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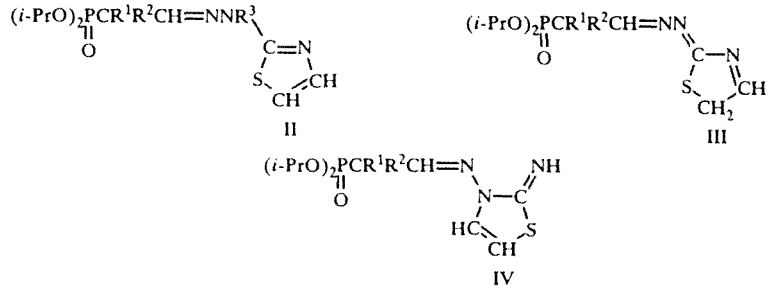
SPECTRAL STUDIES OF PRODUCTS OF REACTION BETWEEN PHOSPHORYLACETALDEHYDE THIOSEMICARBAZONES AND BROMOACETAL

V. A. Pavlov and J. A. S. Smith

We have obtained thiazoline hydrobromides by reacting unsubstituted thiosemicarbazones of phosphoryl-acetaldehydes with bromoacetal. These thiazoline hydrobromides have the structure of the azine of phosphorylacetaldehyde and 1,3-thiazolin-2-one in the crystal phase. Their dissolution is accompanied by thiazoline—thiazole tautomeric conversion to the hydrobromide of phosphorylacetaladehyde thiazolylhydrazone. Reaction of the 2-methyl-substituted phosphorylacetaldehyde thiosemicarbazone with bromoacetal leaas to the hydrobromide of phosphorylacetaldehyde N-methyl-N-2-(1,3-thiazolyl)hydrazone; the thiazole structure of the heterocycle of this compound is also retained when it is dissolved, due to the impossibility of tautomeric conversions due to the structural features. In all cases, salt formation occurs at the endocyclic nitrogen atom. The conversion of salt-like compounds to free bases does not lead to a change in the thiazole structure of the heterocycle.

Phosphorus-containing thiosemicarbazones, exhibiting high antiviral activity [1], are of great interest as starting materials for synthesis of some classes of organophosphorus compounds, in particular heterocyclic organophosphorus compounds. Our investigation included development of a convenient method for synthesis of phosphorus-containing thiazoles and thiazolines from phosphorylated thiosemicarbazones, since unphosphorylated derivatives of these heterocycles display a broad spectrum of biological activity [2] and in particular are used as radioprotectors in combination with some phosphorus-containing compounds [3,4]. However, there is little information in the literature on thiazoles and thiazolines with phosphorus-containing substituents. Accordingly, we studied the reaction of phosphorylacetaldehyde thiosemicarbazones with bromoacetal, i.e., in order to obtain a functionally substituted heterocycle, we used a modified Hantzsch condensation [5], where instead of an α-halocarbonyl compound we used its acetal. In this case, we should consider that different reaction centers contained in the thiosemicarbazone molecules Ia-c can participate in the reaction, with formation of the corresponding thiazoles or thiazolines: thiazolylhydrazone II, thiazolinone azine III, or thiazolinylimine IV. The possibility of formation of 4-(2-ethenyldialkoxyphosphoryl)-1,3,4-thiadiazines as two tautomeric forms is also not excluded: the amine V and the imine VI. The appearance of the latter suggests participation of the hydrogen atom in the active methylene group of the phosphorylacetaldehyde thiosemicarbazone in the reaction. We also demonstrated the possibility of such participation with formation of a phosphono vinyl moiety in the end product of the reaction earlier in the case of the reaction of phosphorylacetaldehyde semicarbazones with orthoformate, when the isolated compounds had an enamine structure [6].



II

III

IV

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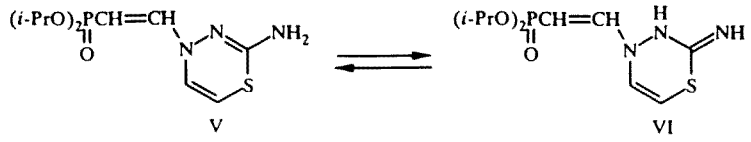
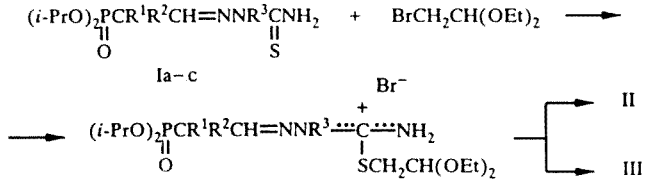


V VI

In order to establish the reaction route, as the starting compounds we used both unsubstituted diisopropoxyphosphorylacetaldehyde thiosemicarbazone (Ia) and its 2-methyl-substituted analog Ib, and also diisopropoxyphosphoryloximinoacetaldehyde thiosemicarbazone (Ic) with partially blocked reaction centers. Based on the data in [7,8] (where it was shown that the thiosemicarbazones Ia-c exist in the same thione form) and studies of the reaction of thioureas with bromoalkylamines [9-11], we can suggest that the first step in the reaction of thiosemicarbazones with bromoacetal is formation of an isothiuronium salt, occurring according to a nucleophilic substitution mechanism involving the bromine atom of the thione sulfur atom. Subsequent cyclization involving the amine nitrogen atom of the thiosemicarbazone leads to a thiazole (II) or thiazoline (III) structure, depending on the structure of the original thiosemicarbazone. The isolated crystalline compounds, according to elemental analysis and spectral studies, are hydrobromide salts.



Ia–c II III

a R^1–R^3 = H; b R^1 = R^2 = H, R^3 = Me; c R^1, R^2 = NOH, R^3 = H

The IR spectral data on the reaction product obtained based on thiosemicarbazone Ib, in which the mobile hydrogen atom at the $N_{(2)}$ nitrogen atom is substituted by a methyl group and the possibility of prototropic shifts is eliminated, showed that they match for the crystalline phase and the solution in $CHCl_3$. In the spectra, we observe a stretching vibration band at 1240 cm^{-1} (P=O) and three absorption bands in the multiple bond region: 1570 cm^{-1} (C=N) exocyclic, 1600 cm^{-1} (C=N) endocyclic, and 1640 cm^{-1} (C=C). Additional support for the presence of a multiple bond (CH=CH) in the ring with *cis* hydrogen atoms may come from the bending vibration band δ 770 cm^{-1}. The spectrum also contains a broad, smeared out band in the 2400-2800 cm^{-1} region with maximum at 2620 cm^{-1}, corresponding to vibrations of the $^+$NH group.

The NMR spectra of the hydrobromide IIb in different solvents (Table 1) provide a basis for saying that the compound under consideration has the structure of diisopropoxyphosphorylacetaldehyde N-methyl-N-2-(1,3-thiazolyl)hydrazone hydrobromide (IIb).

The IR spectrum of the hydrobromide crystals synthesized from unsubstituted thiosemicarbazone Ia is quite different from the considered spectrum of compound IIb in the double bond region. The IR spectrum contains stretching vibration bands (P=O) 1255 cm^{-1} and only two absorption bands in the double bond region. The first band, with absorption maximum at 1585 cm^{-1}, is assigned to the exocyclic C=N bond. The second, more intense absorption band with maximum at 1615 cm^{-1} characterizes vibrations of the endocyclic C=N bond. The shift of the absorption of the endocyclic C=N bond toward higher frequencies compared with the hydrobromide IIb is possibly due to disruption of the conjugation and the coplanarity. In the spectrum, we detect a broad absorption band at 2400-3100 cm^{-1} with maximum at 2680 cm^{-1}, belonging to the stretching vibrations of the $^+$NH group with a salt-like structure. The IR spectrum of this hydrobromide in chloroform solution undergoes changes compared with the solid phase, and becomes very close to the spectrum of the hydrobromide IIb. In this spectrum, we find stretching vibration bands at 1240 cm^{-1} (P=O), 1570 cm^{-1} (C=N) exocyclic, 1615 cm^{-1} (C=N) endocyclic, 1630 cm^{-1} (C=C), and a broad band in the 2500-3200 cm^{-1} region with maximum at 2900 cm^{-1} ($^+$NH).

The data obtained from the IR spectra suggest that the isolated salt in the crystalline phase has the structure of the hydrobromide of the azine of diisopropoxyphosphorylacetaldehyde and 1,3-thiazolin-2-one (IIIa). Dissolving compound IIIa leads to tautomeric conversion in the pentad system from the thiazolinylazine form IIIa to the thiazolylhydrazone form IIa.

The data presented relative to the structure of the compound in crystals and in solution allow for a different interpretation and so we cannot draw a definitive conclusion. Furthermore, it remained to determine which of the three nitrogen atoms available in the molecule is the most basic and participates in the salt formation. Drawing on PMR methods for the solutions and ^{14}N NQR for the crystalline phase could give an unambiguous answer to the questions posed, since the nuclear

TABLE 1. Parameters of ^1H and ^{31}P NMR Spectra (δ, ppm, J, Hz) of Hydrobromides of Thiazolylhydrazones of Diisopropoxyphosphorylacetaldehyde (IIa,b) and Oximinoacetaldehyde (IIc) in Different Solvents

Compound	R^1, R^2	R^3	^{31}P NMR	i-C_3H_7O			PCH_2	$^3J_{HH}$	$^3J_{PH}$	NCH_3	$CH\alpha=CH\beta$			CH=N	$^3J_{PH}$	^+NH NH	Solvent
				CH_3	OCH	$^3J_{HH}$					α-H	β-H	$^3J_{HH}$				
IIa	H_2	H	20,0	1,14	4,50	6	*	–	–	–	7,06	7,35	4	7,60	–	10,00	DMSO
			19,7	1,14	4,56	6	2,81	6	22	–	6,75	7,22	5	7,72	5	10,94	$CDCl_3$
IIb	H_2	CH_3	21,0	*	*	–	*	–	–	*	6,93	7,27	4	7,02	–	10,00	DMSO
			–	1,32	4,67	6	3,01	6	21	3,89	7,06	7,37	4	7,40	–	–	Acetone-D_6
			–	1,20	4,62	6	2,90	6	24	3,90	6,87	7,30	4	7,30	–	12,60	$CDCl_3$
IIc	NOH	H	–	*	*	–	†	–	–	–	6,86	7,18	4	8,11	23	10,60	DMSO

*Parameters not determined due to superposition of solvent signals.

† dNOH 13.40 ppm.

TABLE 2. Parameters of ^{14}N NQR Spectra (ν, kHz), Quadrupole Coupling Constants e^2qQ/h and Asymmetry Parameters (n) of Crystalline Hydrobromides (IIb and IIIa)

Compound	Group	ν_z	ν_y	ν_x*	e^2qQ/h	η
IIb	$-N^+H$	968	1048	2004	2035	0,940
	$-N(CH_3)-$	794	3093	3876	4646	0,337
	$-CH=N-$	1361	2940	4338	4852	0,576
IIIa	$-N^+H$	920	1070	1990	2040	0,902
	$-N=C-$	1477	2216	3700	3944	0,753
	$-CH=N-$	1150	2988	4141	4753	0,485

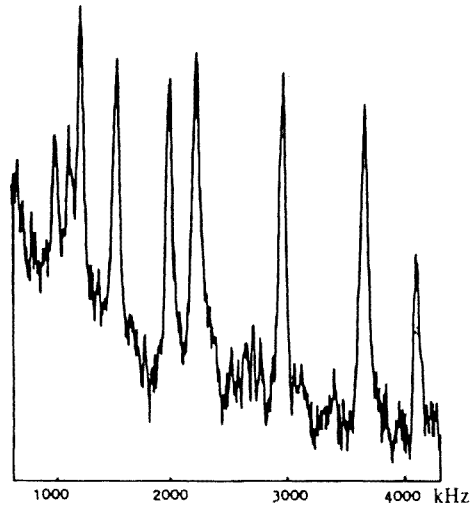


Fig. 1. ^{14}N NQR spectrum of the hydrobromide of the azine of phosphorylacetaldehyde and thiazolinone IIIa.

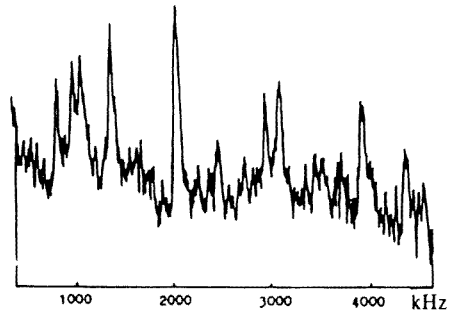


Fig. 2. ^{14}N NQR spectrum of the hydrobromide of phosphorylacetaldehyde N-methyl-N-thiazolylhydrazone IIb.

quadrupole resonance frequencies of the nitrogen atom directly depend on the nature of the chemical bonds and the electronic environment of the nucleus.

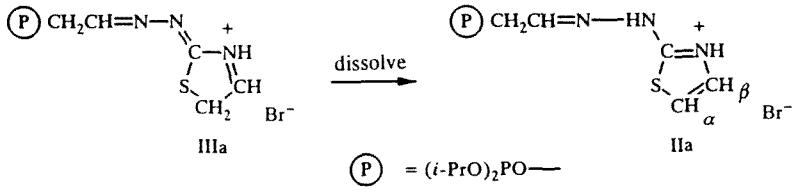
Investigation of the synthesized compound IIIa by PMR using the technique of homonuclear double resonance at the hydrogen nuclei allowed us to confirm the conclusion drawn on the basis of studying the IR spectra that it exists in solutions in the thiazolylhydrazone tautomeric form IIa.

From the spectral data (Table 1) we see that the quadruplet for protons of the methylene group of PCH_2, observed upfield at 2.81 ppm ($^2J_{PH}$ 22 Hz, $^3J_{HH}$ 6 Hz), under homonuclear double resonance conditions is transformed to a doublet due to spin—spin coupling of these protons with the phosphorus. The CH=N azomethine proton resonates downfield as a multiplet

at 7.72 ppm. In the $^1H-\{^1H\}$ double NMR spectrum, its resonance signal is a clear doublet with spin—spin coupling constant $^3J_{PH}$ = 5 Hz. The ethylene protons are represented by a classical AB quartet at 6.75 ppm (α-H) and 7.22 ppm (β-H, $^3J_{\alpha\beta}$ = 4 Hz), uncomplicated by coupling with the NH proton at the C=N bond of the thiazole ring. In considering the line width of the signal from the NH proton at half height (10.94 ppm) with no double NMR and with β-H proton decoupling, in the latter case we observe appreciable narrowing of the line from 24 Hz down to 19 Hz, which indicates that an additional contribution to the line width of the signal for the NH proton comes from coupling with the β-H proton. The fact that the six-membered thiadiazine ring of V or VI is not formed as a result of the reaction is confirmed by the PMR spectra, in which we do not observe signals from the ethylene protons of the P−CH=CH−N moiety. In addition to this, we carried out the cyclization reaction of diisopropoxyphosphoryloximinoacetaldehyde thiosemicarbazone Ic (in which the protons of the active methylene group are replaced by the oxime group), leading to a compound which according to the PMR spectrum (Table 1) has the thiazolylhydrazone structure IIc in DMSO solution.

Investigation of the salts obtained by the nuclear quadrupole resonance method supported the correctness of the hypothesis about their structure in the crystalline state made on the basis of the IR spectra. The ^{14}N NQR spectra were recorded for solid samples at room temperature by the cross relaxation method (see the Experimental section). Since all three quadrupole resonance transitions of the ^{14}N nitrogen (ν_x, ν_y, ν_z) are observed in the cross relaxation spectra (Figs. 1 and 2) [12], we can use the sum rule $\nu_x = \nu_y + \nu_z$ to assign the observed transitions; this equation was used for calculation of the quadruple coupling constants (e^2qQ/h) and the asymmetry parameters (n) given in Table 2. The assignments to specific nitrogen atoms for compounds IIb and IIIa are consistent with their structure and the known [13] quadrupole parameters for such compounds. Since the value of the asymmetry parameter is determined by the electron density distribution at the nucleus, in the observed case the approach of its value to unity suggests an $^+$NH-immonium character. Furthermore, considering that the quadrupole coupling constant has a minimum value at the endocyclic nitrogen atom (2035 and 2040 kHz), we can conclude that the unshared electron pair from the nitrogen atom on the ring participates in the salt formation. This obviously is explained by its accessibility for protonation.

Thus, reaction of unsubstituted diisopropoxyphosphorylacetaldehyde thiosemicarbazone Ia with bromoacetal leads to compound IIIa. Its dissolution is accompanied by complete tautomeric conversion to the hydrobromide salt of phosphoryl-acetaldehyde thiazolylhydrazone IIa.

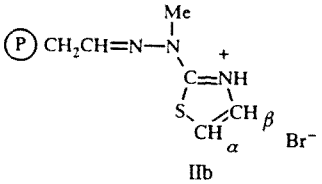


IIIa IIa

Ⓟ = $(i\text{-PrO})_2PO-$

Reaction of 2-methyl-substituted diisopropoxyphosphorylacetaldehyde thiosemicarbazone Ib with bromoacetal gives the hydrobromide of diisopropoxyphosphorylacetaldehyde N-methyl-N-2-(1,3-thiazolyl)hydrazone (IIb), the protonation of which also occurs at the endocyclic nitrogen atom.

The thiazolylhydrazone structure IIb is also retained when this compound is dissolved, because the structural features make tautomeric conversions impossible.



IIb

Treatment of hydrobromide IIa with an alcoholic KOH solution led to isolation of a thick, oily, dark-brown liquid whose spectral characteristics showed that this is diisopropoxyphosphorylacetaldehyde thiazolylhydrazone IIa in the form of the free base. In its IR spectrum, there are stretching vibration bands at: 1250 cm^{-1} (P=O), 1580 cm^{-1} (C=N) — exocyclic, 1610 cm^{-1} (C=N) — endocyclic, 1630 cm^{-1} (C=C), 3000-3700 cm^{-1} with maximum at 3440 cm^{-1} (NH); and bending vibrations of the *cis*-CH=CH bond at 780 cm^{-1}. PMR spectrum ($CDCl_3$): 1.30 (12H, d, $^3J_{HH}$ = 6 Hz, CH_3—Pr-*i*); 2.87 (2H, dd, $^3J_{HH}$ = 6 Hz, $^2J_{PH}$ = 22 Hz, PCH_2); 4.57 (2H, m, OCH—Pr-*i*); 6.51 (1H, d, $^3J_{HH}$ = 3.5 Hz, α-H); 7.10 (1H, d, $^3J_{HH}$ = 3.5 Hz, β-H); 6.90 (1H, broadened s, NH); 7.31 (1H, m, CH=N).

Thus conversion of the salt IIa to the free base does not change the position of the tautomeric equilibrium.

EXPERIMENTAL

The ^{14}N NQR spectra were recorded for solid samples at room temperature by the cross relaxation method on a double NMR-NQR resonance spectrometer with a movable sample [12]. In this case, the proton magnetic resonance signal was detected at high magnetic field (40 MHz) and then the sample was mechanically moved to a low-field solenoid, in which a d.c. current generated the magnetic field. There the ^{1}H magnetic resonance frequency was superimposed on one of the ^{14}N quadrupole resonance frequencies. In this case, the faster relaxation of the ^{14}N nuclei led to substantial loss in the proton magnetization, which was recorded as weakening of the ^{1}H magnetic resonance signal when returned to high field. The spectra were recorded by turning off the current in the low-field solenoid after each cycle and was converted to frequency using the conversion constant 367.5 kHz·A^{-1}. The resonance time in high field was 9 sec; in low field, from 0.15 to 0.25 sec.

The PMR spectra were recorded on the spectrometers Varian T-60, Tesla BS-567 (100 MHz), and Bruker WP-80 with homonuclear $^{1}H—\{^{1}H\}$ spin decoupling. The ^{31}P NMR spectra were recorded on a Bruker WP-80 (32.38 MHz) spectrometer and the NQR spectra were recorded on a KGU-4 (10.2 MHz) spectrometer using $^{31}P—\{^{1}H\}$ spin decoupling. The ^{1}H chemical shifts were determined relative to TMS; the phosphorus chemical shifts were determined relative to H_3PO_4. Their spectra were obtained on a UR-20 instrument. The course of the reactions and the purity of the materials obtained were monitored by TLC on Silufol UV-254 plates.

Diisopropoxyphosphorylacetaldehyde thiosemicarbazone (Ia) was obtained according to the method in [14]. The synthesis of thiosemicarbazones Ib and Ic is described in [7] and [8] respectively.

Hydrobromide of the Azine of Diisopropoxyphosphorylacetaldehyde and 1,3-Thiazolin-2-one (IIIa). Bromoacetal (3.5 g, 18 mmoles) was added to a solution of 5 g (18 mmoles) diisopropoxyphosphorylacetaldehyde thiosemicarbazone (Ia) in 50 ml absolute isopropanol. This mixture was boiled with reflux for 4.5 h at a temperature of 105-110°C until disappearance of the starting materials (monitored by TLC). The solvent was driven off under vacuum and the precipitated crystals were washed with acetone (if oil was separated, then it was washed with acetone and then the oil was crystallized). 5 g (72%) of compound IIIa was isolated with T_{mp} 151-153°C (decomp.). Found, %: Br 19.60, N 10.86, P 8.00. $C_{11}H_{21}BrN_3O_3PS$. Calculated, %: Br 20.72, N 10.88, P 8.03. IR spectrum: 3140, 2400-3100 with max 2680, 1615, 1585, 1525, 1300, 1255, 1210, 1190, 1133, 1111, 1095, 1065, 1040, 1018, 990, 950, 900, 880, 870, 860, 840, 815, 748, 730, 718, 615 cm^{-1}.

Hydrobromide of Diisopropoxyphosphorylacetaldehyde N-Methyl-N-2-(1,3-thiazolyl)hydrazone (IIb). Obtained by the method described for compound IIIa. 2.5 g (41%) thiazolylhydrazone IIb with T_{mp} 145-146°C (decomp.) was obtained from 4.5 g (15 mmoles) diisopropoxyphosphorylacetaldehyde 2-methylthiosemicarbazone (Ib) dissolved in 60 ml isopropanol and 3.1 g (15 mmoles) bromoacetal. Found, %: Br 19.60, N 10.60, P 7.20. $C_{12}H_{23}BrN_3O_3PS$. Calculated, %: Br 20.00, N 10.50, P 7.55. IR spectrum: 3075, 2400-2800 with max 2630, 1640, 1602, 1570, 1550, 1345, 1255, 1240, 1185, 1150, 1115, 1087, 1020, 1000, 950, 940, 895, 860, 840, 820, 770, 725, 555 cm^{-1}.

Hydrobromide of the Azine of Diisopropoxyphosphoryloximinoacetaldehyde and 1,3-Thiazolin-2-one (IIIc). Obtained by the method described for compound IIIa. 0.86 g (32%) azine IIIc was obtained from 2 g (6.5 mmoles) diisopropoxyphosphoryloximinoacetaldehyde thiosemicarbazone (Ic) dissolved in 20 ml isopropanol and 1.3 g (6.6 mmoles) bromoacetal. The precipitating crystals, contaminated with an oily impurity, were purified on a Shemberlen [spelling unverified] filter. The crystals isolated in this way were washed with acetone and the compound IIIc was obtained with T_{mp} 142-144°C (decomp.). Found, %: N 13.50, P 7.10. $C_{11}H_{20}BrN_4O_4PS$. Calculated, %: N 13.49, P 7.47. IR spectrum: 3450, 3370, 3150, 3130, 3080, 3200-3300 with max 2740, 1680, 1620, 1560, 1510, 1420, 1320, 1260, 1240, 1180, 1170, 1140, 1110, 1075, 1010, 945, 925, 905, 835, 785, 740, 730, 680, 645, 625, 612, 565 cm^{-1}.

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