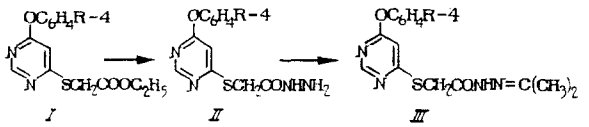
SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF HYDRAZINE DERIVATIVES OF (6-PHENOXY-4-PYRIMIDINYLTHIO) ACETIC ACIDS

P. I. Vainlavichyus, V.-S. M. Rochka,
V. Yu. Syadyaryavichuyute, A. A. Denene,
A. B. Beganskene, M. I. Krenyavichene,
and L. G. Abramova

UDC 615.272.4:547.854.
298.012.1.07

Earlier [3] we showed that ethyl esters of (6-phenoxy-4-pyrimidinylthio)acetic acids (I) have hypolipidemic and pesticidal activities. During our search for new biologically active compounds we have sythesized hydrazines (II) and isopropylidenehydrazones (III) of (6-phenoxy-4-pyrimidinylthio)acetic acids.

Ethyl esters I contain three groups that are susceptible to nucleophiles: the ester, methylene, and phenoxy groups. At a temperature of 18-20°C hydrazine hydrate attacks only the ester group of compounds I and hydrazines II are formed in high yields (90-96%). Reaction of the latter with acetone proceeds smoothly at room temperature (18-20°C) and leads to corresponding isopropylidenehydrazones III.



I II III

R= a)-CH3; b)-H,c.-F; d)-Cl

The structures of the prepared compounds were confirmed by elemental analyses and PMR spectra. For isopropylidenehydrazones III conformational Z,E-isomers are possible as a result of hindered rotation around the N–CO bond. In accordance with the criteria by which with PMR spectroscopy are identified geometric and conformational isomers in the series of hydrazines [1, 4, 12] and acylhydrazones [5, 9, 11]. The signal at 1.75-1.78 ppm in the spectra of compounds IIIa, b, d recorded in $CDCl_3$, is assigned to the methyl group in cis-position with the (pyrimidinylthio)acetic amide moiety relative to the C=N bond, and the lower-field signal at 1.95-1.98 ppm to the methyl group in trans-position to that moiety. The signals of the protons of the SCH_2 group at 3.76-3.80 and 4.30-4.31 ppm, and the signals of the protons of the NH groups at 8.88-9.11 and 10.02-10.14 ppm are assigned to the Z- and E-conformers, respectively. The PMR spectrum of compound IIIc, taken in CF_3COOH, differs significantly from the PMR spectra of compounds IIIa, b, d recorded in $CDCl_3$. First, it contains only one signal for the protons of the SCH_2 group, which is evidence of the presence of one conformer in CF_3COOH solution. Secondly, in addition to the signals of methylene protons at 2.23 and 2.26 ppm, there is one more signal at 1.89 ppm. The total intensity of all three signals corresponds with six protons. Appearance of a high-field signal of protons of the methyl groups probably originates from partial addition of CF_3COOH to the C=N bond of acylhydrozone IIIc [10].

EXPERIMENTAL (CHEMICAL)

The course of the reactions and the purity of the compounds were monitored by TLC on Silufol plates. PMR spectra recorded on a Tesla BS487C spectrometer (80 MHz) at 33°C, internal standard hexamethyldisiloxnae. The solvent was CF_3COOH for compounds II and IIIc, and $CDCl_3$ for compounds IIa, b, d. Data of elemental analyses corresponded with calculated values.

Ethyl esters of [6-(4-substituted-phenoxy)-4-pyrimidinylthio]acetic acids I were prepared according to [3].

V. Kapsukas Vilnius University. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 11, pp. 55-57, November, 1991. Original article submitted April 20, 1988.

 0091-150X/91/2511-0822$12.50

TABLE 1. Physico-Chemical Properties of Compounds II and III

Compound	Yield %	MP., °C	Empirical formula
IIa	90	123—125	$C_{13}H_{14}N_4O_2S$
IIb	96	102—104	$C_{12}H_{12}N_4O_2S$
IIc	95	122—124	$C_{12}H_{11}FN_4O_2S$
IId	96	114—116	$C_{12}H_{11}ClN_4O_2S$
IIIa	90	141—143	$C_{16}H_{18}N_4O_2S$
IIIb	95	127—129	$C_{15}H_{16}N_4O_2S$
IIIc	85	152—154	$C_{15}H_{15}FN_4O_2S$
IIId	90	144—146	$C_{15}H_{15}ClN_4O_2S$

Note. Compounds IIa-d were crystallized from ethanol, IIIa-d from acetone.

TABLE 2. PMR Spectra of Compounds II and III

Compound	PMR spectrum, δ, ppm
IIa	1,98 (s 3H, CH_3), 3,88 (s 2H, SCH_2), 6,54 (s, 1H, 5-CH), 6, 60 (d, j=8 Hz, 2H, Harom), 6,89 (d j=8 Hz., 2H, Harom), 8,45 (s, 1H, 2-CH)
IIb	3,90 (s 2H, SCH_2), 6,58 (s, 1H, 5-CH), 6,96 (m, 5H, Harom 8,45 (s 1H, 2-CH)
IIc	3,90 (s, 2H, SCH_2), 6,65 (m,1H, 5-CH), 6,80 (m, 4H, H_{arom}), 8,47 (s 1H, 2-CH)
IId	3,91 (s, 2H, SCH_2), 6,69 (s, 1H, 5-CH), 6,73 (d J=8 Hz, 2H, H_{arom}), 7,08 (d J=8 Hz, 2H, H_{arom}), 8,45 (s 1H, 2-CH)
IIIa	1,75 (s, CH_3, *E*) 1,98 (s, CH_3, *Z*), 2,29 (s, 3H, CH_3), 3,76 (s, SCH_2, *Z'*), 4,30 (s, SCH_2, *E'*), 6,68 (s, 1H, 5-CH), 7,04 (m, 4H, H_{arom}), 8,53 (s,1H, 2-CH), 8,93 (s,NH, *Z'*), 10,05 (s NH, *E'*)
IIIb	1,76 (s, CH_3 *E*), 1,95 (s. CH_3, *Z*), 3.78 (s SCH_2, *Z'*), 4.30 (s SCH_2, *E'*), 6,70 (s, 1H, 5-CH), 7,16 (m, 5H, Harom), 8,51 (s,1H, 2-CH), 9,11 (s, NH, *Z'*), 10,14 (s,NH, *E'*)
IIIc	1,89 [s, $C(CH_3)_2$)], 2,23 (s CH_3, *E*), 2,26 (s, CH_3, *Z*), 3,93 (s, 2H, SCH_2), 6,63 (s, 1H, 5-CH), 6,75 (m, 4H, Harom), 8,44 (s, 1H, 2-CH)
IIId	1,78 (s, CH_3, *E*), 1,98 (s, CH_3, *Z*), 3,80 (s,SCH_2, *Z'*), 4,31 (s, SCH_2, *E'*), 6,78 (s, 1H, 5-CH), 7,18 (m, 4H, *Z'*), 4,31 (s, SCH_2, *E'*), 6,78 (s, 1H, 5-CH), 7,18 (m, H_{arom} 8,53 (s, 1H, 2-CH), 8,88 (s NH, *Z'*), 10,02 (s, NH, *E'*)

Hydrazides of [6-(4-substituted-phenoxyl)-4-pyrimidinylthioacetic Acids (II). At room temperature, 10 mmole of compound I is dissolved in 10 ml of ethanol and with stirring is added dropwise 2 g (40 mmole) of 99% hydrazine hydrate. The reaction mixture is kept at the same temperature for 0.5 h, the precipitate is filtered off, and crystallized.

Isopropylidenehydrazides of [6-(4-substituted-phenoxy)-4-pyrimidinylthio]acetic Acids (III). A mixture of 10 mmole of compound II and 25 ml of acetone is kept at room temperature for 0.5 h. The precipitate is filtered off and crystallized.

Data on compounds II and III are summarized in Tables 1 and 2.

EXPERIMENTAL (PHARMACOLOGICAL)

The hypolipidemic activity of the compounds was studied in male white rats that received the compounds under investigation perorally as a suspension in 1% starch glue for 7 days. On the eighth day the rats were decapitated and in the blood serum we determined the total cholesterol content with method of Il'k using a selection of standard reagents, triglycerides with the color reaction with chromotropic acid [6], and high-density lipoprotein (HDL) cholesterol with the precipitation method with heparin and manganese chloride [13]. Results were compared with data obtained from the blood serum of rats of the control group. The groups consisted of ten animals. LD_{50} was calculated by the method of Litchfield and Wilcoxon [2].

TABLE 3. Acute Toxicity and Hypolipidemic Activity of Compounds II and II

Compound	LD_{50} mg/kg	Dose, mg/kg	Change of biochemical parameters of lipid metabolism by the compounds under investigation, %		
			total cholesterol	HDL cholesterol	triglycerides
IIa	460 (410.7–515.2)	100	+9.8	+11.9	6.6
IIb	220 (110.0–440.0)	100	−20.4*	+8.8	−25.2*
IIc	400 (235.5–680.0)	100	−12.0	+6.4	+11.7
IId	800 (470.6–1360.0)	50	−8.9	+4.9	−10.5
		100	−20.0*	+21.6	18.1
		200	21.6*	+7.0	+5.0
IIIa	900 (520.6–1395.0)	100	+6.1	+18.4	3.4
IIIb	1075 (741.4–1558.8)	100	25.1*	+6.8	34.1*
IIIc	380 (230.3–627.0)	100	6.3	+10.5	−27.8*
IIId	450 (300.0–675.0)	100	−17.5*	+5.8	14.0
Miscleron	1250	100	−27.9*	−22.4	−38.3*

*p = 0.05.

Results are given in Table 3. Six of the eight compounds showed hypolipidemic activity. With regard to activity an toxicity, compound IIIb is closest to miscleron. Analysis of data on the structure-activity relationship in the series of studied compounds points to the fact that substituting the ethoxy group in esters I for a hydrazine group leads to increased toxicity and has practically no influence on hypolipidemic activity. The effect of the substituent at the benzene ring on the hypolipidemic activity in the series of hydrazines II and hydrazones III is the same as in the series of ethyl esters I [3]. It is advisable to take these data into consideration in the search for active hypolipidemic pre parations among the series of derivatives of pyrimidinecarboxylic acids.

EXPERIMENTAL (BIOLOGICAL)

We have studied the fungicidal and herbicidal activity of compounds II and III by standard methods [7, 8]. Fungicidal activity in vivo is shown by compounds IIa, d and IIIb-d. They suppress the growth of phytophtora infection in tomatoes in comparison with the reference zineb by 76%. Herbicidal activity approaching that of the reference is shown by compounds IIa, b, d and IIIa, b, d. In comparison with the control, they suppress the growth of mustard in the case of treatment in the vegatation period by 80-100%.

LITERATURE CITED

1. I. P. Bekhan, V. A. Khrustalev, K. N. Zelenin, and B. P. Nikolaev, Zh. Org. Khim., 14, 754-759 (1978).
2. M. L. Belen'kii, Elements of the Quantitative Determination of a Pharmacological Effect [in Russian], 2nd edn. Leningrad (1963), pp. 81-106.
3. P. I. Vainilavichyus, V.-S. Rochka, V. Yu. Syadyaryavichyute et al., Khim.-farm Zh., 23. 705-707 (1989).
4. K. N. Zelenin, I. P. Bekhan, and N. V. Dovginevich, Zh. Org. Khim., 20, 1977-1982 (1984).
5. K. N. Zelenin, V. V. Pinson, A. A. Potekhin et al., Zh. Org. Khim., 14, 490-495 (1978).
6. V. G. Kolb and V. S. Kanyshnikov, Handbook of Clinical Chemistry [in Russian], Minsk (1982), pp. 201-248.
7. Methodical Recommendations for the Detection of Insecticidal-Acaricidal, Growth-Regulating, and Other Types of Actions of Compounds on Arthropoda [in Russian], Scientific Research Institute of Technical and Economic Research, Soviet Ministry of the Chemical Industry (NIITÉKhIM), Cherkassy (1984).
8. Methodical Recommendations for the Determination of Fungicidal Activity of Novel Compounds [in Russian], Scientific Research Institute of Technical and Economic Research, Soviet Ministry of the Chemical Industry (NIITÉKhIM), Cherkassy (1984).

9. A. I. Rutavichyus, S. P. Valyulene, and V. V. Mozolis, Zh. Or. Khim., 23, 1198-1203 (1987).
10. T. J. Curphey, J. Am. Chem. Soc., 87, 2063-2064 (1965).
11. G. Palla, G. Predieri, P. Domino, et al., Tetrahedron, 42, 3649-3654 (1986).
12. W. Walter and K.-J. Reubke, Chem. Ber., 103, 2197-2202 (1970).
13. G. R. Warnick and J. J. Alberts, J. Lipid Res., 19, 65-76 (1978).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF THE PERIODATE OXIDATION PRODUCT OF MANNAN

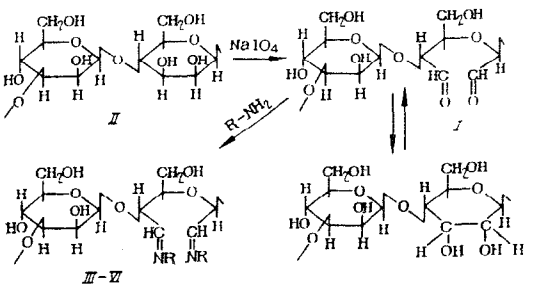
I. G. Smirnova, E. S. Korbelainen,
A. N. Stukov, K. S. Movsesyan,
N. E. Kil'maeva, T. A. Korosteleva,
V. A. Filov, and B. A. Ivin

UDC 615.31:547.458].012.1.07

At the present time, among the numerous classes of biologically active compounds, polysaccharides are being increasingly widely studied. This is because some of them stimulate the nonspecific resistance of the organism to bacterial and viral infections, display cancerostatic and detoxifying action, and cause a prolongation and intensification of the action of chemotherapeutic preparations [1-3].

As known, the problem of immunostimulation and immunoregeneration is of great importance in the complex treatment of malignant neoplasmas [4]. This is primarily related to the inherent nature of the immunological defectiveness of the organism, on the background of which malignant tumors originate and develop, and also due to the immunodepressive action of the radiation sickness and chemotherapy. At the present time intense research is being carried out in the search for preparations having antitumorigenic activity combined with an immunostimulating effect.

In the present work, we report the synthesis of mannan polyaldehyde (I) from microbial polysaccharide (II) mannan, produced by the yeast cultures of Rhodotorula rubra and the study of its antitumorigeneic and immunodulating activity.



Polyaldehyde I was obtained by the periodate oxidation of II with a molecular weight of 40000-60000. The dependence of the consumption of $NaIO_4$ on time shows that the maximal amount of $NaIO_4$, 0.5 mole per fragment of the polysaccharide, undergoes the reaction in the course of 10-12 h, and no further $NaIO_4$ is consumed.

During the periodate oxidation of mannan which is comprised of a chain consisting of alternating β-1,4 and β-1,3-bound mannopyranose units only the β-1,4-bound fragments undergo the oxidation. In the ^{13}C NMR spectrum of solution of I in DMSO-d_6, signals are observed of carbon atoms of β-1.3-bound unit (δ, ppm); 100.6 [C(1)]; 68.2 [C(2)]; 79.2 [C(3)]; 64.8 [C(4)]; 77.1 [C(5)]; 61.2 [C(6)] and the signals of β-1.4-bound fragment which were present in the spectrum of the initial II are absent (cf. [6]).

Leningrad Chemical Pharmaceutical Institute. N. N. Petrov Scientific-Research Institute of Oncology, Leningrad. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 11, pp. 57-59, November, 1991. Original article submitted March 6, 1990.

