. 1) differs somewhat from the usual curve. Thus, in the initial period (portion A) the accumulation of peroxides occurs more rapidly than during the subsequent period (portion B) of inhibition of the autooxidation reaction, after which the reaction reaches the usual curve of autoacceleration (portion C). From this it can be assumed that in the course of the inhibition reaction, some other, stronger inhibitor is formed. A comparison of these data with the ESR signal intensity of the reaction mixture shows that the portion A corresponds to accelerated accumulation of the radical, which passes through a maximum and decreases at the same period of time, i.e., when the concentration of the inhibitor is decreased on account of consumption. According to the data of the control measurements, methyl oleate of the uninhibited reaction does not give any signals of free radicals either before autooxidation or during autooxidation and after the reaction emerges from the induction period under the conditions selected for recording the ESR spectra.

The results can be explained if we assume that in the initial stage of inhibition of the autooxidation of methyl oleate by nifedipine there is a process similar to that described for nitrosobenzene and 2-nitrosotoluene in the reaction with 2,3-dimethylbutene-2 [2], where it was shown that the nitroso compound, interacting with the alkene, forms a hydroxylamine derivative, readily oxidized to a nitroxyl radical:



Nitroxyl radicals, as is well known [3], are strong antioxidants.

To confirm the presence of the same mechanism in our case, we recorded the ESR spectra in the interaction of methyl oleate with nitrobenzene, 2-nitrosotoluene, nifedipine, and 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrosophenyl)pyridine. Solutions of the substances themselves, both in alcohol and in heptane (concentration $6 \cdot 10^{-3}$ M, room temperature), do not give any ESR signals. At the same time, the spectra of these substances, dissolved in methyl oleate, under the same conditions already indicate the appearance of free radicals after a short time.

A comparison of the characteristics of the ESR spectrum of the products of the reaction of nitrosobenzene with methyl oleate with the data of [2] (Table 2) show that free radicals of the same kind are formed. Since the same ESR signals were also obtained in the interaction

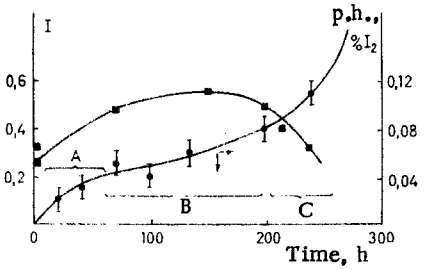
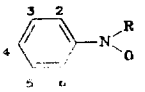


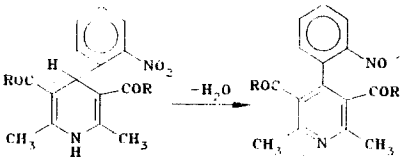
Fig. 1. Kinetic curve of the accumulation of peroxides (-●-) in the case of inhibition of autooxidation of methyl oleate (50°C) by 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl) 1,4-dihydropyridine (c = $6 \cdot 10^{-3}$ M) and relative intensity of the ESR signals (-■-) of the reaction mixture. The first measurements of the concentration of radicals was performed 1 h 30 min after the beginning of the reaction.

TABLE 2. Values of the Constants of the Hyperfine Structure (a, G) of the ESR Spectra of Nitroxyl Radicals



Initial compound	a_N	$a_{H(2,6)}$	$a_{H(3,5)}$	$a_{H(4)}$	$a_{H(R)}$
Nitrobenzene in methyl oleate	10,7	2,7	1,2	2,7	2,7
Nitrobenzene in 2,3-dimethyl-2-butene [2]	11,1	2,44	0,91	2,44	0,43

of 2-nitrosotoluene and 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrosophenyl)pyridine with methyl oleate, it can be assumed that in all cases the addition of the nitroso compound to methyl oleate occurs with subsequent formation of a stable nitroxyl radical — an inhibitor of the autooxidation reaction. In turn, the antioxidant activity of 4-(2-nitrophenyl)-1,4-dihydropyridines, and in particular, nifedipine, is explained by generation of the corresponding nitroso-compound in the reaction mixture, since 4-(2-nitrophenyl)-1,4-dihydropyridines, especially those possessing acyl or alkoxycarbonyl substituents in the 3- and 5-positions of the dihydropyridine ring, are readily oxidized in solutions, for example, photochemically [4], to the corresponding pyridine derivatives with simultaneous reduction of the nitro group to a nitroso group:



To confirm the intramolecular redox processes in compounds of the type of I, their electrochemical investigation was undertaken, the results of which will be reported.

EXPERIMENTAL

The ESR spectra were recorded on an ER-9 spectrometer (Carl Zeiss, Jena) at a rate of scanning of the magnetic field 0.04 G/sec with constant time of recording equal to 0.45 sec and depth of high frequency (100 kHz) modulation of the magnetic field 0.05-0.9 G. The scanning of the magnetic field was calibrated according to the ESR spectrum of the nitrobenzene radical anion [6].

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine and 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-nitrophenyl)pyridine were synthesized and, in the form of chromatographically pure samples, kindly provided by V. V. Kastron. 2,6-Dimethyl-3,5-dimethoxycar-

bonyl-4-(2-nitrosophenyl)pyridine was synthesized according to a somewhat modified procedure of [4] and purified by chromatography on a column with aluminum oxide. Nitrobenzene (Janssen) and 2-nitrotoluene (Aldrich) were used without additional purification. The antioxidant activity was determined according to the procedure of [5].

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SYNTHESIS OF 9-CHLOROPYRAZOLO[4,3-b]QUINOLINES

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A series of 1-methyl-4-arylaminopyrazole-3- and -5-carboxylic acids were synthesized by the reaction of 1-methyl-4-halopyrazole-3- and -5-carboxylic acids with aromatic amines in the presence of a copper catalyst; treatment with phosphorus oxychloride converted them to the corresponding 9-chlorosubstituted 1-methyl-1H- and 2-methyl-2H-pyrazolo[4,3-b]quinolines.

Although pyrazolo[4,3-b]quinolines were produced more than 20 years ago [1], up to the present time no convenient method of their synthesis has been found. The method of [2, 3] are characterized by insufficiently high yields or start with difficult-to-obtain compounds.

Yet, among the isomeric pyrazolo[3,4-b]quinolines, effective optical bleaches [4] and substances possessing a broad spectrum of biological activity [5, 6] have been found.

A convenient method for producing pyrazolo[3,4-b]quinolines, consisting of the interaction of 5-amino-1-methylpyrazole with 2-iodobenzoic acid, followed by treatment of 5-(2-carboxyphenylamino)pyrazole with a condensing agent [7], proved inapplicable to the synthesis of pyrazolo[4,3-b]quinolines in view of the sensitivity of 4-aminopyrazoles to the action of atmospheric oxygen.

We have developed a method including aramination of 1-methyl-4-halopyrazole-3- or -5-carboxylic acids by aromatic amines, followed by treatment of the 4-arylaminosubstituted pyrazolecarboxylic acids with phosphorus oxychloride. The method permits the production of 9-chlorosubstituted pyrazolo[4,3-b]quinolines with a yield of 60-70%.

1-Methyl-4-chloropyrazolecarboxylic acids do not react with aromatic amines. Compound Ia, reacting with pyrazole, forms 1-methyl-4-(1-pyrazolyl)pyrazole-5-carboxylic acid (VII); when other pyrazolecarboxylic acids were used, no replacement of a halogen atom by a pyrazole residue was observed.

Together with arylamination in the interaction with aromatic amines, compounds I and IV undergo reductive dehalogenation with the formation of pyrazolecarboxylic acids.

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