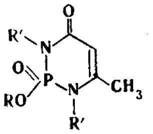
SYNTHESIS AND PROPERTIES OF 1-HYDROXY-5-METHYL-1,2,3,6-TETRAHYDRO-1,2,6-PHOSPHADIAZINE-1,3-DIONE AND ITS ALKYLATED DERIVATIVES

L. D. Garaeva, O. M. Nesterova,
I. S. Levi, B. S. Kikot',
and M. N. Preobrazhenskaya

UDC 547.79'87:543.422.25.4.6

A series of 1-alkoxy(aryloxy)-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-diones (Ia-d) was synthesized by us previously and some chemical properties of these compounds were studied [1]. The problem of the present work was the preparation of the corresponding acid 1-hydroxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (Ie) on the basis of the aryloxy derivatives (I) and the study of the possibility of going to other PO derivatives of this heterocycle.



Ia-e, IIc,d

I $R'=H$; a $R=C_6H_5$; b $R=p\text{-}NO_2C_6H_4$;
I, II c $R=CH_3$; d $R=C_2H_5$; Ie $R=H$;
II $R'=CH_3$

Acid (Ie) was obtained on alkaline hydrolysis or on hydrogenolysis over Adams catalyst of phosphadiazinedione (Ia) by analogy with methods applied in the phenyl phosphate series. The hydrolysis of compound (Ia) was quantitative after 10 h in 1 N NaOH at 50°C and its hydrogenolysis in ethanol took approximately 1 h. In the synthesis of the 1-p-nitrophenoxy derivative (Ib) from the corresponding phosphoric acid diamide and diketene in glacial acetic acid [1] in the presence of traces of moisture, compound (Ie) was formed in place of the ester (Ib).

On careful methylation of acid (Ie) with diazomethane the methyl ester (Ic) was isolated in about 19% yield. Its UV spectrum was similar to the spectrum of the ethoxy derivative (Id). In the PMR spectrum of compound (Ic) there was a signal for methoxy grup protons at 3.69 ppm as a doublet due to interaction with the nucleus of the phosphorus atom ($^3J_{HP}$ = 12 Hz) (Table 1). On exhaustive methylation of acid (Ie) with diazomethane a mixture of methylation products was formed, the main (73%) one being 1-methoxy-2,5,6-trimethyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IIc). The interaction of the 1-methoxy derivative (Ic) with diazomethane also led to products of further methylation, the main one being compound (IIc).

A product of di-N-methylation (IId) was also formed (64%) on treating ethyl ester (Id) with diazomethane. The PMR spectrum of compound (IIc) contained signals for two methyl groups at 3.14 and 3.18 ppm ($^3J_{HP}$ = 6.8 and 7.6 Hz) (Table 1). The signals for the protons of the two methyl groups of compound (IId) had the shape of two doublets at 3.04 and 3.19 ppm ($^3J_{HP}$ = 7.8 and 8.2 Hz). The close values of the spin-spin interaction constants of the protons of both methyl groups with the nucleus of the phosphorus atom indicates that these groups are in the same disposition to it. This demonstrates that the products of exhaustive methylation correspond to structures (IIc) and (IId). In other words methylation actually proceeds at the nitrogen atoms and the possible alternative 3-methoxy-6-methyl derivative is not formed.

The direct transesterification of esters (Ia-d) also seemed of interest. In the work of Ogilvie and co-workers [2, 3] the transesterification of triphenyl phosphate and di(trichloroethyl)alkyl phosphates with primary alcohols in the presence of CsF was described.

Oncological Scientific Center, Academy of Medical Sciences of the USSR, Moscow 115478.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1415-1419, October, 1979. Original article submitted March 7, 1979.

0009-3122/79/1510-1142$07.50

TABLE 1. Data of PMR Spectra of Compounds (Ic, IIc, d)*

Compound	Chemical shifts, δ ppm						
	C_5—CH_3	CH_3 (Et) ($^4J_{HP}$, Hz)	N—CH_3 ($^3J_{HP}$, Hz)	N′—CH_3 ($^3J_{HP}$, Hz)	OCH_3 ($^3J_{HP}$, Hz)	CH_2 (Et) ($^3J_{HP}$, Hz)	C_4—H†
Ic	s, 2,07				d, 3,69 (12)		s, 5,06
IIc	s, 2,11		d, 3,10 (6,8)	d, 3,18 (7,6)	d, 3,67 (12)		s, 5,24
IId	s, 2,16	t, 1,31 (I)	d, 3,04 (7,8)	d, 3,19 (8,2)		q, 4,03 (1,8)	s, 5,24

---

*(Ic) and (IId) in CD_3OD; (IIc) in $CDCl_3$.

†The C_4—H proton is readily exchanged in deuterated solvents.

TABLE 2. UV Spectra of Compounds (Ia, d, e, IIc, d) and Their Ionized Forms

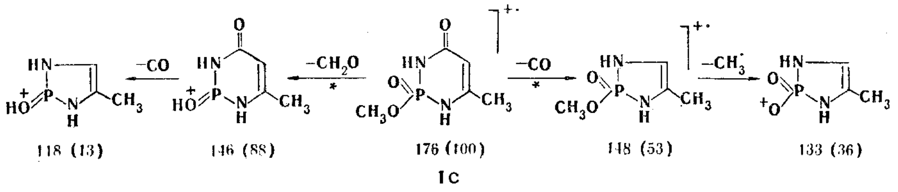
Compound	Ethanol, neutral form λ_{max}, nm (log ε)	Aqueous solutions					
		neutral form		singly charged form		doubly charged form	
		λ_{max}, nm (lg ε)	pH	λ_{max}, nm (lg ε)	pH	λ_{max}, nm (lg ε)	pH
Ia	260 (4,05)	264 (4,05)	1—6	269 (3,85) 292 (3,66)*	0,1 N KOH	289 (4,06)	0,1—5 N KOH
Id	260 (4,05)	264 (4,05)	1—6	267 (3,87) 292 (3,57)*	0,1 N KOH	290 (4,01)	0,1—5N KOH
Ie	272 (4,00)	274 (4,00)	1 N HCl	274 (4,00)	5—12	279 (3,81)	2 N KOH
IIc	271 (4,02)	275 (4,02)					
IId	270 (3,95)	275 (3,95)					

---

*Shoulder.

The conversion of compound (Ia) into (Ic) was achieved by us in methanol in the presence of CsF in a yield of more than 70%. The reaction also goes in ethanol with the formation of ester (Id).

The character of the fragmentations of compounds (Ic, d, IIc, d) under the action of an electron beam were similar. Molecular ion peaks were the most intense. The main directions of fragmentation were the ejection of radicals from the alkoxy groups and the splitting out of CO with the formation of ions with a five-membered ring:



In the mass specturm of methoxy derivative (Ic) the intensity of the $(M - CH_3)^+$ (m/e 161) ion peak was only 3% of that of M^+. Splitting out of CO occurred both from the molecular ion and from the ion which had lost an alkoxy group. The fragmentation scheme shown was confirmed by the presence of metastable transitions. For compounds (Id) and (IId) containing ethoxy groups an initial splitting out of C_2H_4 and then CO was also characteristic. The presence in the mass spectrum of compound (IIc) (M^+ 204) of ions with m/e 176 $(M - CO)^+$ and 161 $(M - CH_2 - CO)^+$ confirmed the proposed structure and indicated retention of the carbonyl group during methylation of methyl ester (Ic). A characteristic special feature of the mass spectra of compounds (Ic, IIc, d) was the presence of peaks for ions $(M + CH_2)^+$ and $(M + 2\ CH_2)^+$ (for Ic) with intensity of 0.1-0.2%, which seemingly were formed by intramolecular realkylation [4].

With the aim of studying the special features of the behavior of compounds (Ia, d, e, IIc, d) in solutions of differing acidity their UV absorption spectra were studied in aqueous solution over the range of acid and alkali concentrations from 2 N HCl to 5 N KOH. The

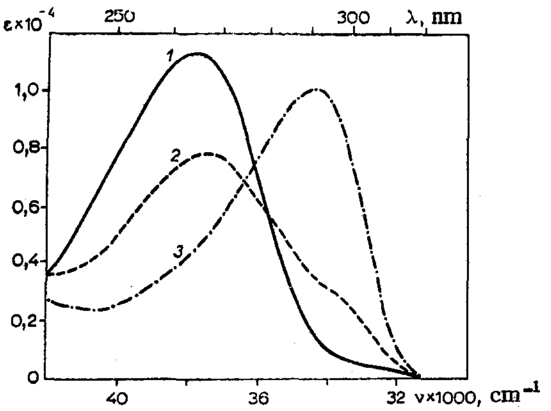


Fig. 1. UV spectra of aqueous solutions of compounds (Ia, d): 1) pH 3.56, 2) pH 9.18, 3) 2 N KOH.

spectra of these compounds in alcoholic solution were also examined. The spectra of the N,N-dimethyl derivatives of (IIc, d), in which there were no labile hydrogen atoms and ionization was impossible, did not change in the pH range 0-13 and were close to the spectra of these substances in alcoholic solution (Table 2). This indicates the existence of compounds (IIc, d) as neutral molecules in the studied solutions. The absorption spectra of compounds (Ia, d) in alcoholic solution and in aqueous solution from pH 1-6 were close to the spectra of compounds (IIc, d) and also corresponded to the neutral forms.

Storage of the studied compounds in 0.1 N HCl and in more concentrated acid solutions led to an irreversible change in absorption spectra. In 1 N HCl the band located at about 260 nm completely disappeared in one day, which indicates breaking of the ring and formation of substances having no absorption in the region under consideration. Neutralization of acidic solutions of compounds (Ia, d, e), where the process of decomposition went almost completely, led to the appearance in the spectrum of a new low intensity maximum in the region of 270-275 nm, which may indicate the formation on neutralization of a new compound, possibly cyclic, the structure of which differed from that of the initial compound. However this compound was unstable and the absorption disappeared on storing the solution for a day.

The behavior of the considered compounds in alkaline solution was more complex. For freshly prepared solutions of esters (Ia, d) beginning from pH 6 to 2 N alkali continuous reversible changes of spectra occurred which evidently are linked with the sequential dissociation of protons from the two NH groups. The intensity of the band located in the spectrum at 260 nm was therefore reduced and the intensity of bands in the 280 nm region increased (Fig. 1, Table 2). Spectrophotometric determination of the first and second ionization constants of the NH groups for these compounds gave approximate values of 8.4 and 12.8 (25°C). More precise determination of these values was difficult as a result of the overlapping pH regions where the neutral form, anion, and dianion exist.

On extended storage of compounds (Ia, d) in 0.01-0.1 N alkaline solution the spectrum changed irreversibly and a new compound was obtained with an absorption maximum located in the region of 270 ± 2 nm, the intensity of which was greater than that of the initial compound. In concentrated solutions of alkali (2 N and 5 N KOH) esters (Ia, d) proved to be unstable in the ionized state. This indicates that the singly charged ion formed in 0.01 N and 0.1 N KOH was less stable than the divalent ion present in solutions of higher concentrations of alkali.

The spectrum of acid (Ie) did not change in aqueous solution in the pH range 1-12 while potentiometric titration gave a value for pK_{a1} = 2.2. It can be assumed that dissociation of acid (Ie) at the P—OH group was not accompanied by a marked change in its absorption spectrum. Ionization at the NH group began for compound (Ie) at large pH values (Table 2). An approximate value for pK_{a2} corresponding to the first dissociation at an NH bond was 12.7 (25°C). In weakly alkaline solution compound (Ie) was stable. However, if the concentration of alkali exceeded 0.1 N, irreversible changes were observed in the spectra with an increase in the absorption maximum at 279 nm.

On storing solutions of esters (IIc, d) in 0.01 N KOH for a day the shape of the spectrum was practically unchanged. In more concentrated alkaline solutions (0.1-5 N KOH) irreversible changes of sbustances occurred accompanied by a reduction in the intensity of absorption maxima and by a displacement of the maximum to 281 nm.

From the obtained data the conclusion may be drawn that compound (Ie) was the strongest acid dissociating first at the P—OH group. Dissociation at one of the NH bonds occurs only at high pH values (12-13) and the second NH group does not dissociate even in 5 N KOH. Compounds (Ia, d) are weak dibasic acids dissociating at the NH bonds. The resulting singly charged anion is less stable than the doubly charged which is observed in alkaline solutions. Compounds (Ia, d, e, IIc, d) were unstable in an acidic medium and the rate of decomposition grew with an increase in acid concentration from 0.1 N to 2 N HCl.

EXPERIMENTAL

PMR spectra were taken on a Jeol JNM-MH-100 instrument, the internal standard was tetramethylsilane. UV spectra were measured on a Specord UV-vis spectrophotometer in water and in ethanol, cuvette thickness 1 and 2 cm, concentration of sample was 1×10^{-4} mole/liter. Samples were prepared in ethanol with subsequent dilution with aqueous buffer solutions to a given pH value. Mass spectra were measured on an MKh-1309 mass spectrometer. A check on the course of reactions was effected with the aid of TLC on Silufol UV-254 plates. Preparative TLC was carried out on LSL_{254} silica gel (Chemapol, Czechoslovakia) 5/40 μm with layer thickness 1 mm.

1-Hydroxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (Ie). A) A solution of compound (Ia) (240 mg; 1 mmole) in 96% ethanol (9 ml) was hydrogenated over PtO_2 (40 mg) at 20°C. Absorption of hydrogen was complete after 1 h. The catalyst was filtered off, washed with ethanol, the combined solution evaporated to dryness, and acid (Ie) (154 mg) was obtained as a colorless crystalline powder. Compound (Ie) was dissolved with heating in 70% ethanol, triethylamine (0.28 ml) added, the solution cooled, and evaporated to dryness. The residue was crystallized from ethanol as colorless star-shaped crystals of mp 178-180°C. Found: P 12.3%. $C_4H_7N_2O_3P \cdot (C_2H_5)_3N$. Calculated: P 11.8%. Acid value, found: 243.2 mg/g; calculated: 246.9 mg/g.

B) The phenoxy derivative (Ia) (480 mg; 2 mmole) was heated in 1 N NaOH solution (3 ml) at 50°C for 10 h until disappearance of a spot for the initial (Ia) from a chromatogram in acetone. The solution was treated with Dowex-50 (H^+) resin until neutral reaction and filtered. The phenol formed on hydrolysis of compound (Ia) was carefully extracted with ether. The aqueous solution was treated once again with resin to pH 1-2, filtered and evaporated to dryness. Acid (Ie) was obtained in quantitative yield.

1-Methoxy-2,5,6-trimethyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IIc) and 1-Methoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (Ic). An ether solution of diazomethane was added dropwise with stirring to the filtrate after removal of catalyst (see hydrogenolysis of Ia) at 20°C until the appearance of a stable yellow color. The solution was filtered and concentrated to small volume. The residue was chromatographed on plates in the system chloroform—methanol (12:1), passing the solvent over the plate twice. The zone of R_f 0.27 was collected and the substance eluted with ethanol. Substance (IIc) (148 mg; 73%) was isolated as a bright yellow oil which crystallized on standing for several days. It had mp 56-58°C. Found: C 41.2; H 6.3; N 14.3; P 15.0%. $C_7H_{13}N_2O_3P$. Calculated: C 41.2; H 6.4; N 13.7; P 15.2%. Mass spectrum, m/e (%): 218 (0.2), 206 (4), 205 (25), 204 (100), 203 (30), 190 (32), 189 (47), 176 (17), 175 (37), 174 (98), 173 (20), 162 (10), 161 (49), 160 (8), 150 (45), 148 (23), 147 (49), 132 (19), 127 (18), 125 (34), 117 (30), 116 (22), 111 (49), 110 (28), 109 (34), 108 (58), 98 (58), 97 (53), 96 (82). Compound (Ic) (30 mg) was also isolated from plates (R_f 0.11), mp 205-207°C. Found: C 33.9; H 5.3; N 16.6; P 17.5%. $C_5H_9N_2O_3P$. Calculated: C 34.1, H 5.2, N 15.9, P 17.6%. UV spectrum, λ_{max}(log ε): 259 nm (4.07).

1-Ethoxy-2,5,6-trimethyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (IId). Compound (Id) (190 mg; 1 mmole) was dissolved in a mixture of methanol and water (5 ml + 0.5 ml) and the solution treated with diazomethane in a similar manner to the previous experiment, then concentrated to small volume, and chromatographed on plates in the system chloroform—methanol (10:1). The zone with R_f 0.28 was collected and the substance eluted with ethanol. Compound (IId) (139 mg; 64%) was isolated as a bright yellow oil. Found: C 43.6; H 6.1; N 12.9; P 13.5%. $C_8H_{15}N_2O_3P$. Calculated: C 44.0; H 6.9; N 12.8; P 14.2%. Mass spectrum, m/e (%): 232 (0.2), 218 (100), 203 (1.7), 190 (49), 174 (99), 164 (23), 162 (16), 161 (13), 160 (16), 153 (15), 147 (20), 134 (16), 133 (55), 127 (23), 125 (9), 117 (33), 116 (16), 111 (35), 110 (21).

1-Methoxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (Ic). Compound (Ia) (120 mg; 0.5 mmole) was dissolved in absolute methanol (3 ml) and calcined CsF (504 mg; 6.62 mmole) was added. After 18 h the solution was filtered, the solid washed with absolute methanol, the filtrate concentrated to half volume, and chromatographed in the system chloroform–methanol (4:1), passing the solvent over the plate three times. The zone of R_f 0.66 was collected and eluted with ethanol. Methoxy derivative (Ic) (64 mg; 73%) was isolated as colorless crystals. The substance gave no depression of melting point with a sample obtained by methylation of acid (Ie) with diazomethane.

The spectral characteristics of compounds (Ia, d, IIc, d) are given in Tables 1 and 2.

LITERATURE CITED

1. I. S. Levi, L. D. Garaeva, É. M. Osipova, and M. N. Preobrazhenskaya, Khim. Geterotsikl. Soedin., No. 7, 972 (1978).
2. K. K. Ogilvie and S. L. Beaucage, J. Chem. Soc. Chem. Commun., No. 11, 443 (1976).
3. K. K. Ogilvie, S. L. Beaucage, N. Theriault, and D. W. Entwistle, J. Am. Chem. Soc., 99, 1277 (1977).
4. V. V. Takhistov, Practical Mass Spectrometry of Organic Compounds [in Russian], Leningrad (1977), p. 237.