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2-Diphenylphosphinoyloxybenzaldehyde 4-Nitrophenyl-, 4-Phenyl-1-phthalazinyl-, and Aroylhydrazones and Thiosemicarbazone

F. V. Bagrov and T. V. Vasil'eva

Ul'yanov Chuvash State University, Moskovskii pr. 15, Cheboksary, 428015 Russia

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Abstract—Condensation of aryl- and aroylhydrazines and thiosemicarbazide with 2-diphenylphosphinoyloxybenzaldehyde results in formation of the corresponding hydrazones and thiosemicarbazone. The products give rise to conformational equilibrium between rotational and *Z,E* isomers, which is strongly displaced toward the *E,E′,Z″* isomer and is determined by the nature of substituent in the hydrazine fragment.

Hydrazones are physiologically active compounds, some of which are successfully used in chemotherapy of tuberculosis [1, 2]. The therapeutic action of organophosphorus compounds is based on their ability to inactivate choline esterase. Phosphorus compounds are known as myotic drugs which are successfully used in the treatment of glaucoma, paralyses, and disturbances of central nervous system, as well as in obstetrics and oncology [3]. It is known that introduction of pharmacophoric fragments into molecules of biologically active compounds could lead to more efficient analogs or substances possessing quite a different kind of biological activity. From this viewpoint, hydrazones having a phosphorus-containing group in the carbonyl fragment attract considerable interest in both chemical and pharmacological aspects.

Acylhydrazones derived from aldehydes [4–6] exist in solution as two rotational isomers (about the amide N–C or hydrazine N–N bond) of a single *E* isomer (about the C=N bond). The isomeric composition of benzaldehyde aroylhydrazones strongly depends on the nature of substituents in both acyl and benzylidene fragments. The effect of phosphorus-containing groups in the carbonyl moiety on the state of equilibrium between different hydrazone isomers has not been studied. Taking into account the above stated and the results reported in [4–11], in the present work we studied the structure of products formed by reactions of 2-diphenylphosphinoyloxybenzaldehyde with nucleophilic reagents (monosubstituted hydrazine derivatives as α-nucleophiles). The goal of the study was to elucidate the effect of diphenylphosphinoyloxy group on the above equilibrium.

We have found that chlorodiphenylphosphine oxide readily reacts with salicylaldehyde in dry benzene in the presence of triethylamine as hydrogen chloride acceptor. The reaction involves exclusively the phenol hydroxy group and gives 2-diphenylphosphinoyloxybenzaldehyde (**I**) in a good yield; here, triethylamine hydrochloride is formed in a quantitative yield.

Phosphorylated salicylaldehyde **I** reacted in boiling ethanol with various α-nucleophiles, namely 4-nitrophenylhydrazine, 4-phenyl-1-phthalazinylhydrazine, substituted benzohydrazides, and thiosemicarbazide (Scheme 1). The presence of diphenylphosphinoyloxy group in the *ortho* position of the aromatic ring in the aldehyde molecule did not affect appreciably the reactivity of the carbonyl group. The condensation readily occurs, following the usual scheme of nucleophilic addition at the aldehyde carbonyl group with subsequent elimination of water. Regardless of the α-nucleophile nature, the final products were the corresponding hydrazones **II**–**IX** and thiosemicarbazone **X**. Products **II**–**X** (Table 1) are colored finely crystalline substances which are stable on exposure to air. Compounds **II**–**X** are insoluble in water, diethyl ether, and hexane, but soluble in DMF and DMSO; Their purity was checked by TLC, and the composition was determined by elemental analysis.

2-Diphenylphosphinoyloxybenzaldehyde hydrazones **II**–**X** can exist as different stereoisomers (or their equilibrium mixture) originating from *E,Z* isomerism with respect to the double C=N bond and rotation about the single C–N and N–N bonds. Among a large number of possible structures,

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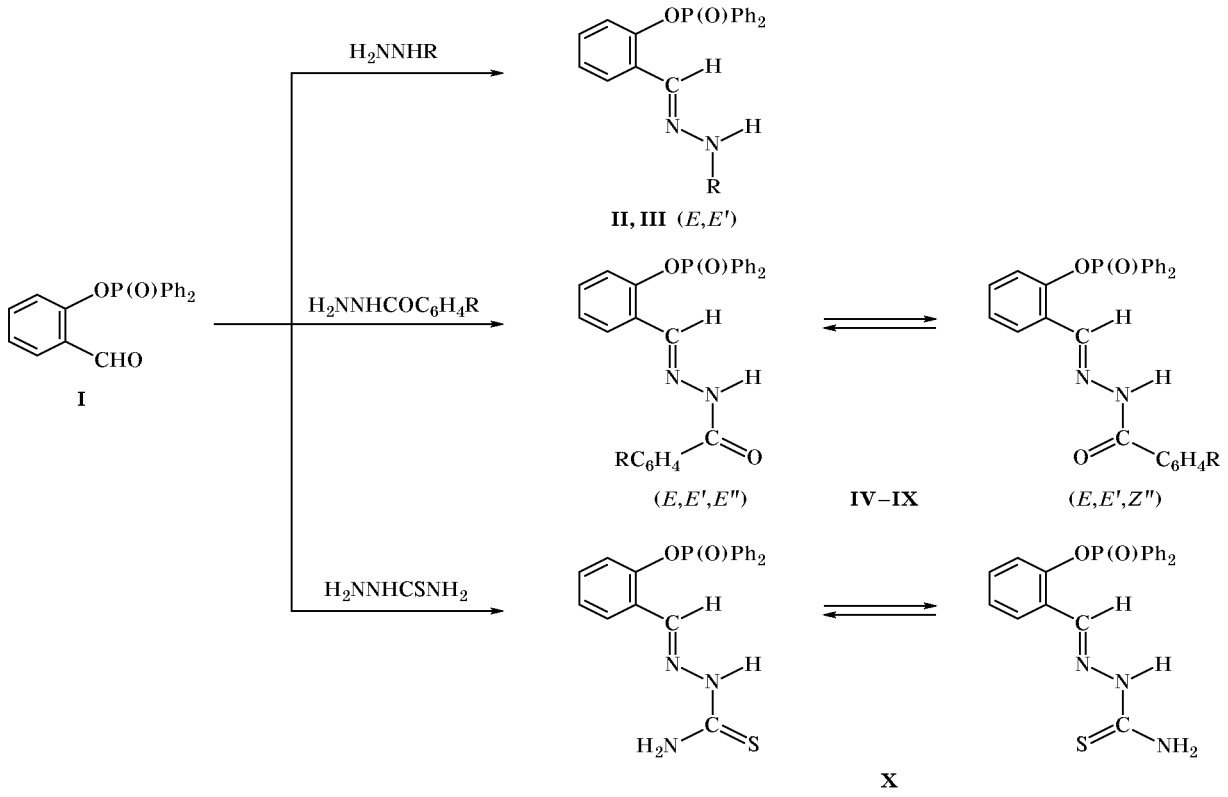
Scheme 1.

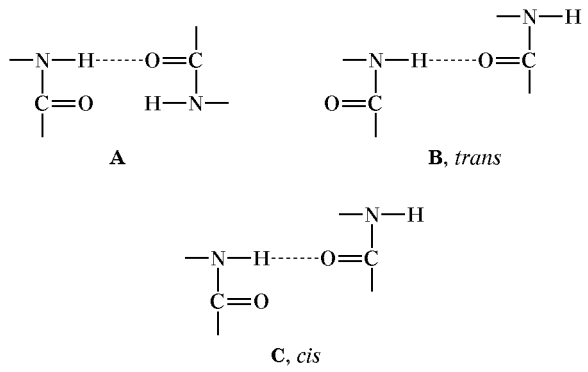


II, R = 4-$O_2NC_6H_4$; **III**, R = 4-phenyl-1-phthalazinyl; **IV**, R = H; **V**, R = 4-I; **VI**, R = 4-O_2N; **VII**, R = 4-Me; **VIII**, R = 2-OH; **IX**, R = 2-H_2N.

Scheme 1 shows *E*,*E*′,*E*″ and *E*,*E*′,*Z*″ rotamers of one *E* isomer with respect to the C=N bond.

The IR spectra of all crystalline compounds **II**–**X** (Table 2) contain absorption bands in the regions 1175–1203 and 1435–1445 cm^{-1}, which belong, respectively, to vibrations of the P–O–Ar and P–Ph groups. Strong absorption bands in the region 1195–1275 cm^{-1} correspond to vibrations of the phosphinoyl group. Stretching vibrations of the C=N bond give rise to strong absorption at 1585–1602 cm^{-1}, which is overlapped by absorption of the aromatic ring. Amide I bands in the spectra of **IV**–**VIII** appear at 1610–1675 cm^{-1}, and amide II bands are observed at 1510–1550 cm^{-1}. Broad medium-intensity bands in the high-frequency region (3167–3225 cm^{-1}) belong to stretching vibrations of the N–H bonds. It should be noted that some authors [12, 13] assign the amide absorption at 3150–3200 cm^{-1} to N–H vibrations in dimers like **A**, and bands at 3250–3350 cm^{-1}, to polyassociates like **B** and **C** (Scheme 2).

Scheme 2.



The presence in the IR spectra of benzoylhydrazones **IV**–**VIII** of amide II band at 1530 cm^{-1}, which is typical of *trans*-configuration [13] and also of N–H absorption below 3200 cm^{-1} led us to conclude that the isolated products in the crystalline state exist as equilibrium mixtures of the *E*,*E*′,*E*″ and *E*,*E*′,*Z*″ rotamers as associates **A** and **B**. Hydrazone **VIII** is additionally stabilized by intramolecular hydrogen bond in the 2-hydroxybenzoyl radical; the IR spectrum of **VIII** lacks absorption bands typical of stretching vibrations of free phenolic hydroxy group. The IR spectra of hydrazones **IX** and **X** are analogous

Table 1. Yields, melting points, and elemental analyses of 2-diphenylphosphinoyloxybenzaldehyde hydrazones **II**–**X**

Comp no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	P		C	H	N	P
II	65	222–224	65.69	4.51	9.14	6.81	$C_{25}H_{20}N_3O_4P$	65.64	4.47	9.19	6.77
III	86	185–187	73.35	4.65	10.33	5.67	$C_{33}H_{25}N_4O_2P$	73.32	4.66	10.36	5.73
IV	60	117–119[a]	70.96	4.87	6.40	7.06	$C_{26}H_{21}N_2O_3P$	70.90	4.81	6.36	7.03
V	61	201–203	55.12	3.60	5.01	5.52	$C_{26}H_{20}IN_2O_3P$	55.14	3.56	4.95	5.47
VI	76	220	64.37	4.13	8.67	6.35	$C_{26}H_{20}N_3O_5P$	64.33	4.15	8.66	6.38
VII	74	194–196	71.33	5.14	6.19	6.88	$C_{27}H_{23}N_2O_3P$	71.36	5.10	6.16	6.82
VIII	60	228[a]	68.48	4.62	6.11	6.73	$C_{26}H_{21}N_2O_4P$	68.42	4.64	6.14	6.79
IX	70	110	68.54	4.89	9.28	6.84	$C_{26}H_{22}N_3O_3P$	68.57	4.87	9.23	6.80
X	78	244	60.80	4.64	10.66	7.79	$C_{20}H_{18}N_3O_2PS$	60.75	4.59	10.63	7.83

[a] With decomposition.

Table 2. Data of TLC (R_f) and IR spectra (ν, cm^{-1}) of 2-diphenylphosphinoyloxybenzaldehyde hydrazones **II**–**X**

Comp. no.	R_f (system)[a]	N−H	Amide I	Amide II	C=N	P=O	P−O−Ar	P−C_{arom}
II	0.47 (A)	3167			1589	1275	1191	1440
III	0.40 (A)	3186			1602	1203	1167	1435
IV	0.47 (A)	3190	1625, 1660	1535	1590	1240	1185	1440
V	0.43 (B)	3200	1648, 1675	1535	1597	1195	1175	1435
VI	0.47 (A)	3200	1640, 1670	1510	1590	1210	1185	1445
VII	0.51 (B)	3180	1635	1535	1595	1275	1202	1435
VIII	0.48 (A)	3225	1630	1550	1595	1210	1185	1435
IX	0.48 (A)	3200, 3335, 3370	1610, 1625	1540	1590	1220	1190	1445
X	0.41 (A)	3110, 3170, 3260, 3290	1475 (C=S)	1535	1585	1220	1190	1435

[a] Eluent benzene–2-propanol, 10:1 (A) or 7:1 (B).

to those considered above, but in the high-frequency region, apart from the secondary amide N−H band, two bands corresponding to symmetric and antisymmetric vibrations of the primary amino group are observed.

Final conclusions on the structure of compounds **II**–**X** were drawn on the basis of their ^{1}H NMR spectra (Table 3). The downfield region of the ^{1}H NMR spectrum of 4-nitrophenylhydrazone **II** contains a set of aromatic proton signals at δ 7.17–8.11 ppm (with an overall intensity corresponding to 18 protons) and two one-proton singlets with δ 8.39 and 11.29 ppm. The latter corresponds to proton of the secondary amino group, and the former belongs to the benzylidene CH proton. The spectrum of **III** is analogous to that of hydrazone **II**. The presence in the ^{1}H NMR spectra of one-proton singlets from the NH and CH protons indicates that arylhydrazones **II** and **III** in solution exist exclusively as *E*,*E*′ stereoisomers with *E* configuration of the C=N bond. Benzoylhydrazones **IV**–**IX** and thiosemicarbazone **X** in DMSO solution exist as mixtures of two stereoisomers due to isomerism in the hydrazone fragment. This follows from the presence of a double set of signals from the secondary amide NH and benzylidene CH protons. According to published data [14, 15], the NH signal of the *E*,*E*′,*Z*″ conformer of hydrazones **IV**–**IX** is located in a stronger field, and the aldehyde CH signal, in a weaker field relative to the corresponding signals of the *E*,*E*′,*E*″ isomer. In the ^{1}H NMR spectrum of **X**, the amide proton signal of the *E*,*E*′,*Z*″ isomer is displaced downfield relative to the analogous signal from the *E*,*E*′,*E*″ isomer due to effect of the thiocarbamoyl group. The fractions of stereo-

Table 3. Stereoisomeric composition (ω) and parameters of the ^{1}H NMR spectra (δ, ppm) of 2-diphenylphosphinoyloxybenzaldehyde hydrazones **II**–**X**

Comp. no.	ω(*E*,*E*′,*Z*″), %	N–H	CH=	Aromatic (other) protons
II	100 (*E*,*E*′)	11.29 s	8.38 s	7.17 d, 7.22 t, 7.27 d, 7.56 m, 7.64 t, 7.88 d, 7.90 d, 7.97 d, 8.11 d
III	100 (*E*,*E*′)	12.28 s	8.74 s	7.16 t, 7.23 t, 7.25 q, 7.45 m, 7.55 m, 7.59 m, 7.66 t, 7.72 t, 7.75 m, 7.90 d, 7.92 d
IV	96	11.87 s, 11.99 s	8.63 s, 8.82 s	7.19 t, 7.30 t, 7.40 d, 7.56 m, 7.62 q, 7.91 d, 7.94 d
V	70	11.90 s, 12.00 s	8.63 s, 8.80 s	6.91 t, 7.18 t, 7.30 t, 7.38 d, 7.49 d, 7.55 m, 7.62 t, 7.72 t, 7.90 d, 7.93 d
VI	65	12.15 s, 12.25 s	8.68 s, 8.83 s	6.93 d, 7.21 t, 7.31 q, 7.38 d, 7.57 m, 7.64 t, 7.91 d, 7.94 d, 8.18 t, 8.38 d
VII	96	11.79 s, 11.90 s	8.61 s, 8.80 s	7.18 t, 7.29 t, 7.34 d, 7.40 d, 7.54 m, 7.63 t, 7.83 d, 7.94 d, (CH_3, 2.43 s)
VIII	96	11.90 s, 11.99 s	8.67 s, 8.81 s	6.96 t, 6.98 d, 7.20 t, 7.32 t, 7.39 d, 7.44 t, 7.56 m, 7.63 t, 7.89 d, 7.92 d, 7.95 d, (HO, 11.78 s)
IX	80	11.66 s, 11.80 s	8.57 s, 8.75 s	6.50 t, 6.60 t, 6.77 d, 7.17 t, 7.20 t, 7.28 t, 7.42 d, 7.55 m, 7.61 q, 7.92 d, 7.95 d, (NH_2, 6.25 br.s)
X	80	11.26 s, 11.60 s	8.37 s, 8.52 s	6.81 t, 6.86 d, 7.12 t, 7.19 t, 7.27 t, 7.45 d, 7.56 m, 7.62 t, 7.81 d, 7.90 d, 7.92 d, 8.13 d, (NH_2, 7.86 s, 8.07 s)

isomers (ω) were estimated from the intensities of the corresponding proton signals.

The data in Table 3 show that the conformational equilibrium of 2-diphenylphosphinoyloxybenzaldehyde benzoylhydrazones and thiosemicarbazone in polar DMSO is strongly displaced toward the *E*,*E*′,*Z*″ isomer and that its position depends on the substituent in the hydrazine fragment. This is explained by the presence of a bulky diphenylphosphinoyloxy group in the *ortho*-position relative to the aldehyde moiety. Introduction of an electron-acceptor substituent into the *para*-position of the benzoyl group (compounds **IV** and **V**) leads to displacement of the equilibrium toward less polar *E*,*E*′,*E*″ conformer. The fraction of the latter increases with rise in electron-acceptor power of the substituent (compound **VI**). Methyl and hydroxy groups in the aromatic ring of hydrazones **VII** and **VIII** do not affect the conformational equilibrium, while the presence of primary amino group in molecule **IX** slightly increases the fraction of the *E*,*E*′,*E*″ rotamer.

EXPERIMENTAL

The IR spectra of compounds **I**–**X** were recorded on a Specord 75IR instrument from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker DRX-500 spectrometer in DMSO-d_6 using HMDS as internal reference. Silufol UV-254 plates were used for thin-layer chromatography; eluent 2-propanol–benzene; development with iodine vapor.

2-Diphenylphosphinoyloxybenzaldehyde (I). Triethylamine, 32 mmol, was added over a period of 30 min to a solution of 32 mmol of chlorodiphenylphosphine oxide and 32 mmol of salicylaldehyde in 70 ml of dry benzene, maintaining the temperature at 0–5°C. The mixture was heated to 70°C and was kept for 1.5 h at that temperature, triethylamine hydrochloride was filtered off, the filtrate was evaporated, and the residue was recrystallized from benzene. Yield 83%, mp 60°C, R_f 0.73 (2-propanol–benzene, 1:10). Found, %: P 9.66, 9.60. $C_{19}H_{15}O_3P$. Calculated, %: P 9.61.

2-Diphenylphosphinoyloxybenzaldehyde 4-nitrophenylhydrazone (II). 2-Diphenylphosphinoyloxybenzaldehyde, 11 mmol, was added to a warm solution of 10 mmol of 4-nitrophenylhydrazine in 15 ml of anhydrous ethanol. The mixture was refluxed for 15 min, the solvent was distilled off under reduced pressure (water-jet pump), and the residue was recrystallized from ethanol and washed with diethyl ether.

2-Diphenylphosphinoyloxybenzaldehyde 4-phenyl-1-phthalazinylhydrazone (III) was synthesized in a similar way from 10 mmol of 4-phenyl-1-phthalazinylhydrazine in 15 ml of ethanol and 11 mmol of aldehyde **I**.

2-Diphenylphosphinoyloxybenzaldehyde benzoylhydrazones IV–IX were synthesized as described above for hydrazone **II** using 10 mmol of the corresponding substituted benzohydrazide in 20 ml of ethanol and 11 mmol of aldehyde **I**.

2-Diphenylphosphinoyloxybenzaldehyde thiosemicarbazone (X) was synthesized in a similar way by reaction of 10 mmol of thiosemicarbazide with 11 mmol of aldehyde **I** in 15 ml of ethanol.

The yields, melting points, and elemental analyses of compounds **II–X** are given in Table 1.

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