5% NaOH in alcohol, and the mixture was allowed to stand at room temperature for 1 h. It was then acidified to pH 1 with concentrated HCl, and the precipitate was removed by filtration, washed with water, and dried to give 0.1 g of product.

Compound IX was similarly synthesized (Table 1).

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1,2,6-PHOSPHADIAZINE-1,3-DIONE DERIVATIVES

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UDC 547.854:543.422.25.4.6

A number of new 1-aryloxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones were obtained from arylphosphoric acid dichlorides through the corresponding diamidophosphoric acid esters. Conversion of the 1-phenoxy and 1-ethoxy derivatives to 6-methyl-4-hydroxypyrimidine under Vilsmeier formylation conditions was observed. These compounds were thionated to give the corresponding 1,3-dithiones; the 1-phenoxy derivative was subsequently methylated in the 6 position and animated to give the phosphorus-containing analog of 6-methyl-2-thiocytosine. The bromination of the 1-ethoxy compound and replacement of the bromine by a secondary amine residue were studied.

1-Alkoxy(aryloxy)-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones are structural analogs of 6-methyluracil. The introduction of hydrophobic or hydrophilic substituents in the uracil molecule affects the ability of the compounds to react with enzymes. We have previously synthesized phosphoric analogs of 6-methyluracil containing various alkoxy groups in the 1 position [1]. In the present paper we describe the preparation of a number of 1-aryloxyphosphadiazinediones (IIa-e) from the corresponding diamidophosphoric acid esters (Ia-e, Table 1) by the method proposed by Zavialov and co-workers [2] for the synthesis of 1-phenoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IIf). The reactivities of compounds of this class were studied in the case of phosphauracil IIf and 1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IIg) in order to create from them analogs of the components of nucleic acids or coenzymes (analogs of uridine, cytidine, and folic acid).*

Bromination of 1-ethoxy compound IIg in carbon tetrachloride–dimethylformamide (DMF) leads to 4-bromo-1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (III), in the UV spectrum of which, as in the spectra of 5-halouracils, a bathochromic shift to 276 nm (Table 3) as compared with the spectrum of the starting compound (λ_{max} 258 nm) is observed. The PMR spectrum does not contain a signal of the 4-H proton, and, as in the spectrum of starting IIg, the signals of the protons of the ethoxy group are doubled because of coupling with the phosphorus atom ($J_{\alpha\text{-HP}} = 9$ Hz, $J_{\beta\text{-HP}} = 1$ Hz).

* See the display at top of next page after Table 1.

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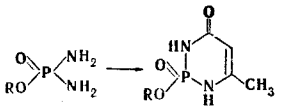
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 972-976, July, 1978. Original article submitted August 1, 1977.

0009-3122/78/1407-0784$07.50

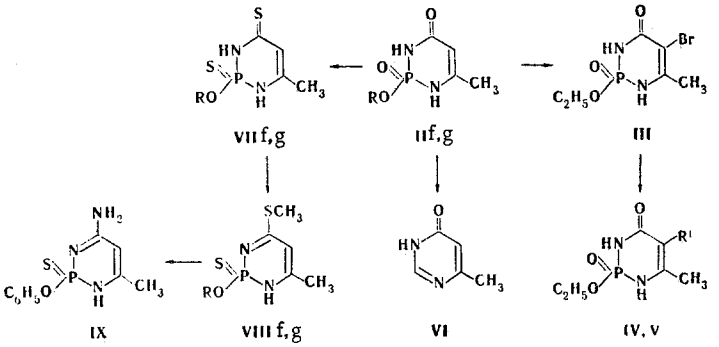
TABLE 1. Diamidophosphoric Acid Esters and 1-Aryloxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones



I a-e II a-e

Compound	R	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
Ia[f]	p-$C_2H_5OC_6H_4$	198—199[a]	44,5	6,1	13,7	$C_8H_{13}N_2O_3P$	44,5	6,2	13,0	70
Ib	p-$NO_2C_6H_4$	174—175[b]	33,6	3,8	19,5	$C_6H_8N_3O_4P$	33,2	3,8	19,4	60
Ic	p-$CH_3C_6H_4$	186—188[a]	45,2	5,9	14,8	$C_7H_{11}N_2O_2P$	45,2	6,0	15,1	60
Id	p-ClC_6H_4	175—176[a]	35,3	4,0	13,4	$C_6H_8ClN_2O_2P$	35,2	3,9	13,6	75
Ie	β-Naphthyl	208—209[a]	53,9	5,3	12,8	$C_{10}H_{11}N_2O_2P$	54,1	5,0	12,6	75
IIa	p-$C_2H_5OC_6H_4$	198—200[c]	50,5	5,3	9,6	$C_{12}H_{15}N_2O_4P$	51,1	5,4	9,9	60
IIb	p-$NO_2C_6H_4$	245—246[a]	42,5	3,7	15,0	$C_{10}H_{10}N_3O_5P$	42,4	3,6	14,8	22
IIc	p-$CH_3C_6H_4$	235—237[d]	52,1	5,3	11,0	$C_{11}H_{13}N_2O_3P$	52,2	5,2	11,1	99
IId	p-ClC_6H_4	249—251[e]	43,7	3,8	9,9	$C_{10}H_{10}ClN_2O_3P$	44,1	3,7	10,3	63
IIe	β-Naphthyl	258—259[e]	54,9	4,9	9,1	$C_{14}H_{13}N_2O_3P \cdot H_2O$	54,9	4,9	9,3	80

[a]From ethanol. [b]From acetonitrile and absolute ethanol. [c]From 60% ethanol. [d]After chromatography in an acetone–water system (2 : 3.5). [e]From 50% ethanol. [f]p-Ethoxyphenylphosphoric acid dichloride had mp 101-102°C (0.4 mm).



VII f,g IIf,g III

IX VIII f,g VI IV, V

IIf, VIIf, VIIIf, R = C_6H_5; IIg, VIIg, VIIIg, R = C_2H_5; IV R' = 4-piperidyl; V R = 4-morpholino

Bromine undergoes exchange with a secondary amine residue in III at room temperature, and the product is obtained in ~30% yield; the starting compound decomposes when the mixture is heated. A hypsochromic shift of the absorption maximum to 262-263 nm as compared with the spectrum of starting III (Table 3) is noted in the UV spectra of the resulting 4-piperidino and 4-morpholino derivatives (IV, V).

An attempt to formylate 1-ethoxy- or 1-phenoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones (IIg or IIf) under the conditions of the Vilsmeier reaction with a twofold excess of the $POCl_3$ · DMF complex at room temperature leads to 4-hydroxy-6-methylpyrimidine (VI) instead of the expected 4-formyl derivatives.* The alternative synthesis of pyrimidine VI was accomplished by desulfuration of 2-thio-6-methoxyuracil [4]. The reaction of the Vilsmeier reagent with IIf produced a precipitate, which was evidently an intermediate of the IIf → VI transformation. According to the results of elementary analysis, this substance does not contain phosphorus. Its PMR spectrum does not contain signals of the protons of the benzene ring. The UV spectrum is characterized by a low molecular extinction value. This intermediate is probably noncyclic and is formed as a result of cleavage of phosphamide bonds (it is known that phosphamides are hydrolyzed in acidic media [5]). Treatment of the precipitate with polar solvents (ethanol, methanol) leads to pyrimidine VI, the PMR spectrum of which contains a singlet of the CH_3 group at 2.34 ppm and 2-H and 5-H singlets at 8.16 and 6.34 ppm, respectively.

4-Thiouracil is incorporated as a minor base in the composition of some t-RNA. The cytostatic effect of 4-thiouracil in a cell culture was observed; this effect is associated with inhibition of the biosynthesis of

*We previously published a brief communication [3].

TABLE 2. 1-Phenoxy(ethoxy)-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione Derivatives

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
III	183[a] (dec.)	26,7	4,1	10,3	$C_6H_{10}BrN_2O_3P$	26,8	3,8	10,4	84
IV	163—165[a] (dec.)	47,9	7,5	15,5	$C_{11}H_{20}N_3O_3P$	48,3	7,4	15,4	28
V	197—198[a] (dec.)	43,4	6,6	14,9	$C_{10}H_{18}N_3O_4P$	43,6	6,6	15,3	30
VI	146—148[b]	54,6	5,8	25,7	$C_5H_6N_2O$	54,6	5,4	25,4	36
VIIf	176—177[c]	44,6	4,3	10,9	$C_{10}H_{11}N_2OPS_2$	44,5	4,1	10,4	91
VIIg	154—155[c]	32,5	5,2	13,6	$C_6H_{11}N_2OPS_2$	32,4	4,9	12,6	79
VIIIf	171—173[c]	46,1	4,8	10,2	$C_{11}H_{13}N_2OPS_2$	46,5	4,6	9,8	57
IX	215—217[c] (dec.)	47,2	4,6	17,0	$C_{10}H_{12}N_3OPS$	47,4	4,8	16,6	36

[a]From ethanol. [b]From benzene. [c]From 50% ethanol.

TABLE 3. Data from the UV and PMR Spectra

Compound	UV spectrum (in ethanol), λ_{max} (log ε)	Chemical shifts, δ, ppm						Solvent
		5-CH_3 ($^4J_{HP}$, Hz)	4-H	CH_2(Et) ($^3J_{HP}$, Hz)	CH_3(Et) ($^4J_{HP}$, Hz)	C_6H_5	SCH_3	
IIf	259 (5,14)	s 1,92	s 4,88			m 7,0—7,40		CD_3OD
III	276 (3,92)	d 2,28 (1)		m 4,06	t 1,20			CD_3OD
IV	263 (3,90)	d 2,46 (2)		m 4,14 (9)	m 1,32 (1)			$CDCl_3$+ +CD_3OD
V	263 (3,90)	d 2,20 (2)		m 4,02 (9)	m 1,28 (0,8)			$CDCl_3$+ +CD_3OD
VIIf	333 (4,31)	s 1,95	s 5,87			m 7,0—7,56		CD_3OD
VIIg	338 (4,17)	s 1,97	s 5,88	m 4,09 (11,2)	t 1,27			CD_3OD
VIIIf	278 (3,90), 318 (3,82)	s 1,96	s 5,36			m6,96—7,48	s 2,43	$CDCl_3$+ +CD_3OD
VIIIg	262 (4,92), 305 (5,07)	s 2,12	s 5,68	m 3,60	t 1,34		s 2,46	CD_3OD
IX	243 (3,87), 283 (3,68)	s 1,86	s 4,90			m 6.80—7,60		$(CD_3)_2SO$

RNA [6]. In this connection, we carried out the thionation of the phosphauracils, taking into account the fact that phosphorus pentasulfide is used not only for the thionation of the keto group but also for the conversion of the phosphoryl group to a thiophosphoryl group [7]. Phosphadiazinedithiones VIIf and VIIg are formed in the reaction of IIf,g with P_2S_5 in refluxing dioxane. The mass spectrum of VIIf contains a molecular ion peak with m/e (here and subsequently) 270, as well as intense peaks of fragment ions corresponding to detachment of a methyl group ($[M-CH_3]^+$ 255), a phenoxy group ($[M-C_6H_5O]^+$ 177 and $[M-1-C_6H_5O]^+$), both of these groups ($[M-1-C_6H_5O-CH_3]^+$ 161), as well as ring cleavage with ejection of a $C-CH_3$ fragment ($[M-1-C_2H_3-C_6H_5O]^+$ 149) and splitting out of C_6H_5O, SH, and CH_3 groups ($[M-1-CH_3-SH-C_6H_5O]^+$ 128). Like 4-thiopyrimidines, thio derivatives VIIf and VIIg are characterized by a strong bathochromic shift in the UV spectra to 330-340 nm. A weak-field shift of the signal of the 4-H proton as compared with the spectra of starting IIf and IIg is observed in the PMR spectra of dithiones VIIf,g; this shift is characteristic for the $-\underset{|}{CH}-\underset{|}{C}=O \rightarrow -\underset{|}{CH}-\underset{|}{C}=S$ transformation (Table 3).

Methylation of VIIf with methyl iodide in the presence of sodium methoxide in methanol leads to the S-methyl derivative (VIIIf). The PMR spectrum contains a signal of the protons of the SCH_3 group as well as a signal of the protons of the 5-CH_3 group. The mass spectrum of derivative VIIIf contains a molecular ion peak at 284, as well as $[M-C_6H_5]^+$ 207, $[M-C_6H_5O]^+$ 191, $[M-1-C_6H_5O-CH_3]^+$ 175, and $[M-1-CH_3-C_6H_5O-CH_3]^+$ 160. The methylation of 1-ethoxy compound VIIg proceeds ambiguously, but the principal product is S-methyl derivative VIIIg (Table 3).

Replacement of the methylthio group in dithione VIIIf by an amino group was carried out by the action of a saturated solution of ammonia in methanol at 100°C for 20 h. A hypsochromic shift of the absorption maxima as compared with the spectrum of starting VIIIf is observed in the UV spectrum of 3-amino-1-phenoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1-thione (IX) (Table 3). The PMR spectrum contains a signal of the PNH proton at 9.13 ppm in the form of a doublet (J_{HP} = 6 Hz), and a multiplet of phenyl protons at 6.60-7.80 ppm, the integral curve of which corresponds to seven protons, is superimposed on the signal of the protons of the NH_2 group. The addition of water brings about exchange of the NH_2 and PNH protons: the integral

curve of the multiplet at 6.60-7.80 ppm in the spectrum recorded at 50°C corresponds to five protons of the phenyl ring. The absence of a signal of the protons of a methyl group at 2.43 ppm (see Table 3) serves as additional confirmation of the VIIIf structure.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a JNM-MH-100 spectrometer with tetramethylsilane as the internal standard. The UV spectra of solutions of the compounds in ethanol (cuvette thickness 1 cm) were recorded with a Unicam SP-800 spectrophotometer. The mass spectra were obtained with an LKV-9000 mass spectrometer at an ionizing-electron energy of 70 eV. Preparative thin-layer chromatography (TLC) was carried out on 20 × 20 cm glass plates in a loose layer of Chemapol LSL-254 5/40 silica gel with a thickness of 1 mm.

Diamidophosphoric acid esters Ia-e (Table 1) were obtained from the corresponding arylphosphoric acid dichlorides as described in [8]. The 1-aryl-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones (IIa-e) (Table 1) were obtained by cyclization of esters Ia-e with diketene in the presence of $HgSO_4$ by the method in [2].

4-Bromo-1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (III). A solution of 0.1 ml (2 mmole) of bromine in 4.5 ml of carbon tetrachloride was added with stirring to a solution of 0.38 g (2 mmole) of 1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione in 3.5 ml of dry DMF, and the mixture was stirred at room temperature for 2 h. The solvent was then removed by vacuum evaporation, the oily residue was triturated with 20 ml of CCl_4, and the mixture was placed in a refrigerator. The resulting precipitate was removed by filtration, washed with CCl_4 and ether, and dried.

4-Piperidyl-1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IV). A 2-ml (20 mmole) sample of piperidine was added to 0.27 g (1 mmole) of bromide III, and the mixture was stirred at room temperature for 2 h. The precipitated piperidine hydrobromide was removed by filtration and washed with piperidine, and the filtrate was vacuum evaporated. The residue was subjected to preparation TLC in a chloroform–methanol system (4 : 1).

4-Morpholino-1-ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (V). This compound was similarly obtained.

4-Hydroxy-6-methylpyrimidine (VI). The Vilsmeier reagent, prepared from 0.25 ml of $POCl_3$ and 0.83 ml of DMF, was added at 0°C to a solution of 0.53 g (2.7 mmole) of 1-ethoxy derivative IIg in 7.5 ml of DMF, and the mixture was stirred at room temperature for 6 h. It was then poured into two volumes of ice water, and the aqueous mixture was neutralized to pH 7 with Dowex-50 (1 × 8) (OH^-). It was then vacuum evaporated, and the residue was chromatographed in a chloroform–methanol system (4 : 3).

B) A 0.95-g (4 mmole) sample of 1-phenoxy derivative IIf was treated with the Vilsmeier reagent as in the preceding experiment. After 4 h, the resulting precipitate was removed by filtration, washed with DMF, and dried. It was then dissolved in ethanol, and the solution was refluxed for 10 min. The solvent was removed by vacuum evaporation, and the residue was subjected to column chromatography in a chloroform–methanol system (3 : 1). The mother liquor was worked up as described in part A, and both portions were combined.

1-Phenoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dithione (VIIf). A 2.22-g sample in P_2S_5 was added to a suspension of 1.19 g (5 mmole) sample of IIf in 25 ml of dry dioxane, and the mixture was refluxed for 45 min. The resulting solution was cooled and filtered, and the solvent was removed from the filtrate by vacuum evaporation. Cold water (5 ml) was added to the residue, and the resulting precipitate was removed by filtration, washed with water, and dried.

1-Ethoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dithione (VIIg). This compound was similarly obtained from IIg.

1-Phenoxy-3-methylthio-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1-thione (VIIIf). A 0.38-g (1.4 mmole) sample of thione VIIf was added with stirring to a solution of sodium methoxide (from 35 mg of sodium and 10 ml of absolute methanol), after which 0.19 ml of methyl iodide was added. After 1.5 h, the solution was vacuum evaporated, 10 ml of chloroform was added to the residue, and the solution was filtered and evaporated.

3-Amino-1-phenoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1-thione (IX). A solution of 0.53 g (1.87 mmole) of VIIIf in 20 ml of dry methanol saturated with ammonia at 0°C was heated in a steel ampul at

100°C for 20 h, after which the mixture was cooled, and the solvent was removed by vacuum evaporation. The residue was chromatographed in a chloroform–methanol system (4:1).

The constants, spectral characteristics, and yields of III-IX are presented in Tables 2 and 3.

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HETEROCYCLIC ANALOGS OF PLEIADIENE

XXXV.* INVESTIGATION OF CHLORINATION OF PERIMIDINE AND ITS 1- AND 2-METHYL DERIVATIVES

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UDC 547.856.7:542.944.2:543.422.25.4.6

The mono-, di-, tri-, and tetrachloro derivatives of perimidine and 1- and 2-methylperimidines were obtained by chlorination with sulfuryl chloride and 1-chlorobenzotriazole. Primarily the 6 and 7 positions are initially attacked by the electrophile in acidic media (SO_2Cl_2–CH_3COOH), whereas the 9 and 4 positions of the perimidine system become more active under neutral conditions (1-chlorobenzotriazole in $CHCl_3$).

The naphthalene ring of the perimidine molecule (Ia) has a high degree of π-surplus character and readily undergoes attack by electrophilic reagents. The 6 and 7 (para) positions are more active in the nitration [2] and acylation [3] of perimidine; the 4 and 9 (ortho) positions are the next most active positions. Electrophilic substitution in the 5 and 8 (meta) positions could not be accomplished. These reactions proceeded most rapidly in strongly acidic media through a perimidinium cation. In the present research we studied the chlorination of some perimidines (Ia-d) with sulfuryl chloride and 1-chlorobenzotriazole (CBT) [4] for the first time. It was assumed that the use of the latter reagent in aprotic solvents would make it possible for the first time to observe electrophilic substitution in the neutral perimidine molecule.

The chlorination of perimidine Ia with an equimolar amount of sulfuryl chloride in acetic acid leads to the formation of a mixture of 6(7)-chloro- and 4(9)-chloroperimidines (IIa and IIIa) in a ratio of 8:1, which are separable by chromatography. The structures of the monochloroperimidines cannot be established by means of the PMR, IR, and UV spectra, since they differ very little for the isomers. It is interesting that ν_{NH} bands appear at 3420-3450 cm^{-1} in the IR spectra of both compounds in dilute solutions in chloroform; this indicates the absence of the intramolecular hydrogen bond that is very characteristic for 4(9)-nitro- and 4(9)-acetylperimidines, which are easily distinguished from the 6(7) isomers on this basis. They were therefore identified by alternative synthesis (by reduction and cyclization with formic acid of 4-chloro- and 2-chloro-1,8-dinitronaphthalenes).

* See [1] for communication XXXIV.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 977-984, July, 1978. Original article submitted July 4, 1977.

0009-3122/78/1407-0788$07.50