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1,5-Thione-thiol Isomerization of 3-*O*-Phosphorylated 1,4-Benzodiazepine

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Abstract—Diphenylphosphinite, 1,4-benzodiazepine 3-*O*-derivative, was converted into the corresponding imides by the Staudinger reaction with azides of diphenylphosphinic, diphenylthiophosphinic, and diphenylphosphoric acids. The imide derived from azide of diphenylthiophosphinic acid undergoes the isomerization into the corresponding thiol when heated in the presence of catalytic amounts of a substituted 3-chloro-1,4-benzodiazepine.

Keywords: 1,5-thione-thiol rearrangement, 1,4-benzodiazepine, diphenylchlorophosphine, Staudinger reaction, azides of diphenyl(thio)phosphonic acid

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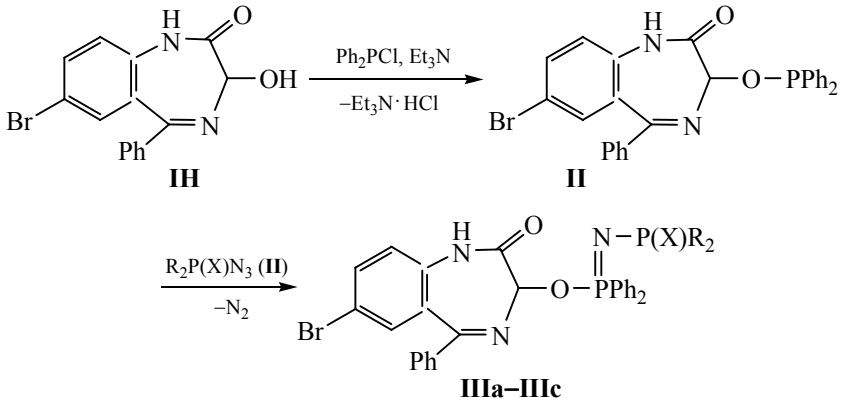
Substituted 1,4-benzodiazepines are well known because many specimens of this class of heterocyclic compounds are used in medicine. In recent years, much attention is paid to the study of their analgesic activity [1, 2]. At the same time, the chemistry and medicinal chemistry of the phosphorylated 1,4-benzodiazepines are not virtually developed. Only some phosphorylated 1,4-benzodiazepines have been described [3, 4]; generally, they were used in organic synthesis as CH acids. Recently we reported [5] on new approaches towards synthesis of 3- and 5-substituted phosphine oxides of 1,4-benzodiazepine series. Here we describe a new method of the synthesis of substituted 1,4-benzodiazepines where a phosphorus moiety is linked to the heterocycle via the oxygen or sulfur atom.

Under certain conditions the esters of thionic acids are rearranged into the thermodynamically more stable thiols. Thus, heating *O*-arylthiocarbamates resulted in

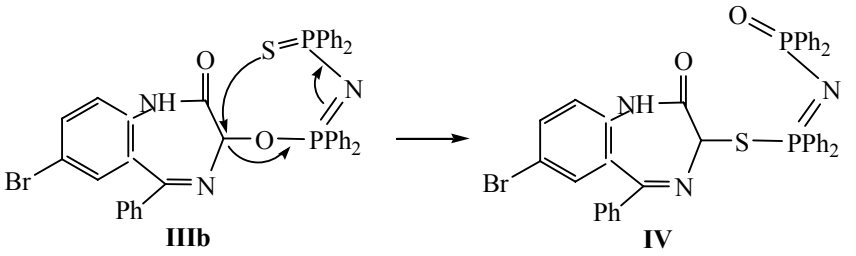
Scheme 1.



IH **II** **IIIa–IIIc**

R = Ph, X = O (**a**); R = Ph, X = S (**b**); R = PhO, X = O (**c**).

Scheme 2.



S-arylthiocarbamates [6]. Similarly, thionephosphates rearranged into tiolphosphates [7]. In the latter case the isomerization occurred in 1,3-system: R–O–P=S → R–S–P=O. Thione–thiol isomerization in the 1,5-conjugated system R–O–P=N–P=S → R–S–P=N–P=O has been also described by two examples [8, 9].

In order to search for new biologically active compounds in a series of phosphorylated 1,4-benzodiazepines, we brought diphenylphosphine **I** [5] into the Staudinger reaction [10, 11] with azides of phosphorus acids **II**. The reaction proceeded in THF at 60°C to afford imides **III** and **IV**. The reactions were accompanied with nitrogen evolution (Scheme 1).

Imides **IIIa** and **IIIc** were stable and did not change when heated to 150–180°C. This suggests that imide-amide rearrangement is not characteristic of these compounds obviously due to the low nucleophilicity of the imine nitrogen. However thione **IIIb** was completely rearranged into thiol **IV** by heating in the presence of 3-chloro-1,4-benzodiazepine (Scheme 2).

The composition and structure of imides **IIIa**, **IIIb**, and **IV** were confirmed by elemental analysis data, IR, NMR spectroscopy and X-ray diffraction (XRD) analysis (Figs. 1–3).

Compounds **IIIa**, **IIIb**, and **IV** have a similar molecular structure (Table 1). The central 1,4-diazepine ring has a *boat* conformation consisting of the N^1, C^2, N^4, and C^5 atoms. The angle between the planes of the benzene ring, connected with the 1,4-diazepine ring, and of the phenyl substituent at the position *5* equal varies in the range 58.35(5)° (**IIIa**) to 76.57(6)° (**IV**). The nitrogen atom N^1 of the amino group has a trigonal-planar configuration. Bulky phosphoryl substituents occupy the sterically preferred equatorial

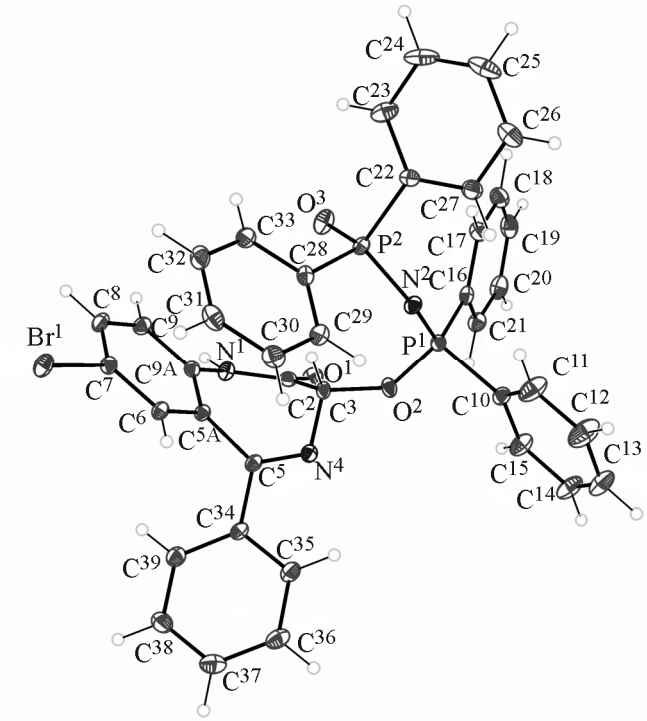


Fig. 1. General view of the molecule of **IIIa**.

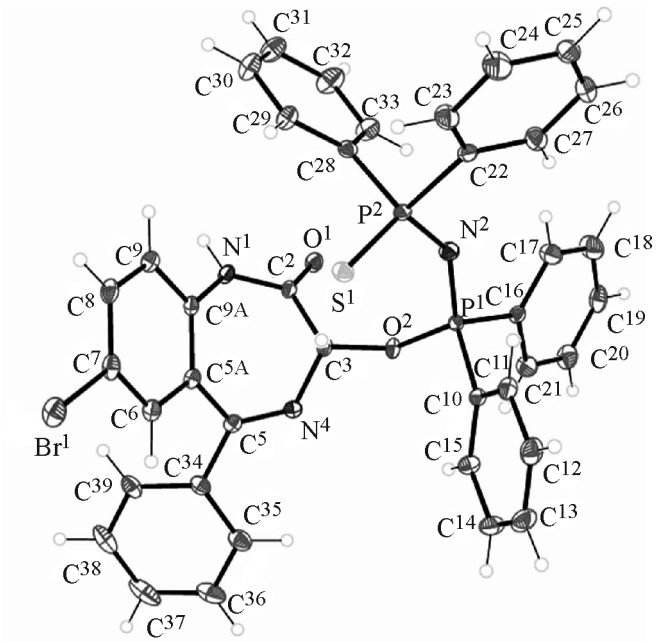


Fig. 2. General view of the molecule of **IIIb**.

Table 1. Bond lengths (*d*, Å) and bond angles (ω, deg) of compounds **IIIa**, **IIIb**, and **IV**

Bond, angle	**IIIa** (X = O^2, Y = O^3)[a]	**IIIb** (X = O^2, Y = S^1)	**IV** (X = S^1, Y = O^2)	Bond, angle	**IIIa** (X = O^2, Y = O^3)[a]	**IIIb** (X = O^2, Y = S^1)	**IV** (X = S^1, Y = O^2)
P^1–X	1.5983(12)	1.6028(14)	2.0868(7)	C^{5A}–C^{9A}	1.409(2)	1.402(3)	1 . 3 9 8 4
	1.6011(12)				1.408(2)		(18)
P^1–N^2	1.5505(14)	1.5546(17)	1.5635(18)	N^2P^1X	116.43(7)	117.73(9)	116.67(7)
	1.5520(13)				116.51(7)		
P^2–N^2	1.6125(14)	1.6113(17)	1.6126(17)	N^2P^2Y	118.86(7)	120.29(7)	116.73(9)
	1.6125(13)				118.71(7)		
P^2–Y	1.4928(12)	1.9694(7)	1.4964(15)	C^3XP^1	122.92(10)	121.28(12)	99.42(7)
	1.4956(12)				122.17(10)		
N^1–C^2	1.366(2)	1.350(2)	1.360(3)	$P^1N^2P^2$	137.38(10)	139.92(12)	137.36(12)
	1.366(2)				134.94(9)		
N^1–C^{9A}	1.412(2)	1.412(2)	1.411(2)	$C^2N^1C^{9A}$	126.34(14)	125.84(17)	128.26(16)
	1.406(2)				127.04(14)		
C^2–O^1	1.2140(19)	1.226(2)	1.218(3)	$N^1C^2C^3$	112.84(14)	113.80(16)	114.38(18)
	1.2141(19)				112.93(13)		
C^2–C^3	1.531(2)	1.531(3)	1.533(3)	$C^2C^3N^4$	109.73(13)	106.97(15)	109.10(16)
	1.531(2)				108.47(12)		
C^3–X	1.4292(18)	1.429(2)	1.830(2)	$C^3N^4C^5$	117.67(14)	117.46(16)	118.37(17)
	1.4267(18)				117.36(13)		
C^3–N^4	1.442(2)	1.447(2)	1.456(3)	$N^4C^5C^{5A}$	124.51(15)	124.14(18)	125.71(17)
	1.441(2)				124.59(14)		
N^4–C^5	1.289(2)	1.287(2)	1.283(3)	$C^5C^{5A}C^{9A}$	122.15(14)	121.72(17)	122.35(14)
	1.293(2)				121.93(14)		
C^5–C^{5A}	1.484(2)	1.489(3)	1.491(2)	$C^{5A}C^{9A}N^1$	123.05(14)	121.93(17)	123.07(14)
	1.486(2)				123.34(14)		

[a] Data for two crystallographically independent molecules are given.

position. The distribution of the bond lengths in the chains X–P^1=N^2–P^2=Y (X, Y = O, S) in the molecules of all three compounds (Table 1) agree well with each other and correspond to the presence of a sufficiently strong conjugation. The bond angle at the nitrogen atom N^2 varies within a narrow range of 134.94(9)°–139.92(12)°.

The main difference between the structures of **IIIa**, **IIIb**, **IV** lies in the conformation of the conjugated chains X–P^1=N^2–P^2=Y (X, Y = O, S), namely in the values of virtual torsion angle X–P^1···P^2=Y. Thus, in the molecule of imide **IIIa** the torsion angle O^2–P^1···P^2=O^3 equals –56.59(8)° and –49.39(7)° (for two crystallographically independent molecules); in the molecule of **IIIb** the angle O^2–P^1···P^2=S^1 is equal to –70.62(6)°. The torsion angle S^1–P^1···P^2=O^2 in the molecule of **IV** is –10.46(7)°. Presumably, the observed conformations of the phosphoryl substituents in imides **IIIa**, **IIIb**, and **IV** were defined by two main factors: the presence (or absence) of solvate solvent molecules and, consequently, the total effect of the crystal packing and various hydrogen bonding systems (Table 2).

It was found that the molecule of imide **IIIa** in the crystal form centrosymmetric dimers connected by two intermolecular hydrogen bonds N–H···O(=P) (Table 2). Dimers, in turn, are connected by weak intermolecular hydrogen bonds C–H···O to form the layers parallel to the (010) plane.

The molecules of imide **IIIb** in the crystal also form centrosymmetric hydrogen bond-linked dimers. However, unlike imide **IIIa** they are formed by two intermolecular hydrogen bonds N–H···O(=C) (Table 2). In turn, the dimers are linked by weak intermolecular hydrogen bonds C–H···O to form stacks along the [010] direction. It should be noted that chloroform

Table 2. Parameters of the hydrogen bonds (*d*, Å) for compounds **IIIa**, **IIIb**, and **IV**

D–H···A[a]	D–H	H···A	D···A	∠D–H···A, deg
		IIIa		
N^{1}–H^{1}···O^{3} [–*x* + 1, –*y* + 1, –*z* + 1]	0.90(2)	1.91(2)	2.798(2)	169(2)
N^{1A}–H^{1A}···O^{3A} [–*x*, –*y* + 1, –*z*]	0.86(2)	1.89(2)	2.751(2)	177(2)
C^{24}–H^{24}···O^{3A} [–*x* + 1, –*y* + 1, –*z*]	0.95	2.56	3.383(2)	145
C^{31A}–H^{31A}···O^{1} [*x* – 1, *y*, *z* – 1]	0.95	2.48	3.198(2)	133
		IIIb		
N^{1}–H^{1}···O^{1} [–*x* + 2, –*y* + 2, –*z* + 1]	0.91	1.92	2.817(2)	171
C^{20}–H^{20}···O^{1} [–*x* + 2, –*y* + 1, –*z* + 1]	0.95	2.50	3.303(2)	143
C^{40}–H^{40}···S^{1}	1.00	2.74	3.698(2)	161
		IV		
N^{1}–H^{1}···O^{2} [–*x*, –*y* + 1, –*z* + 1]	0.88	1.88	2.740(2)	166
C^{18}–H^{18}···O^{3} [*x*–1, *y*, *z*]	0.95	2.29	3.138(5)	148
C^{25}–H^{25}···O^{1} [*x* + 1, *y*, *z*]	0.95	2.51	3.394(3)	156

[a] (D) proton-donor, (A) proton-acceptor.

solvate molecules are retained in the crystalline structure of **IIIb** due to weak hydrogen bonds C–H···S (Table 2).

Finally, the molecule of imide **IV** in the crystal form centrosymmetric dimers due to two intermolecular hydrogen bonds N–H···O(=P) (Table 2). The crystal structure of **IV** was similar to the structure of **IIIb**, i.e., the dimers are linked by weak intermolecular hydrogen bonds C–H···O to form the stacks along the [100] direction. As in the molecule of imide **IIIb**, dimethylformamide solvate molecules are retained in the crystal of **IV** due to weak hydrogen bonds C–H···O (Table 2).

Mechanism of the considered 1,5-thione-thiol rearrangement has not been studied. According to our data, the rearrangement is irreversible. The isomerization of thione **IIIb** into thiol **IV** is apparently due to energetically favorable formation of the P=O bond in **IV**. The possibility of simultaneous electron transfer in imide **IIIb** under heating suggests that the rearrangement **IIIb**→**IV** was intramolecular.

Thus, 7-bromo-3-({[(diphenyl(sulfanylidene)-λ^5-phosphanyl]imino}diphenyl-λ^5-phosphanyl)oxy]-5-phenyl-2,3-dihydro-1*H*-1-benzodiazepin-2-one undergoes 1,5-thione-thiol rearrangement into the isomeric 7-bromo-3-({[(diphenylphosphoryl)imino]diphenyl-λ^5-phosphanyl}sulfanyl)-5-phenyl-2,3-dihydro-1*H*-1-benzodiazepin-2-one.

EXPERIMENTAL

NMR spectra were obtained on a Bruker Avance TM-400 spectrometer [400.1 (^{1}H), 100.68 (^{13}C), 162.02 (^{31}P) MHz]. IR spectra were recorded on a Magna-IR-750 Nicolet Fourier spectrometer. All reactions were performed under nitrogen atmosphere.

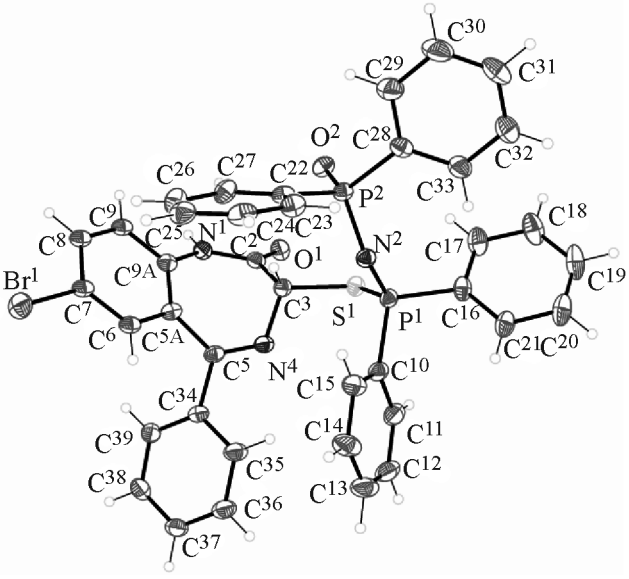


Fig. 3. General view of the molecule of **IV**.

Table 3. Main crystallographic and refinement parameters for compounds **IIIa**, **IIIb**, and **IV**

Parameter	**IIIa**	**IIIb**·$CHCl_3$	**IV**·1.5DMF
Formula	$C_{39}H_{30}BrN_3O_3P_2$	$C_{40}H_{31}BrCl_3N_3O_2P_2S$	$C_{40.5}H_{33.5}BrN_{3.5}O_{2.5}P_2S$
M	730.51	865.94	783.12
T, K	120(2)	110(2)	120(2)
Crystal system	Triclinic	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a, Å	12.6366(5)	11.7504(5)	10.7577(4)
b, Å	15.0821(5)	11.9850(5)	12.5990(4)
c, Å	19.6643(7)	16.1198(6)	14.5246(5)
α, deg	107.464(1)	97.141(1)	77.891(1)
β, deg	101.853(1)	103.582(1)	77.041(1)
γ, deg	97.487(1)	115.946(1)	72.147(1)
V, Å^3	3424.0(2)	1916.11(13)	1804.86(11)
Z	4	2	2
d_{calc}, g cm^{-3}	1.417	1.501	1.441
F(000)	1496	880	804
μ, mm^{-1}	1.337	1.460	1.328
$2\theta_{max}$, deg	65.2	65.2	60.0
Reflections collected	54043	30325	24263
Unique reflections (R_{int})	24894 (0.038)	13983 (0.047)	10522 (0.034)
Reflections observed with $I > 2\sigma(I)$	17265	9392	7320
Parameters refined	871	469	457
$R_1[I > 2\sigma(I)]$	0.042	0.046	0.047
wR_2 (all data)	0.097	0.103	0.126
GOF	1.028	0.999	1.047
T_{min}; T_{max}	0.731; 0.776	0.759; 0.811	0.777; 0.826

General procedure for the preparation of compounds IIIa–IIIc and IV. To a cooled to +3°C mixture of 1.51 mmol of alcohol **I** and 1.81 mmol of triethylamine in 12 mL of THF was added dropwise a solution of Ph_2PCl (1.81 mmol) in 5 mL of THF. After 30 min, 1.8 mmol of the corresponding azide was added to the reaction mixture at room temperature. Then the mixture was stirred at 60°C for 1–1.5 h, cooled, filtered and evaporated in a vacuum. The residue was recrystallized from acetone.

7-Bromo-3-({[(diphenylphosphoryl)imino]diphenyl-λ^5-phosphanyl}oxy)-5-phenyl-2,3-dihydro-1*H*-1-benzodiazepin-2-one (IIIa). Yield 30%, mp 215°C. IR spectrum (KBr), ν, cm^{-1}: 1725 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.94 d (1H, CHOP, J_{HP} 7.9 Hz), 6.91–8.08 m (28H, Ph), 11.09 s (1H, NH). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 24.97 (P=N), 11.80 (P=O). Found, %: C 62.97; H 4.28; N 5.62; P 9.46; Br 11.03. $C_{39}H_{30}BrN_3O_3P_2$. Calculated, %: 64.11; H 4.11; N 5.75; P 8.96; Br 10.96.

7-Bromo-3-[({[diphenyl(sulfanylidene)-λ^5-phosphanyl]imino}diphenyl-λ^5-phosphanyl)oxy]-5-phenyl-2,3-dihydro-1*H*-1-benzodiazepin-2-one (IIIb). Yield 30%, mp 145°C. IR spectrum (KBr), ν, cm^{-1} : 1705 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.21 d (1H, CHOP, J_{HP} 8.0 Hz), 6.85–8.10 m (28H, Ph),

11.08 s (1H, NH). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 26.96 (P=N), 41.71 (P=S). Found P, %: 8.30. $C_{39}H_{30}BrN_3O_2P_2S$. Calculated P, %: 8.38.

7-Bromo-3-({[(diphenylphosphoryl)imino]diphenyl-λ^5-phosphanyl}sulfanyl)-5-phenyl-2,3-dihydro-1*H*-1-benzodiazepin-2-one (IV). Yield 50%, mp 230°C. IR spectrum (KBr), ν, cm^{-1}: 1697 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.94 d (1H, CHOP, J_{HP} 8.52 Hz), 6.68–8.21 m (28H, Ph), 11.20 s (1H, NH). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 23.04 d (P=N, J_{PP} 19.3 Hz), 12.64 d (P=O, J_{PP} 19.3 Hz). Found, %: C 63.23; H 4.26; N 5.36; P 7.53; S 4.11. $C_{39}H_{30}BrN_3O_2P_2S$. Calculated, %: C 62.70; H 4.02; N 5.63; P 8.31; S 4.29.

7-Bromo-3-({[(diphenylphosphoryl)imino]diphenyl-λ^5-phosphanyl}oxy)-5-phenyl-2,3-dihydro-1*H*-1-benzodiazepin-2-one (IIIc). Yield 50%, mp 180°C. IR spectrum (KBr), ν, cm^{-1}: 1719 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.84 d (1H, CHOP, J_{HP} 7.92 Hz), 6.87–7.91 m (28H, Ph), 11.17 s (1H, NH). ^{31}P NMR spectrum (DMSO-d_6), δ_P, ppm: 24.14 (P=N), 11.08 (P=O). Found, %: C 69.97; H 4.28; N 5.62; P 9.46; Br 11.03. $C_{39}H_{30}BrN_3O_3P_2$. Calculated, %: C 64.11; H 4.11; N 5.75; P 9.46; Br 10.96.

X-Ray diffraction studies were performed on a Bruker SMART APEX-II CCD automatic diffractometer (MoK_α-radiation, graphite monochromator, φ- and ω-scanning). The correction for extinction was performed using SADABS software [12]. Main crystallographic parameters are presented in Table 3. The structures were solved by the direct method and refined by the full-matrix least-squares method with respect to F^2 in the anisotropic approximation for non-hydrogen atoms.

The bromobenzene fragment in **IV** is disordered over two provisions with equal occupancies. The crystals of **IIIb** and **IV** contained 1 solvate molecule of chloroform and 1.5 solvate molecules of dimethylformamide, respectively. The hydrogen atoms of the amino groups in all compounds were localized objectively in the difference Fourier syntheses and refined isotropically (in the case of **IIIa**) with the fixed displacement parameters $U_{iso}(H) = 1.2U_{eq}(N)$; in the case of **IIIb** and **IV** the parameters of the hydrogen atoms were refined in the isotropic approximation by a *rider* model [$U_{iso}(H) = 1.2U_{eq}(N)$]. Positions of the remaining hydrogen atoms were geometrically calculated; parameters of the hydrogen atoms were refined in the isotropic approximation by a *rider* model [$U_{iso}(H) = 1.5U_{eq}(C)$ for CH_3-groups and $U_{iso}(H) = 1.2U_{eq}(C)$ for the other groups]. All calculations were performed using SHELXTL software [13]. Atomic coordinates, bond lengths and angles for compounds **IIIa**, **IIIb**·$CHCl_3$ and **IV**·1.5DMF were deposited in the Cambridge Crystallographic Data Center (CCDC 1007437–1007439).

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