The compounds of group C were prepared by nucleophilic substitution of the bromine atom in 4-bromoacetylaminoantipyrine by a carboxylic acid residue. A mixture of equimolar amounts of 4-bromoacetylaminoantipyrine and the sodium salt of the carboxylic acid in absolute ethanol was refluxed for 15 h with continuous stirring. After cooling, the solid mass was filtered, dried, and treated with hot water. The residue was again filtered, washed with water to negative reaction of bromide ions, and recrystallized from alcohol or dioxane.

The compounds prepared were identified by mp, elemental analyses, and selectively by infrared spectra. The data for the synthesized compounds are presented in Table 1.

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SYNTHESIS OF DIACYLHYDRAZINES AND OXADIAZOLES STARTING FROM 3-PHENYL-5-METHYL-4-ISOXAZOYL HYDRAZIDE

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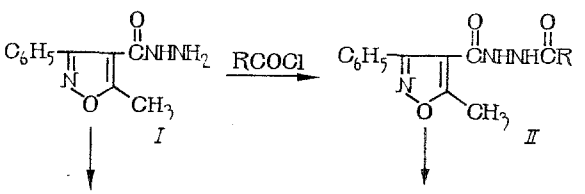
This communication is a continuation of the studies on the synthesis and properties of 3-phenyl-5-methyl-4-isoxazoylhydrazide (I) derivatives [1]. The synthesis and the study of diacylhydrazines (II) and 2- and 2,5-substituted oxadiazoles (III) is reported. These compounds are of interest for biological studies, as some of them were found to show a wide spectrum of physiological activity [2, 3].

The synthesis was carried out according to the following reaction sequence:



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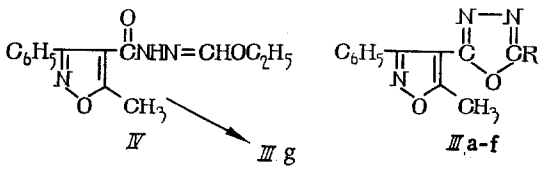

Diacylhydrazines II were prepared by acylation of hydrazide I with the chloroanhydrides of the following acids: furan-2-carboxylic, 5-bromo- and 5-nitrofuran-2-carboxylic, furyl-2-acrylic, and 5-nitrofuryl-2-acrylic. The furancarboxylic acids were prepared according to the published method [4], and their chloroanhydrides, by reaction with thionyl chloride. In the case of acylation of hydrazide I with the chloroanhydride of 3-phenyl-5-methyl-4-isoxazolecarboxylic acid, symmetric disubstituted hydrazine is formed.

2,5-Disubstituted oxadiazoles were prepared by cyclodehydration of diacylhydrazines using phosphorus oxychloride [5, 6]. The 2-substituted oxadiazole IIIg was obtained by reaction of the orthoformate with hydrazide I. An intermediate was isolated from the first stage of the reaction and identified as 1-(3'-phenyl-5'-methyl-4'-isoxazoyl)-2-ethoxymethylenehydrazine [6]. The cyclization of the latter compound yielded the 2-substituted oxadiazole [IIIg].

The structure of the obtained compounds was confirmed by elemental analyses and infrared spectra, while thin layer chromatography showed that they were sufficiently pure. Infrared spectra of 2- and 2,5-substituted oxadiazoles show absorption at 1580 cm^{-1} characteristic of the stretching vibrations of the oxadiazole ring, and in the region 680-740 cm^{-1} due to ring deformation vibrations, according to the reported data [7, 8].

The antitumor activity of the compounds was studied on mongrel mice with transplanted tumors of the following types: sarcoma 180, sarcoma 37, adenocarcinoma AK-755, Lewis tumor, and leucosis L-1210. In view of their low solubility, the compounds were administered in a starch paste.

It was found that the synthetic compounds did not show pronounced antitumor activity. The maximum growth inhibition by compounds IIc and IIIc against adenocarcinoma AK-755 was 21 and 26%, respectively. Compounds IId,f, and IIIb,f,g stimulated adenocarcinoma AK-755 growth by 25-41%.

Investigation of the antiviral activity of the compounds with respect to influenza A2 and B viruses was carried out on developing chicken and mice embryos. The protective index value against A2 influenza virus for some compounds (IId-IIf, IIId-IIIf) is in the range of 30-79%.

EXPERIMENTAL

Infrared spectra were taken on a UR-20 apparatus in vaseline oil. For analytical thin layer chromatography Silufol UV-254 plates were used with solvent system chloroform:benzene: methanol (4:4:1) and UV light (254 nm) detection.

1-(3'-Phenyl-5'-methyl-4'-isoxazoyl-)-2-(furoyl-2") hydrazine (IIa). To a solution of hydrazide I (6.51 g, 0.03 moles) in dioxane (80 ml) is added dropwise the chloroanhydride of furan-2-carboxylic acid (3.9 g, 0.03 moles). The mixture is heated and additional dioxane added if the precipitate does not dissolve on heating; the refluxing is continued for 2 h, and the solution is filtered and cooled; then the precipitate is collected.

Compounds IIb-g are synthesized in an analogous manner. The data are shown in Table 1.

2-(3'-Phenyl-5'-methyl-4'-isoxazolyl)-5-(furyl-2")-1,3,4-oxadiazole (IIIa). To a solution of hydrazine IIa (3.1 g, 0.01 moles) in dioxane is added phosphorus oxychloride (2 ml), and the mixture is stirred at 100°C for 4 h. Then the mixture is poured into cold water and the precipitate collected and washed with cold water.

Compounds IIIb,e,f were prepared in an analogous manner. In the preparation of compound IIId, stirring at 80°C for 4 h is necessary. The data are shown in Table 2.

1-(3'-Phenyl-5'-methyl-4'-isoxazoyl)-2-ethoxymethylenehydrazine (IV). A mixture of hydrazide I (2.17 g 0.01 moles) and freshly distilled orthoformate (7 ml) is heated to boiling. After boiling for 10 min abundant precipitation occurs; the mixture is cooled and the precipitate collected. Yield 91.50%, mp 145-146°C (from absolute alcohol). Calculated for $C_{14}H_{15}N_3O_3$: C 61.53; H 5.53; N 15.37%. Found: C 61.8; H 6.0; N 15.47%.

TABLE 1. Diacylhydrazines II a-f

Compound	R	Yield, %	mp*, °C	Found, %			Empirical formula	Calculated, %			R_f
				C	H	N		C	H	N	
IIa	2-Furoyl	83,7	203—5	61,79	4,39	13,48	$C_{16}H_{13}N_3O_4$	61,73	4,2	13,49	0,28
IIb	5-Bromo-2-furoyl	94,7	201—3†	49,55	3,18	10,86	$C_{16}H_{12}BrN_3O_4$	49,25	3,09	10,76	0,35
IIc	5-Nitro-2-furoyl	95,8	203—5	54,22	3,6	16,10	$C_{16}H_{12}N_4O_6$	53,93	3,39	15,72	0,36
IId	CH = CH-2-furyl	99,0	221—2	64,48	4,7	12,66	$C_{18}H_{15}N_3O_4$	64,11	4,48	12,47	0,31
IIe	5-Nitrofuryl-2 CH = CH	96,3	231—2	56,66	3,93	14,68	$C_{18}H_{14}N_4O_6$	56,54	3,69	14,65	0,31
IIf	3-Phenyl-5-methyl-4-isoxazoyl	83,1	207—8	65,95	4,72	14,41	$C_{22}H_{18}N_4O_4$	65,66	4,51	13,92	0,35

*Compound IIa was crystallized from dioxane, IIb,c from aqueous alcohol, IId from aqueous dioxane, IIe from a mixture of alcohol and dioxane, and IIf from alcohol.
†Found: Br, 20.56%. Calculated: Br, 20.47%.

TABLE 2. 2- and 2,5-Substituted 1,3,4-Oxadiazoles IIIa-g

Compound	R	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			R_f
				C	H	N		C	H	N	
IIIa	2-Furoyl	98,0	87—8	65,47	3,86	14,0	$C_{16}H_{11}N_3O_3$	65,52	3,52	14,32	0,67
IIIb	5-Bromo-2-furyl	96,8	204—6†	51,15	2,85	11,37	$C_{16}H_{10}BrN_3O_4$	51,63	2,7	11,28	0,62
IIIc	5-Nitrofuryl-2	89,0	130—1	56,86	3,07	16,84	$C_{16}H_{10}N_4O_5$	56,8	2,97	16,56	0,67
IIId	Furyl -2-CH = CH	97,3	124—6 (decomp.)	67,73	4,36	12,86	$C_{18}H_{13}N_3O_3$	67,7	4,1	13,15	0,62
IIIe	5-Nitrofuryl-2-CH = CH	79,0	177—9	59,5	3,17	15,46	$C_{18}H_{12}N_4O_5$	59,34	3,32	15,37	0,69
IIIf	3-Phenyl-5-methyl-isoxazolyl	82,4	114—6	69,07	4,3	15,0	$C_{22}H_{16}N_4O_3$	68,74	4,21	14,57	0,72
IIIg	H	99,7	58—60	63,52	4,02	18,63	$C_{12}H_9N_3O_2$	63,43	3,99	18,49	0,52

*Compounds IIIa,c,f were crystallized from alcohol, IIIb from dioxane, IIId,g from aqueous ethanol, and IIIe from a mixture of alcohol and dioxane.
†Found: Br, 21.08%. Calculated: Br, 21.47%.

2-(3'-Phenyl-5'-methyl-4'-isoxazolyl)-1,3,4-oxadiazole (IIIg). A mixture of hydrazide I (2.17 g, 0.01 moles) and freshly distilled orthoformate (20 ml) is refluxed for 15 h and the ester is removed under reduced pressure. The data are given in Table 2.

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SYNTHESIS AND ANTIVIRAL ACTIVITY OF SOME BENZO-2,1,3-THIADIAZOLE DERIVATIVES

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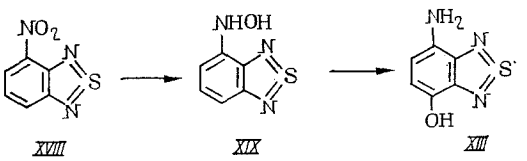
It is known that some of the naphthalene derivatives show antiviral activity [1, 2]. Since benzo-2,1,3-thiadiazoles are similar to naphthalene and its derivatives in some chemical, physical, and physicochemical properties [3], it was of interest to synthesize some benzo-2,1,3-thiadiazole derivatives as well as 2,1,3-thiadiazoledicarboxylic-4,5 acid (I) (a conversion product of the former compounds) and study their antiviral activity.

4,7-Dioxo- and 5-methyl-4,7-dioxobenzo-2,1,3-thiadiazoles (II, III) were prepared by the oxidation of the corresponding benzo-2,1,3-thiadiazole derivatives [4-6] (Table 1). The identity of quinones II and III was established by paper and thin-layer chromatography as well as by UV spectroscopy.

Compound VIII was prepared by reacting compound VII with acetic anhydride. This reacted with phosphorus oxychloride to form the chloro derivative which, in its turn, was easily hydrolyzed to yield compound IX. By reaction of potassium persulfate with an alkaline solution of 4-hydroxybenzo-2,1,3-thiadiazole (XV), followed by acid hydrolysis, compound X was isolated. 4-Methylamino- and 4-dimethylaminobenzo-2,1,3-thiadiazoles (XI, XII) were also prepared [7]. 4-Hydroxy-7-aminobenzo-2,1,3-thiadiazole (XIII) was prepared by two new methods. 4-Hydroxylaminobenzo-2,1,3-thiadiazole (XIX) was prepared by reduction of 4-nitrobenzo-2,1,3-thiadiazole (XVIII); it was easily rearranged in the acid media to give XIII, whose O,N-diacetyl derivative was identical to that obtained by another method [5].



XVIII XIX XIII

The other method of preparing XIII was based on the formation of a mixture of two isomers on nitrosation of compound XV. 4-Hydroxy-5-nitrosobenzo-2,1,3-thiadiazole (XX) was isolated as a complex with cobalt dichloride; it was dissolved in 25% ammonia and filtered, the filtrate was treated with hydrogen sulfide, and compound XIII was isolated from the residue. The

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