SYNTHESIS AND BIOLOGICAL ACTIVITY OF ETHYL (6-PHENOXY-4-PYRIMIDINYLTHIO)ACETATES

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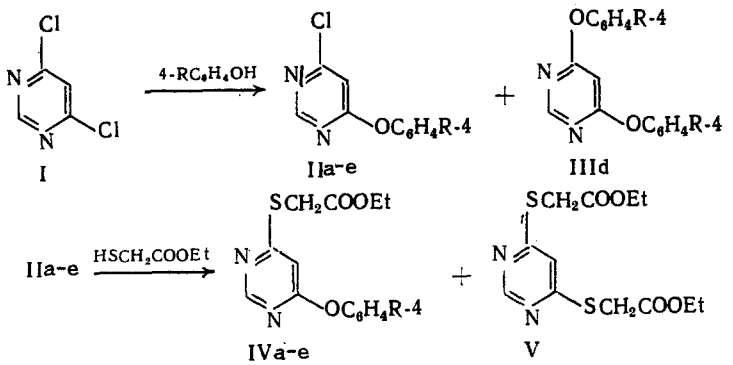
It has been found [2] that some (4-pyrimidinylthio)acetic acid derivatives possess hypolipidemic activity. Continuing this investigation, we have synthesized the ethyl (6-phenoxy-4-pyrimidinylthio)acetates (IVa-e). The rationale for introducing substituted phenoxy groups into the 6-position of the pyrimidine ring was that some phenoxypyrimidines show biological activity [3, 7-9, 12].

The reaction between equimolar amounts of (I) and 4-chlorophenol in ethanol in the presence of EtONa gave a mixture of mono- (IId) and bis-(4-chlorophenoxy)pyrimidine (IIId) in a ratio of 1:1. Similar results were obtained when the reaction was carried out in the weakly polar, aprotic solvent toluene, in the presence of potassium carbonate. The pure 6-phenoxy-4-chloropyrimidines (IIa-e) were obtained by phase-transfer catalysis (phases aqueous sodium hydroxide and dichloroethane, catalyst tetrabutylammonium bromide). The duration of the reaction and the yields of (II) depended on the substituent R. Electron-donor substituents accelerated the reaction and raised the yields of phenoxypyrimidines (II), while electron-acceptor substituents had the opposite effect.



R = CH_3 (a), H (b), F (c), Cl (d), NO_2 (e)

The 6-phenoxy-4-chloropyrimidines (II) were reacted with ethyl thioglycolate (ETC) as described in [2]. The course of the reaction was highly dependent on the concentration of ETG in the reaction mixture. For example, when the ETG was added all at once to (IId), both the chlorine in the 4-position and, to some extent, the 4-chlorophenoxy group in the 6-position, underwent nucleophilic replacement, with the result that the required product (IVd) was accompanied by the undesired product (V). This side reaction could be avoided by maintaining an excess of (II) in the reaction mixture by the gradual addition of the ETG.

The structures of (II-IV) were confirmed by elemental analysis and the ^1H NMR spectra. The ^1H NMR spectra of (IIa-e) showed signals for the pyrimidine ring protons in the 5- and 2- positions at 6.71-7.11 and 8.30-8.61 ppm, respectively, together with signals for the benzene protons with splitting characteristic of p-substitution. In the ^1H NMR spectra of the ethyl esters (IVa-e), the above-mentioned signals were accompanied by characteristic signals for the thiomethylene protons at 3.81-3.90 ppm, and for the methylene and methyl protons of the ethyl group at 4.04-4.13 and 1.15-1.20 ppm, respectively.

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TABLE 1. Physicochemical Properties of the Compounds

Compound	Yield, %	mp, °C, or bp, °C (mm)	Empirical formula
IIa	91	55—7	$C_{11}H_9ClN_2O$
IIb	86	33—5	$C_{10}H_7ClN_2O$
IIc	78	75—7	$C_{10}H_6ClFN_2O$
IId	79	61—3	$C_{10}H_6Cl_2N_2O$
IIe	37	124—6	$C_{10}H_6ClN_3O_3$
IIId	27	123—5	$C_{16}H_{10}Cl_2N_2O_2$
IVa	68	203—5 (3)	$C_{15}H_{16}N_2O_3S$
IVb	67	208—12 (7)	$C_{14}H_{14}N_2O_3S$
IVc	70	44—6	$C_{14}H_{13}FN_2O_3S$
IVd	75	77—9	$C_{14}H_{13}ClN_2O_3S$
IVe	58	59—61	$C_{14}H_{13}N_3O_5S$
V	18	51—3* (51—51.5 [2])	$C_{12}H_{18}N_2O_4S_2$

Note. Compounds (IIa-e) and (V) were crystallized from hexane, and (IIId) and (IVc-e) from ethanol.

EXPERIMENTAL (CHEMISTRY)

The progress of the reactions was followed and the purity of the products checked by TLC on Silufol plates. Column chromatography was carried out using Chemapol L 100/160 silica gel. ^1H NMR spectra were obtained on a Tesla BS 487C spectrometer (80 MHz) at 33°C, internal standard hexamethyldisiloxane. The solvents used were CCl_4 for (IIa-d) and (IVa-d), CF_3COOH for (IIe) and (IIId), and $CDCl_3$ for (IVe) and (V).

4,6-Dichloropyrimidine (I) was obtained from 4,6-dihydroxypyrimidine [10] as described in [11].

4-Chloro-6-(4-chlorophenoxy)- (IId) and 4,6-Bis-(4-chlorophenoxy)pyrimidine (IIId). A. To a solution of 0.86 g (6.7 mmole) of 4-chlorophenol and 0.46 g (6.7 mmole) of EtONa in 5 ml of absolute ethanol was added dropwise at room temperature a solution of 1 g (6.7 mmole) of 4,6-dichloropyrimidine in 5 ml of absolute ethanol. After stirring for 0.5 h, the precipitated sodium chloride was filtered off, and the filtrate evaporated under reduced pressure. The residue was treated with hot hexane, to give 0.46 g (29%) of hexane-soluble (IId). The hexane-insoluble residue was recrystallized from ethanol to give 0.6 g (27%) of (IIId).

B. To a suspension of 1 g (6.7 mmole) of 4,6-dichloropyrimidine and 0.94 g (6.7 mmole) of potassium carbonate in 5 ml of dry toluene was added a suspension of 0.86 g (6.7 mmole) of 4-chlorophenol in 5 ml of dry toluene. The mixture was boiled with stirring for 2 h, cooled, and diluted with 10 ml of water. The organic layer was separated, washed with water, and dried over calcium chloride. The toluene was removed under reduced pressure, and the residue worked up as in method A, to give 0.84 g (52%) of (IId) and 0.18 g (7.5%) of (IIId).

6-(4-R-Phenoxy)-4-chloropyrimidines (II). To a solution of 1 g (6.7 mmole) of 4,6-dichloropyrimidine in 35 ml of dichloroethane was added dropwise with stirring at room temperature a solution of 6.7 mmole of the 4-substituted phenol, 0.6 g (6.7 mmole) of NaOH, and 0.3 g (0.9 mmole) of tetrabutylammonium bromide in 35 ml of water. The mixture was stirred for 2 h at room temperature, then at 50-70°C for 0.5 h in the case of (IIa), 1 h for (IIb), 2 h for (IIc), and 3 h for (IIe). The organic layer was separated, washed with water, and dried over $CaCl_2$. The solvent was removed, and the residue crystallized.

Ethyl [6-(4-Chlorophenoxy)-4-pyrimidinylthio]acetate (IVd) and 4,6-Bis(ethoxycarbonylmethylthio)pyrimidine (V). A mixture of 2.57 g (10 mmole) of (IId), 1.2 g (10 mmole) of (IId), and 3 ml of triethylamine was heated at 80-100°C for 6 h, cooled, and poured into water. The solid was filtered off, dissolved in a mixture of dichloroethane and ethyl acetate (10:1), and separated on a column [eluent dichloroethane—ethyl acetate (10:1)], to give 1.23 g (38%) of (IVd) (R_f 0.76) and 0.54 g (18%) of (V) (R_f 0.65).

TABLE 2. Acute Toxicities and Hypolipidemic Activity of Test Compounds

Compound	LD_{50}, mg/kg	Dose, mg/kg	Change in biochemical indices of lipid metabolism on treatment with test compounds, as % of controls		
			total cholesterol	HDLP cholesterol	triglycerides
IId	1250	100	—6,8	—1,2	—6,3
IVa	>2000	100	—0,8	—3,4	—15,3*
IVb	1775	100	—16,3*	+8,0	—15,1*
IVc	500	100	—7,5*	+1,4	+34,1
IVd	1100	50	—3,8	+8,9	—5,9
		100	—24,9*	+18,3	—30,3*
		200	—17,8*	+6,4	—16,5*
IVe	>2000	100	+10,5	+4,9	—21,5*
Misclerone	1250	100	—27,9*	—22,4	—38,3*

Note. Doses greater than 2000 mg/kg were not tested. An asterisk indicates P = 0.05.

Ethyl [6-(4-R-Phenoxy)-4-pyrimidinylthio]acetates (IV). To a mixture of 10 mmoles of (II) and 3 ml of triethylamine was added over 0.5 h a solution of 1.2 g (10 mmole) of ETG in 3 ml of triethylamine. The mixture was stirred at 80-100°C for 5-7 h, cooled, and poured into water. In the case of (IVa) and (IVb), the aqueous solution was extracted with dichloroethane, dried over $MgSO_4$, the solvent evaporated, and the residue fractionated in vacuo. In the case of (IVc-e), the solid which separated was filtered off and crystallized.

Data for (II), (IIId), (IV), and (V) are given in Table 1.

EXPERIMENTAL (PHARMACOLOGY)

The acute toxicities of the test compounds were examined in mongrel white mice by the oral route. The dose causing the deaths of 50% of the animals (LD_{50}) was calculated by the method of Litchfield and Wilcoxon [1]. Hypolipidemic activity was examined in male white rats receiving the standard laboratory diet and the test compound for 7 successive days as a suspension in 1% starch mucilage. On the 8th day, the rats were decapitated, and the blood serum concentrations of total cholesterol, high-density lipoprotein (HDLP) cholesterol, and triglycerides determined. The results were compared with the values obtained for the blood serum of rats in the control groups. Each group comprised 10 animals. The total cholesterol was measured by the Ilk method using a standard set of reagents, and triglycerides by the color reaction with chromotropic acid [4]. The HDLP cholesterol was measured by precipitation with heparin and manganese chloride [13].

The test results are shown in Table 2. The acute toxicities of the test compounds in white mice by the oral route are relatively low (the LD_{50} values range from 500 to more than 2000 mg/kg), so that they may be regarded as being in hazard class III. Halogens in the 4-position of the benzene ring increase the toxicity of the esters (IV), fluorine to a greater extent than chlorine. Hypolipidemic activity is seen to depend both on the acid residue and on the benzene ring substituents, although no clear correlation is apparent. The highest hypolipidemic activity (comparable with that of the drug misclerone at the same concentration) was shown by (IVb) and (IVd), i.e., ethyl (6-phenoxy-4-pyrimidinylthio)acetates in which the 4-position of the benzene ring is either unsubstituted or bears a chlorine substituent. Replacement of the chlorine by fluorine, methyl, or nitro markedly reduces the hypolipidemic activity.

EXPERIMENTAL (BIOLOGY)

The insecticidal, acaricidal, fungicidal, and herbicidal activity of compounds (II) and (IV) were examined by standard methods [5, 6].

The results showed that (IVb) and (IVc) display insecticidal and acaricidal activity against rice weevil at a level ten times less than that of the standard, metaphos. Fungicidal activity was shown in vitro by (IIa) and (IId). These inhibited mycelia of Fusarium monofiliforma by 70 and 100% as compared with the standard HMTD. In addition, moderate in vivo herbicidal activity was shown by (IIa, b) and (IVb, c), which suppressed the growth of mustard by 60-80% as compared with the control during the vegetative growth period.

The low toxicities of the novel pyrimidines (II) and (IV) and their activities indicate the desirability of further studies of compounds of these types as potentially biologically active agents.

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SYNTHESIS AND RADIOPROTECTANT PROPERTIES OF SOME S-SUBSTITUTED BIS-(2,2'-MERCAPTOETHYL)AMINES

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It has been found over the last three decades that some of the most active antiradiation agents are aminothiols and their S-derivatives, for example thiophosphates, thiosulfates (Bunte salts), isothiuronium salts, etc. [1, 3, 5, 9, 10].

We here describe the synthesis and examination for radioprotectant activity of the 2,2'-bisthiophosphato- (I), bisthiosulfo- (II), and bisisothiuronium (III) derivatives of dimethylamine.

The compounds were obtained by reacting bis-(2-bromoethyl)amine hydrobromide with Na_3SPO_3, $Na_2S_2O_3 \cdot 5H_2O$, or $SC(NH_2)_2$, as follows:

$$HN(CH_2CH_2Br)_2 \cdot HBr \longrightarrow HN(CH_2CH_2R)_2,$$

where R = $-SPO_3H_2$ (I), $-S_2O_3Na$ (II), $-SC(=NH_2)NH_2^+Br^-$ (III).

EXPERIMENTAL (CHEMISTRY)

Infrared spectra were obtained on a Bruker instrument. 2,2'-Dibromodiethylamine was obtained as described in [7], yield 41.7%, mp 198-199°C (literature mp 198-200°C).

Bis-(2-thiophosphatoethyl)amine (I). To a suspension of 4.46 g (25 mmole) of Na_3SPO_3 in 25 ml of water was added portionwise with vigorous stirring 3.9 g (12.5 mmole) of bis-(2-bromoethyl)amine. After a few minutes, 13 ml of dimethylformamide was added, and the re-

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