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Synthesis and Molecular Structure of Substituted 4-[*N*-Phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,2,4λ^5-diazaphosphorines

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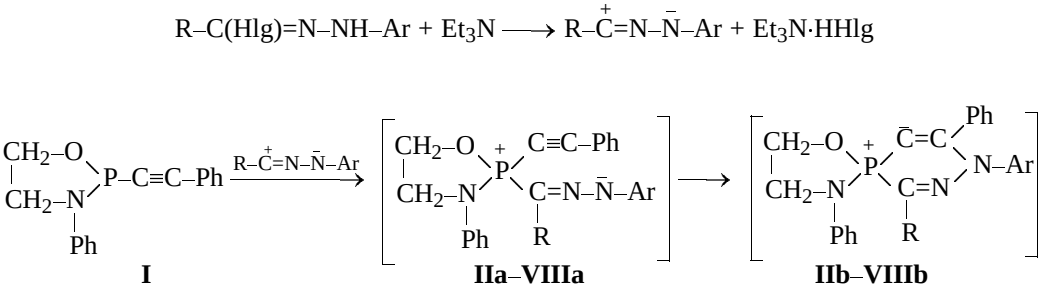
Abstract — The reaction of 3-phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine with nitrilimines is a multistep process involving formation of the diazaphosphorine ring and cleavage of the oxazaphospholidine ring. The final products are the substituted 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,2,4λ^5-diazaphosphorines. According to X-ray structural data obtained for 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,5-diphenyl-3-ethoxycarbonyl-1,2,4λ^5-diazaphosphorine, the heteroring of these compounds has the conformation of a flattened *P-envelope.*

We have shown recently [1] that 2-ethoxy-3-methyl-1,3,2λ^3-oxazaphospholidine reacts with nitrilimines (Huisgen 1,3-dipoles) to form alicyclic compounds with a P–C bond, which suggests the nucleophilic attack of the nitrilimine carbenium atom nitrilimine by the trivalent phosphorus atom, protonation of the intermediate bipolar P^+CNN^- ion by triethylamine hydrohalide present in the reaction mixture, and cleavage of the five-membered heterocycle across the C–O bond.

In this study we found that the introduction of an acetylenic group instead of the ethoxy group at the phosphorus atom in 1,3,2λ^3-oxazaphospholidines provides the formation of a six-membered diazaphosphorine heterocycle under the similar conditions, but does not exclude the cleavage of the oxazaphospholidine ring. In particular, the reactions of 3-phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine **I** with nitrilimines containing various substituents at the carbenium atom yielded substituted 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,2,4λ^5-diazaphosphorines **II**–**VIII**.

The reaction probably starts with a nucleophilic attack of the carbenium atom of nitrilimine by phosphorus (the nitrilimine was generated *in situ* from the appropriate halohydrazones under the action of triethylamine). The arising bipolar ion **IIa**–**VIIIa** undergoes intramolecular nucleophilic addition to form the cyclic ylide **IIb**–**VIIIb**, which is protonated with triethylamine hydrohalide to form the cyclic quasiphosphonium salt **IIc**–**VIIIc**. The latter transforms into the stable final product **II**–**VIII** by the cleavage of the oxazaphospholidine ring as a result of the attack of the oxygen-bonded carbon atom of the five-membered heterocycle by the halide ion. This reaction step is similar to the second step of the classical Arbuzov reaction. It yields the phosphoryl and *N*-phenyl-*N*-2-haloethyl groups.



I **IIa**–**VIIIa** **IIb**–**VIIIb**

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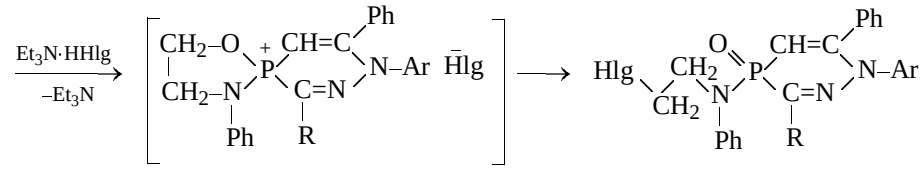
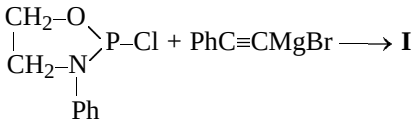


IIc–**VIIIc**

R = C(O)Me, Ar = Ph (**II**), C_6H_4Br-*p* (**III**); R = C(O)OEt, Ar = Ph (**IV**), C_6H_4Br-*p* (**V**), $C_6H_4NO_2$-*p* (**VI**); Ar = Ph, R = $C(O)C_6H_4NO_2$-*p* (**VII**), Ph (**VIII**).

Note that 2-phenylethynyl-1,3,2λ^3-dioxaphospholane, the analog of compound **I** containing the oxygen atom instead of the nitrogen atom in the five-membered heterocycle, reacts with nitrilimines similarly [2].

The starting 1,3,2λ^3-oxazaphospholidine **I** was prepared by the reaction of 3-phenyl-2-chloro-1,3,2λ^3-oxazaphospholidine with 2-phenylethynylmagnesium bromide.



The signal of the phosphorus atom in the ^{31}P NMR spectrum of **I** (δ_P 97.7 ppm) is shifted upfield as compared to the signal of the related 2-phenylethynyl-1,3,2λ^3-dioxaphospholane (δ_P 127.4 ppm) [2], in line with the trend observed in going from amido esters to *O*,*O*-diesters of trivalent phosphorus [3]. In the ^1H NMR spectrum, the OCH_2 and NCH_2 protons give multiplets with δ 4.67 and 3.47 ppm, respectively. The presence of the C≡C bond is confirmed by the IR spectrum [ν(C≡C) 2120 cm^{-1}].

Substituted diazaphosphorines **II**–**VIII** were prepared in 50–90% yield (Tables 1, 2). They are crystalline compounds readily soluble in THF and acetone and poorly soluble in hexane and ether. Their ^{31}P NMR spectra contain the signals in the range of δ_P from –0.6 to –8.6 ppm, characteristic of substituted 1,2,4-diazaphosphorines [2, 4]. The signals are shifted upfield by 8–10 ppm as compared to the related compounds containing a 2-haloethoxy substituent at the P atom [2]. This fact confirms the presence of the exocyclic P–N bond in **II**–**VIII**. The ^1H NMR spectra contain the signals of the alkenyl proton at δ 5.69–6.06 ppm. The coupling constant $^3J_{PH}$ (0–3.3 Hz) in many cases is close to zero, so that the signals appear as singlets. The protons of the methylene groups $HlgCH_2$ and NCH_2 are anisochronous. They give pairs of multiplets at δ 3.62–4.51 and 3.51–3.63 ppm, respectively. In the IR spectra of **II**–**VIII**, the absorption band characteristic of the C≡C bond is absent, which additionally confirms its conversion. Note that compounds **II** and **III** containing the acetyl group at the C^3 atom were obtained as mixtures of two diastereomers **A** and **B**. This is indicated by the presence of two signals in the ^{31}P NMR spectra and by doubling of all the signals (primarily, of the alkenyl proton signals) in the ^1H NMR spectra (Table 2). The relative content of the isomers changes in the course of recrystallization. The **A** : **B** ratio in the finally isolated compounds **II** and **III** was 1 : 4 and 2 : 3, respectively.

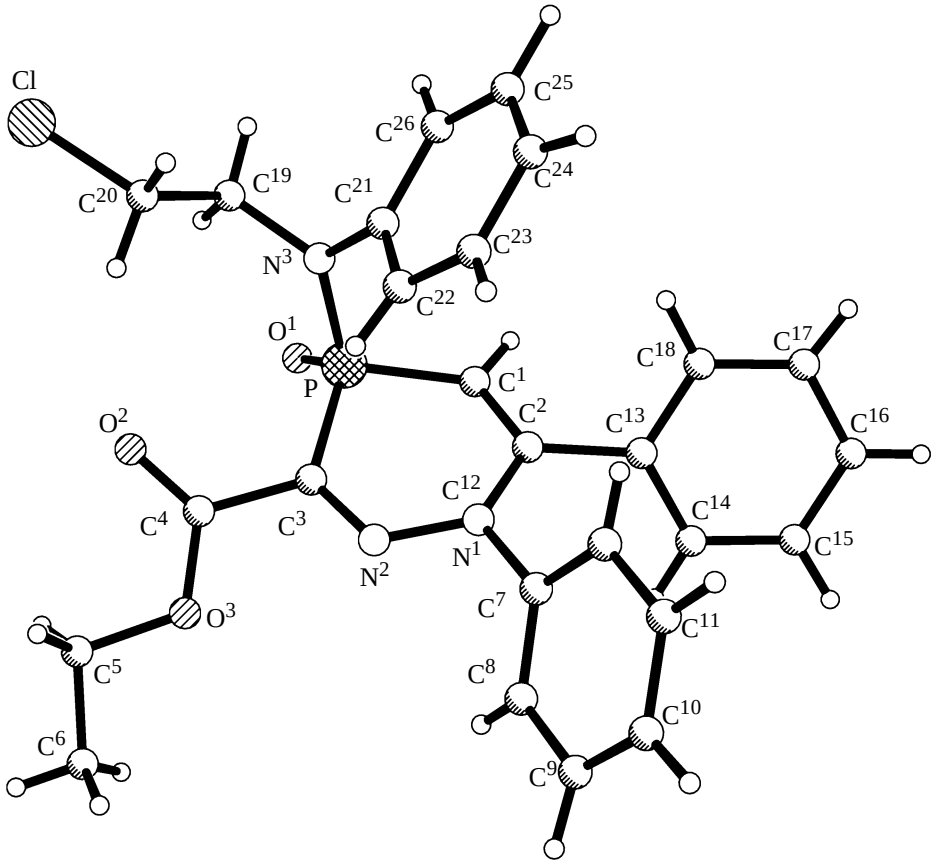
Table 1. Yields, melting points, and elemental analyses of substituted 4-[*N*-phenyl-*N*(2-chloroethyl)amino]-1,4-dihydro-1,2,4-diazaphosphorines **II**–**VIII**

Comp. no.	R	Ar	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
					C	H	P		C	H	P
II	C(O)Me	Ph	72	171–172	64.87	5.20	6.47	$C_{25}H_{23}ClN_3O_2P$	64.73	5.00	6.68
III	C(O)Me	C_6H_4Br-*p*	67	183–184	55.04	4.18	5.87	$C_{25}H_{32}BrClN_3O_2P$	55.32	4.09	5.71
IV	C(O)OEt	Ph	70	180–182	63.01	5.02	6.11	$C_{26}H_{25}ClN_3O_3P$	63.22	5.10	6.27
V	C(O)OEt	C_6H_4Br-*p*	90	161–162	54.68	4.32	5.65	$C_{26}H_{24}BrClN_3O_3P$	54.52	4.22	5.41
VI	C(O)OEt	$C_6H_4NO_2$-*p*	46	185–187	57.76	4.56	5.86	$C_{26}H_{24}ClN_4O_5P$	57.95	4.49	5.75
VII	$C(O)C_6H_4NO_2$-*p*	Ph	75	167–168	63.17	4.34	5.48	$C_{30}H_{24}BrN_4O_4P$	63.11	4.24	5.42
VIII	Ph	Ph	52	139–141	70.08	5.30	6.19	$C_{29}H_{25}ClN_3OP$	69.95	5.06	6.22

Table 2. IR and ^{1}H and ^{31}P NMR data for substituted 4-[*N*-phenyl-*N*(2-chloroethyl)amino]-1,4-dihydro-1,2,4-diazaphosphorines **II**–**VIII**

Comp. no.	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)					^{31}P NMR spectrum, δ_P, ppm
	C=O	P=O	=CH, d ($^2J_{Ph}$)	$HlgCH_2$, two m	NCH_2, two m	Ar–H, m	other groups	
II	1625	1280	Isomer **A**: 6.06 (2.8)	4.48, 3.63	3.51, 3.58	7.02–7.85	2.65 s [C(O)Me]	–0.6
			Isomer **B**: 5.67 (~0)	4.45, 3.82	3.52, 3.65	6.65–7.38	2.38 s [C(O)Me]	–7.4
III	1700	1240	Isomer **A**: 6.09 (3.4)	4.48, 3.72	3.51, 3.60	6.92–7.70	2.64 s [C(O)Me]	–1.1
			Isomer **B**: 5.69 (~0)	4.46, 3.80	3.53, 3.67	6.60–7.30	2.39 s [C(O)Me]	–7.8
IV	1760	1250	5.64 (~0)	4.53, 3.79	3.56, 3.63	6.61–7.35	1.43 t (Me), 4.42 m (OCH_2)	–7.3
V	1766	1260	5.65 (~0)	4.51, 3.77	3.55, 3.62	6.50–7.30	1.43 t (Me), 4.42 m (OCH_2)	–7.8
VI	1710	1245	5.74 (~0)	4.51, 3.75	3.55, 3.62	6.82–7.95	1.45 t (Me), 4.45 m (OCH_2)	–8.6
VII	1760	1250	5.81 (3.3)	4.57, 3.94	3.42, 3.58	6.55–8.18	–	–
VIII	–	1260	5.45 (1.1)	4.12, 3.68	3.35, 3.40	6.65–8.18	–	–

The molecular structure of diazaphosphorines **II**–**VIII** was studied by single crystal X-ray diffraction for 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,5-diphenyl-3-ethoxycarbonyl-1,2,4λ^5-diazaphosphorine **IV** as example (see figure; Tables 3, 4). We found that all the atoms of the heterocycle except phosphorus are coplanar within 0.030 Å. The phosphorus atom deviates from this plane by 0.294 Å,



Molecular structure of 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,5-diphenyl-3-ethoxycarbonyl-1,2,4λ^5-diazaphosphorine **IV**.

Table 3. Interatomic distances in the molecule of 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,5-diphenyl-3-ethoxycarbonyl-1,2,4λ^5-diazaphosphorine **IV**

Bond	*d*, Å	Bond	*d*, Å
$Cl–C^{20}$	1.780(6)	$C^7–C^{12}$	1.368(7)
$P–O^1$	1.464(3)	$C^8–C^9$	1.375(7)
$P–N^3$	1.662(4)	$C^9–C^{10}$	1.356(9)
$P–C^1$	1.737(4)	$C^{10}–C^{11}$	1.361(8)
$P–C^3$	1.786(4)	$C^{11}–C^{12}$	1.387(7)
$O^2–C^4$	1.197(5)	$C^{13}–C^{18}$	1.380(6)
$O^3–C^4$	1.314(5)	$C^{13}–C^{14}$	1.381(6)
$O^3–C^5$	1.455(6)	$C^{14}–C^{15}$	1.378(7)
$N^1–N^2$	1.340(4)	$C^{15}–C^{16}$	1.359(8)
$N^1–C^2$	1.398(5)	$C^{16}–C^{17}$	1.374(8)
$N^1–C^7$	1.448(5)	$C^{17}–C^{18}$	1.369(7)
$N^2–C^3$	1.296(5)	$C^{19}–C^{20}$	1.509(9)
$N^3–C^{21}$	1.419(5)	$C^{21}–C^{26}$	1.383(7)
$N^3–C^{19}$	1.469(6)	$C^{21}–C^{22}$	1.386(7)
$C^1–C^2$	1.341(6)	$C^{22}–C^{23}$	1.377(8)
$C^2–C^{13}$	1.479(6)	$C^{23}–C^{24}$	1.345(8)
$C^3–C^4$	1.492(6)	$C^{24}–C^{25}$	1.377(9)
$C^5–C^6$	1.455(10)	$C^{25}–C^{26}$	1.357(8)
$C^7–C^8$	1.359(7)		

Table 4. Bond angles in the molecule of 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,5-diphenyl-3-ethoxycarbonyl-1,2,4λ^5-diazaphosphorine **IV**

Angle	ω, deg	Angle	ω, deg
O^1PN^3	109.77(19)	$C^8C^7C^{12}$	120.4(5)
O^1PC^1	118.1(2)	$C^8C^7N^1$	119.2(4)
N^3PC^1	106.01(19)	$C^{12}C^7N^1$	120.3(4)
O^1PC^3	114.32(19)	$C^7C^8C^9$	119.6(5)
N^3PC^3	111.00(19)	$C^{10}C^9C^8$	120.6(6)
C^1PC^3	96.8(2)	$C^9C^{10}C^{11}$	120.0(5)
$C^4O^3C^5$	117.0(4)	$C^{10}C^{11}C^{12}$	119.9(5)
$N^2N^1C^2$	124.2(3)	$C^7C^{12}C^{11}$	119.4(5)
$N^2N^1C^7$	112.6(3)	$C^{18}C^{13}C^{14}$	118.6(4)
$C^2N^1C^7$	123.2(3)	$C^{18}C^{13}C^2$	118.5(4)
$C^3N^2N^1$	122.1(3)	$C^{14}C^{13}C^2$	122.8(4)
$C^{21}N^3C^{19}$	118.2(4)	$C^{15}C^{14}C^{13}$	120.1(5)
$C^{21}N^3P$	122.4(3)	$C^{16}C^{15}C^{14}$	120.9(5)
$C^{19}N^3P$	119.5(3)	$C^{15}C^{16}C^{17}$	119.4(5)
C^2C^1P	125.0(3)	$C^{18}C^{17}C^{16}$	120.3(5)
$C^1C^2N^1$	122.1(4)	$C^{17}C^{18}C^{13}$	120.7(5)
$C^1C^2C^{13}$	120.9(4)	$N^3C^{19}C^{20}$	110.4(4)
$N^1C^2C^{13}$	117.0(3)	$C^{19}C^{20}Cl$	109.5(5)
$N^2C^3C^4$	115.6(4)	$C^{26}C^{21}C^{22}$	117.4(5)
N^2C^3P	126.8(3)	$C^{26}C^{21}N^3$	120.5(4)
C^4C^3P	117.6(3)	$C^{22}C^{21}N^3$	122.0(4)
$O^2C^4O^3$	124.5(4)	$C^{23}C^{22}C^{21}$	120.6(5)
$O^2C^4C^3$	122.1(4)	$C^{24}C^{23}C^{22}$	121.1(6)
$O^3C^4C^3$	113.3(4)	$C^{23}C^{24}C^{25}$	119.0(6)
$O^3C^5C^6$	107.0(6)	$C^{26}C^{25}C^{24}$	120.8(5)
$C^{25}C^{26}C^{21}$	121.1(5)		

which allows the structure of the heterocycle to be considered as a flattened *P-envelope*. The angle between the phosphorus triangle ($C^1–P–C^3$) and the remaining part of the heterocycle is 14°. The angles between the planes of the heterocycle and phenyl rings $C^7–C^{12}$ and $C^{13}–C^{18}$ are 125.2° and 61.2°, respectively. The tetrahedral configuration of phosphorus is distorted; the XPY angles vary in the range 96.8°–118.1°.

Thus, by the reaction of 3-phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine **I** with nitrilimines we prepared previously unknown substituted 1,4-dihydro-1,2,4λ^5-diazaphosphorines **II**–**VIII** containing the aminohalomethyl group at phosphorus. The presence of this group in the molecules of organophosphorus compounds is important for realization of their anticancer propeties.

EXPERIMENTAL

The IR spectra of **I**–**VIII** were recorded on an IKS-29 spectrometer in thin film (for **I**) or in KBr pellets (for **II**–**VIII**). The ^1H NMR spectra were taken on a Bruker AM-500 (500 MHz) spectrometer in $CDCl_3$ with the internal stabilization by the resonance line of ^2H. The ^{31}P NMR spectra were measured on a Bruker AC-200 spectrometer (81.4 MHz) in $CDCl_3$. The chemical shift was measured against 85% phosphoric acid.

A single crystal X-ray diffraction study of 4-[*N*-phenyl-*N*-(2-chloroethyl)amino]-1,4-dihydro-1,5-diphenyl-3-ethoxycarbonyl-1,2,4λ^5-diazaphosphorine **IV** was carried out on a CAD-4 diffractometer (MoK_α radiation, θ/2θ scanning). Triclinic crystals: $C_{26}H_{25}\cdot ClN_3O_3P$; *a* 10.910(2), *b* 10.967(2), *c* 12.134(2) Å, α 72.52(3)°, β 68.21(3)°, γ 67.54(3)°, *V* 1224.4(4) Å^3; space group $P\bar{1}$, *Z* 2, d_{calc} 1.340 g cm^{-3}. The structure was solved by the direct method, *R* 0.0538, R_W 0.1387 [2394 reflections with $I > 2\sigma(I)$]. The atomic coordinates and their isotropic temperature factors are deposited at the Cambridge Structural Database (registry no. CCDC 235900).

Synthesis of 3-phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine **I** and its reactions with nitrilimines were performed under dry argon in anhydrous solvents.

3-Phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine I. A solution of phenylethynylmagnesium bromide prepared from 4.0 g of magnesium, 14.2 g of ethyl bromide, and 14.0 g of phenylacetylene in 40 ml of THF was added dropwise with vigorous stirring at –60°C to a solution of 24.9 g of 2-chloro-3-phenyl-1,3,2λ^3-oxazaphospholidine [5] in 200 ml of THF. After that the reaction mixture was gradually heated to 20°C, stirred for 30 min, and then 50 ml of pyridine was added. The resulting precipitate was filtered off, THF was distilled off at reduced pressure, and the residue was extracted with diethyl ether (3 × 100 ml). The ether was removed in a vacuum, and the residue was crystallized on cooling to 0–5°C to obtain 24.7 g (77%) of 3-phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine **I**, mp 67–70°C. IR spectrum, ν, cm^{-1}: 2120 (C=C), 1010 (P–O–C). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.47 m (2H, NCH_2), 4.67 m (2H, OCH_2), 6.90–7.52 m (10H, Ph). ^{31}P NMR spectrum: δ_P 97.7 ppm. Found, %: C 71.78; H 5.39; P 11.45. $C_{16}H_{14}NOP$. Calculated, %: C 71.90; H 5.28; P 11.59.

Substituted 4-[*N*-phenyl-*N*-(2-chloroethyl)-amino]-1,4-dihydro-1,2,4λ^5-diazaphosphorines II and III. A solution of 0.005 mol of 3-phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine **I**, 0.005 mol of appropriate hydrazonoyl chloride, and 2 ml of triethylamine in 20 ml of benzene was refluxed for 2 h. The abundant precipitate that formed after cooling to 20°C was filtered off, washed with water (2 × 50 ml) to remove an impurity of triethylamine hydrochloride, and crystallized from 1:1 acetone–hexane (compound **II**) or benzene (compound **III**).

Substituted 4-*N*-[*N*-phenyl-*N*-(2-chloroethyl)]-1,4-dihydro-1,2,4λ^5-diazaphosphorines IV–VIII. A solution of 0.005 mol of 3-phenyl-2-phenylethynyl-1,3,2λ^3-oxazaphospholidine **I**, 0.005 mol of appropriate hydrazonoyl halide, and 2 ml of triethylamine in 20 ml of benzene was refluxed for 2 h. A small amount of triethylamine hydrochloride (14–20%) was filtered off. In the case of **V** and **VIII**, the residue was a solid which was crystallized from 1:1 acetone–hexane. In the case of **IV**, **VI**, and **VII**, the residue was an oily substance which was treated with diethyl ether (compounds **IV** and **VI**) or with 2:1 ether–hexane mixture (**VII**). The crystalline products were filtered off and crystallized from 3:1 hexane–benzene (compound **IV**), 1:1 acetone–hexane (compound **VI**), or 2:1 hexane–benzene (compound **VII**).

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