109. F. Marchini, et al., Cardiologia (Basel), 36, 659-662 (1987).
110. M. A. Matlib, J. F. French, I. L. Grupp, et al., Calcium Antagonists in Hypertension, Basel (1988), Abstr. 41.
111. K. Meguro and M. Airava, Chem. Pharm. Bull., 33, 3787-3797 (1985).
112. A. Miura, I. Ukai, and T. Matsizaki, Arzneim.-Forsch., 36, 1323-1326 (1986).
113. M. Ohtsuka, T. Ono, and F. Shibayawa, Calcium Antagonists in Hypertension, Basel (1988), Abstr. 151.
114. M. Safar, J. Duchier, J. Bons, et al.,ibid., Abstr. 187.
115. K. H. Sanders, N. Kolassa, K. D. Beller, et al., ibid., Abstr. 89.
116. Sukemoto Fukuda, Hiroschi Saito, and Shioyki, Kobayashi, ibid. Abstr. 91.
117. T. Takabatake, Y. Yamamoto, S. Nakamura, et al., Eur. J. Clin. Pharmacol., 33, 215-219 (1987).
118. S. H. Taylor, N. C. Jackson, J. Allen, et al., Am. J. Cardiol., 59, 123-129 (1987).
119. T. Tejerina, C. Cauvin, C. Breeman, et al., Calcium Antagonists in Hypertension, Basel (1988), Abstr. 71.
120. Toichi Takenaka, Osamu Inagaki, Michio Terai, et al, Jpn. J. Pharmacol., 39, Suppl. 215 (1985).
121. Udho Thadani, Calcium Antagonists in Hypertension, Basal (1988), Abstr. 163.
122. W. Vater, G. Kronebern, F. Hoffmeister, et al., Arzneim.-Forsch., 22, 1-14 (1972).
123. D. C. Warltier, M. G. Zyvoloski, H. L. Brooks, et al., Eur. Pharmacol., 80, 149-153 (1982).
124. D. Vatanabe, T. Fukutani, H. Ikawa, et al., Chem. Pharm. Bull., 34, 4855-4858 (1986).
125. T. Yamaura, N. Kase, H. Kita, et al., Arzneim.-Forsch., 36, 29-34 (1986).

SYNTHESIS AND ANTIOXIDANT ACTIVITY OF 4-ACYLOXY-3-ACYLMETHANO-2,5,6-TRIMETHYLPHENOLS

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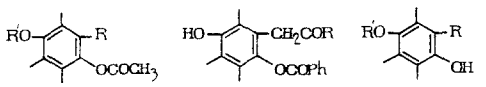
The investigation of synthetic highly effective medicinals with antioxidant-type activity is a significant concern of bio-organic chemistry and pharmacology, as a result of their wide spectrum of potential usage for different pathological conditions accompanying activation of the lipid peroxidation process.

The present portion of work is a logical continuation of our work in progress, searching for new physiologically active substances possessing antioxidant properties in the modified tocopherol series and attempting to establish the connection between their chemical structure and their pharmacological activity [6].

The following compounds, prepared earlier, were used in this study: Ia-h [2, 3, 5, 8], IIa-b [4, 5], IIIa-c [1]:



I a-h II a,b III a,c

R = CH_2COCH_3 (Ia), $CH_2COC_2H_5$ (Ib), CH_2CO-cyclopropyl (Ic), $CH_2COC_6H_5$ (Id, IIIa), CH_2COCH_2Br (Ie), $CH_2C(CH_3)=NNHCONH_2$ (If), $CH_2C(CH_3)=NOH$ (Ig), $CH_2C(CH_3)C(CN)_2$ (Ih,i); CH_3 (IIb), C_6H_5 (IIb), 1-Phenyl-3,5-dimethylpyrazol-4- (IIIb), $CH(COCH_3)_2$ (IIIc); $R^1 = CH_3$ (Ii, IIIa,b), H (Ia-h, IIIc).

The methoxy derivative Ii was obtained by methylation of the dicyano derivative Ih with dimethyl sulfate in acetone.

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EXPERIMENTAL (CHEMICAL)

The IR spectrum of compound Ii was obtained with a UR-20 spectrometer (GDR) in a KBr pellet.

1,1-Dicyano-2-methyl-3-(3-methoxy-6-acetoxy-2,4,5-trimethylphenyl)-propen-1 (Ii). A mixture of 1 g of Ih, 1 ml of dimethyl sulfate, and 1 g of calcined potash was boiled in 15 ml of dry acetone for 5 h. The reaction mixture was then cooled and added to 100 ml of cold water. The precipitate was filtered off and washed with water.

EXPERIMENTAL (BIOLOGICAL)

The antioxidant activity of the compounds was studied on the basis of the auto-oxidation of the methyl esters of unsaturated fatty acids, stimulated by the presence of divalent iron ions. The source of the fatty acid methyl esters was the pharmacopeal preparation linetol [7].

The influence of the studied compounds on the peroxide oxidation of lipids (POL) was studied by the method of [9] in our modification according to which 0.5 g of linetol was treated with 0.25 g of Tween-80 and the mixture was sonicated in 4.25 ml of phosphate buffer (0.05 mole, pH 7.4) in a UZDN-2T ultrasound dispersor (USSR) for 5 min at a frequency of 20 kHz. Then to 0.5 ml of the prepared dispersion was added 0.05 ml of a solution of the studied compound in a known concentration such that the molar ratio in the incubation medium of lipid substance was 500:1. The mixture was brought with phosphate buffer to a final volume of 4.5 ml and POL was stimulated with 0.5 ml of 0.14% aqueous solution of $FeSO_4 \cdot 7H_2O$. The final mixture was incubated at 37°C and aliquots of 0.05 ml were withdrawn after 20, 40 and 60 min to determine lipoperoxide.

The intensity of occurrence of the POL process was measured by the content of lipoperoxide by the method of [10]. The results were treated statistically by means of the Student t test.

It was experimentally shown that the studied series of compounds possesses variable antioxidant activity, depending upon the properties of the substituent R in position 3 of the tri-

TABLE 1. Antioxidant Activity (in relative units) of 4-Acyloxy-3-acylmethano-2,5,6-trimethylphenols and Their Derivatives

Compound	Study time, min			
	0	20	40	60
Control (without addition of antioxidant)	0,140±0,018	0,230±0,020	0,360±0,033	0,530±0,041
α-Tocopherol	0,080±0,009	0,120±0,010	0,195±0,020	0,240±0,025
Ia	0,077±0,008	0,100±0,010	0,155±0,022	0,215±0,029
p	>0,05	0,05	>0,05	>0,05
Ib	0,130±0,015	0,165±0,018	0,237±0,025	0,296±0,030
p	<0,05	<0,05	>0,05	>0,05
Ic	0,130±0,013	0,180±0,020	0,260±0,020	0,310±0,034
p	<0,05	<0,05	<0,05	<0,05
Id	0,095±0,010	0,122±0,015	0,188±0,016	0,230±0,025
p	>0,05	>0,05	>0,05	>0,05
Ie	0,085±0,010	0,105±0,012	0,124±0,014	0,150±0,018
p	>0,05	>0,05	<0,05	<0,05
If	0,125±0,014	0,145±0,016	0,220±0,024	0,280±0,030
p	<0,05	>0,05	>0,05	>0,05
Ig	0,120±0,014	0,135±0,013	0,205±0,022	0,270±0,025
p	<0,05	>0,05	>0,05	>0,05
Ih	0,080±0,009	0,105±0,010	0,120±0,011	0,140±0,015
p	>0,05	>0,05	<0,05	<0,05
Ii	0,130±0,015	0,199±0,020	0,280±0,025	0,395±0,040
p	<0,05	<0,05	<0,05	<0,05
IIa	0,090±0,010	0,115±0,010	0,180±0,019	0,225±0,027
p	>0,05	>0,05	>0,05	>0,05
IIb	0,080±0,009	0,125±0,014	0,195±0,020	0,235±0,019
p	>0,05	>0,05	>0,05	>0,05
IIIa	0,055±0,008	0,086±0,009	0,108±0,010	0,169±0,015
p	<0,05	<0,05	<0,05	<0,05
IIIb	0,075±0,009	0,095±0,011	0,120±0,014	0,190±0,021
p	>0,05	0,05	<0,05	<0,05
IIIc	0,073±0,008	0,115±0,015	0,167±0,018	0,206±0,022
p	>0,05	>0,05	>0,05	>0,05

Note. ρ gives a comparison with α-tocopherol at the corresponding time.

methylphenol derivative. The data shown in Table 1 indicate that the acetoxy derivatives IIa-h posses some antioxidant activity, not exceeding that of α-tocopherol acetate (etalon).

From the study of the influence of different donor-acceptor groups in the acetonyl fragments of the acetoxy derivatives Ia-h clearly show that the antioxidant activity noticeably increased by the use of a less voluminous (compund Ia) and more electronegative substituent (compounds Ie and Ih).

The data indicate the significant influence of the acetonyl groups and some of their modifications of the molecular structure of I on the degree of antioxidant activity and, in part, on the acidity of the phenolic hydroxyl, fulfilling, as is known, a basic role in the inactivation of the POL process. This is confirmed also by the activity of compounds with the structures IIa and IIb where in the presence of the more electronegative unsaturated ester, the benzoyloxy groups increase antioxidant properties by comparison with Ia (Table 1).

At the same time the anisols IIIa and IIIb and the hydroxide IIIc show sufficiently high inhibitory activity in the lipid peroxidation process, exceeding that of α-tocopherol acetate. Structural features of these compounds, in which the OH group is ortho to the carbonyl or the pyrazol-containing substituent, apparently promotes their mutual steric/electronic influence, leading to a strengthening of antioxidant activity.

Thus, these studies indicate the prospects for a search for new highly effective antioxidants in the substituted trimethylphenol series.

LITERATURE CITED

1. I. B. Dzvinchuk, V. P. Makovetskii, Yu. M. Volovenko, et al. Dokl. Akad, Nauk UkrSSR, Ser. B, No. 7 537-540 (979).
2. V. P. Makovetskii, I. B. Dzvinchuk, and A. A. Svishchuk, Ukr. Khim. Zh., 44, No. 12, 1311-1312 (1978).
3. V. P. Makovetskii, I. B. Dzvinchuk, and A. A. Svishchuk, ibid., 45, No. 7, 637-5641 (1979).
4. V. P. Makovetskii, I. B. Dzvinchuk, Yu. M. Volovenko, et al., Dokl. Akad. Nauk UkrSSR, Ser. B, No. 6, 439-442 (1979).
5. V. P. Makovetskii, I. B. Dzvinchuk, Yu. M. Volovenko, et al. Ukr. Khim. Zh., 48, NO. 12, 1299-1302 (1982).
6. V. P. Makovetskii, V. D. Luk'yanchuk, and V. I. Kalinina, Khim.-farm. Zh., No. 12, 1441-1446 (1987).
7. M. D. Mashkovskii, Drug Materials [in Russian], 11th edition, Vol. 2, Moscow (1988), pp. 92-94.
8. A. B. Uzinko, T. K. Nikolavenko, V. P. Makovetskii, et al, Dokl. Akad. Nauk UkrSSR, Ser. B, No. 7, 52-54 (1984).
9. N. Fernandez, A. Valenzuela, and V. Fernandez, Lipids, 17, No. 5, 393-395 (1982).
10. H. Ozawa, N. Ohnishi and K. Yagi, Anal. Biochem., 95, No. 2, 351-358 (1979).