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Multinuclear magnetic resonance study of the structure and tautomerism of azide and iminophosphorane derivatives of chloropyridazines

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Some azido- and iminophosphorane derivatives of 3,6-dichloro- and 3,4,5,6-tetrachloropyridazine were synthesized and studied by means of NMR measurements. Based on multinuclear data (chemical shifts, coupling constants) for compounds containing the azide group, no potentially possible tetrazole–azide equilibrium can be observed, even under acidic conditions. An unusual substitution of a chlorine atom (in position 4) of tetrachloropyridazine in the reaction with hydrazine was demonstrated by NMR measurements of two newly synthesized compounds containing azido- and iminophosphorane groups. Using multinuclear magnetic resonance data, the sites of ethylation and protonation of azido- and iminophosphorane derivatives of chloropyridazines were established. In the case of the tetrazolopyridazines, ethylation occurs at the N1′ and N2′ atoms, whereas for monocyclic compounds it takes place at the N1 and/or N2 atoms of the pyridazine ring. Preferred sites of protonation are the N1′ atom of the tetrazole ring and the N1 atom of the pyridazine ring. Moreover, the structures of potassium salts of 6-(3-cyano-1-triazeno)tetrazolo[1,5-*b*] pyridazine and its amido derivative were established using NMR data, especially ^{15}N NMR chemical shifts. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; ^{15}N NMR; ^{31}P NMR; ^{13}C,^{13}C, ^{31}P,^{1}H, ^{31}P,^{13}C, ^{31}P,^{15}N coupling; tetrazoles; azides; ethylation; *N*-pyridazinium salts

INTRODUCTION

Derivatives of 3,6-dichloropyridazine (**1**) play an important role in chemical synthesis, pharmacology and agrochemistry.[1] It is known, for instance, that 3-azidopyridazine derivatives, existing mainly as tetrazolo[1,5-*b*]pyridazines, have a high cytostatic activity in KB and HeLa human cancer cells[2] and also sedative effects and anticonvulsant activity.[3]

All 3-azidopyridazine derivatives may exhibit tetrazole–azide tautomerism, but this equilibrium depends strongly on the nature and the position of substituents, and on temperature and polarity of the solvent. In continuation of our studies of such tautomerism, compounds **3** and **5**, which potentially might exist in a tetrazole–azide equilibrium, were synthesized. Both of them reacted with triphenylphosphine yielding **4** and **8**, respectively, but only **8** containing the azide group may exhibit tetrazole–azide equilibrium (see Fig. 1).

Additionally, on the basis of NMR data, mainly ^{15}N NMR chemical shifts, the structures of two previously synthesized compounds, **6** and **7**,[4] have also been described (Fig. 1).

In contrast to **1** and its derivatives, little is known about the reactivity of 3,4,5,6-tetrachloropyridazine (**10**)[5–7] and, therefore, derivatives **11**–**13** (see Fig. 3) were synthesized and studied by NMR spectroscopy in order to determine their structures.

Our previous results[8–10] demonstrate that the tetrazole–azide equilibrium can also be observed under acidic conditions. Usually, the presence of strong acids increases the relative concentration of the azide form. In order to verify this rule for compounds **3**, **5** and **8**, the ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR spectra in trifluoroacetic acid (TFA) solution were measured.

For compounds **1**, **3**–**5**, **8**, **12** and **13**, containing at least three nitrogen atoms, protonation and ethylation studies were undertaken, using excess of TFA and triethyloxonium tetrafluoroborate (see Fig. 4), respectively. Protonation and ethylation sites of **1**, **3**–**5**, **12** and **13** were recognized by the observation of changes in the NMR parameters before and after the reactions.

RESULTS AND DISCUSSION

The ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR data (chemical shifts and coupling constants) for compounds **1**–**13** (in acetone, chloroform or TFA solutions) are given in Tables 1, 2 and 4, and Table 3 contains multinuclear magnetic resonance data (in acetone) for the *N*-ethylated compounds **14**–**27**.

The ^{1}H, ^{13}C and ^{15}N NMR signals for all of the compounds studied were assigned by the use of the results

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Table 1. ^{1}H, ^{13}C and ^{15}N NMR chemical shifts of compounds **1**, **2** and **9**–**11** at 298 K

	1 (acetone)	**1** (TFA)	**2** (DMSO)	**9**[a] (DMSO)	**10** (acetone)	**10** (TFA)	**11** (DMSO)
H4	7.90	8.00	7.12	8.20	—	—	—
H5	7.90	8.00	7.54	7.15	—	—	—
N*H*	—	—	9.45	8.91	—	—	8.33
NH_2	—	—	4.20	4.50	—	—	4.79
C3	156.9	156.2	159.7	140.3	155.3	154.6	142.9
C4	132.0	135.8	117.2	122.8	138.3	140.0	141.1
C5	132.0	135.8	129.9	119.0	138.3	140.0	113.5
C6	156.9	156.2	147.5	157.9	155.3	154.6	154.0
N1′	—	—	−282.0	—[b]	—	—	−277.9[b]
N2′	—	—	−330.8	—[b]	—	—	−329.9[b]
N1	+9.7	−53.4	−10.0	−144.5	+4.5	−33.3	−43.3[b]
N2	+9.7	−53.4	−52.0	−106.8	+4.5	−33.3	−9.6[b]

[a] ^{15}N chemical shifts in DMSO: *N*H, −321.2 ppm; *N*H_2, −276.5 ppm; N3′, not observed in ^{1}H–^{15}N gradient selected HMBC experiment.

[b] Not observed in ^{1}H–^{15}N gradient selected HMBC experiment.

of ^{1}H–^{13}C and ^{1}H–^{15}N gradient selected HMBC and, ^{1}H–^{13}C gradient selected HSQC correlation experiments (for NMR nomenclature of experiments, see Experimental), and the values of $^{1}J(^{13}C,^{13}C)$, $^{n}J(^{31}P,^{1}H)$, $^{n}J(^{31}P,^{13}C)$ and $^{n}J(^{31}P,^{15}N)$ couplings. In order to assign the NMR signals of compounds **6** and **7**, selectively labeled molecules **6*** and **7*** (Fig. 2) were prepared and measured in addition to the methods described above. In the case of compound **12** and its *N*-ethylated salts **24** and **25**, the ^{13}C and ^{15}N NMR signal assignment was made using differences in chemical shifts between **1** and its *N*-ethyl salt **20 = 21**.

There are two main routes for the synthesis of azide derivatives of pyridazine described in the literature.[11] In Figs 1–3, the reaction schemes leading to different derivatives of 3,6-dichloro- (**1**) and 3,4,5,6-tetrachloropyridazine (**10**) are presented.

Derivatives of 3,6-dichloropyridazine (1)

The pyridazine **1,** similarly to 2,6-dichloropyridine, reacts with hydrazine hydrate yielding monohydrazine **2**.[9,12] Treatment of **2** with sodium nitrite in acidic solution leads to derivative **3**, which may exhibit tetrazole–azide tautomerism (the numbering of the tetrazolo[1,5-*b*]pyridazines does not correspond to the IUPAC system and is in accordance with pyridazine ring). On the basis of ^{1}H and ^{13}C NMR spectra of the product of reaction of **1** with sodium azide, Shin *et al*.[1] suggested the presence of 3-azido-6-chloropyridazine (**3A**) in chloroform solution. The NMR data obtained previously[13] supplemented by the current results (Table 2) confirm the presence of only one set of ^{1}H, ^{13}C and ^{15}N NMR signals. This observation excludes the presence of a tetrazole–azide equilibrium, which is slow on NMR time-scale.[9] In our previous paper[9] we demonstrated in several cases the existence of two sets of appropriate NMR signals for both forms typical for azide and tetrazole. If only one set of signals is observed in the NMR spectra, it means that only one tautomeric form, azide (A) or tetrazole (T), exists in solution. The presence of only one set of ^{15}N NMR signals of **3** in the range typical for the tetrazole form (at +16.3, −25.1 and −63.2 ppm in $CDCl_3$ solution; Table 2)[8–10] provides unambiguous evidence that **3** exists as the bicyclic form **3T**, exclusively. This means that the structure **3A** suggested by Shin *et al*.[1] does not exist; in fact, the NMR data presented in Ref. 1 for **3A** are characteristic for **5TA**.

Reaction of **3T** with triphenylphosphine in chlorobenzene at 110 °C yields (6-chloropyridazin-3-yl)(triphenyl-λ^5-phosphanylidene)amine (**4**).[14] Introduction of phosphorus as an $NPPh_3$ group, causes additional splittings of the ^{1}H, ^{13}C and ^{15}N NMR signals associated with scalar spin–spin interactions $J(^{31}P,X)$ (where X = ^{1}H, ^{13}C and ^{15}N). With their presence, NMR signal assignments and the determination of the structures of the compounds studied are much easier. The most characteristic values are $^{1}J(^{31}P,^{15}N)$ ≈40 Hz, $^{3}J(^{31}P,^{15}N)$ ≈7 Hz, $^{3}J(^{31}P,^{13}C)$ ≈25 Hz and $^{2}J(^{31}P,^{13}C)$ ≈7 Hz (Table 2).

The second route leading to azide derivatives of azines is based on substitution of the halogen atom, located at the *ortho* position to the ring nitrogen atom, by the azide group. Reaction of **1** with excess of sodium azide leads to **5**, in which two azide groups replace both chlorine atoms. Analysis of the ^{1}H, ^{13}C and, especially, ^{15}N NMR spectra of **5** reveals only one unsymmetrical form. The presence of eight signals in the ^{15}N NMR spectrum of **5** taken in acetone solution (Table 2), in a typical range for both azide and tetrazole forms,[8–10] excludes the existence of both **5AA** and **5TT** and indicates the presence of 6-azidotetrazolo [1,5-*b*]pyridazine **5TA**. This conclusion is in agreement with x-ray results obtained by Katrusiak *et al*.[15] Moreover, the ^{13}C NMR signal assignment of **5TA** made by Krivopalov *et al*.[16] is now corrected (Table 2), using results of $^{1}J(^{13}C,^{13}C)$ measurements.

6-Azidotetrazolo[1,5-*b*]pyridazine (**5TA**) reacts with potassium cyanide yielding the potassium salt of 6-(3-cyano-1-triazeno)tetrazolo[1,5-*b*]pyridazine (**6**) (Fig. 1). The reaction of **6** with hydrochloric acid in acetone at 60 °C leads to 6-(3-carbamoylo-1-triazeno)tetrazolo [1,5-*b*]pyridazine (**7**), which

Table 2. ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR chemical shifts of compounds **3**–**8**, **12** and **13** at 298 K

	3 (acetone)	**4**[a,b] ($CDCl_3$)	**5**[c] (acetone)	**6**[d] (DMSO)	**7**[e] (DMSO)	**8**[a,f] ($CDCl_3$)	**12** ($CDCl_3$)	**13**[a,g] ($CDCl_3$)
H4	8.76 (9.5)	7.04[h]	8.62 (9.5)	7.86	8.54	7.83 (9.5) [2.5]	—	—
H5	7.95 (9.5)	7.04[h]	7.43 (9.5)	8.41	8.81	7.26 (9.5)	—	—
C3	143.5 (70.5)[i]	163.9 [6.4]	143.1 (69.8)[i]	142.5	143.0	140.0 (69.8)[i]	148.6 (69.5)[i]	153.8 [11.7]
C4	127.8 (60.3, 70.5)[i]	125.6 [24.9]	127.7 (61.7, 69.8)[i]	120.4	119.4	121.6 [4.0] (69.8, 61.2)[i]	137.3 (69.5,71.4)[i]	146.1 [3.1]
C5	128.6 (60.3, 61.4)[i]	128.3	121.8 (61.7, 64.3)[i]	124.2	125.9	128.4 [24.9] (61.2, 60.1)[i]	128.5 (71.3,71.4)[i]	126.7 [9.8]
C6	152.3 (61.4)[i]	145.8	155.8 (64.3)[i]	163.1	160.3	160.5 [6.8] (60.1)[i]	154.6 (71.4)[i]	153.7
N1′	−63.2	−290.9 [40.2]	−63.5	−65.2	−65.6	−68.6	−287.8[j]	—[l]
N2′	+16.3[j]	—	+12.3[j]	+10.0	+13.6	+3.8[j]	−150.2[j]	—
N3′	−25.1[j]	—	−27.0[j]	−26.4	−26.1	−28.6[j]	−141.1[j]	—
N1	−80.8	−9.4	−108.8	−103.0	−103.7	−121.4 [6.9]	−7.3[h,k]	−39.2[j,k]
N2	−102.2	−25.9 [6.1]	−106.2	−103.8	−88.5	−103.9	+0.8[h,k]	−13.3[j,k]
N1″	—	—	−276.8	−29.5	[n]	−284.0[38.8]	—	—
N2″	—	—	−146.0	+159.7	+86.9	—	—	—
N3″	—	—	−140.3[j,m]	−108.3[m]	−177.7[m]	—	—	—
C1′	—	128.7 [100.0]	—	—	—	127.0 [101.0]	—	130.6 [106.8]
C2′/C6′	—	128.4 [12.3]	—	—	—	128.7 [12.5]	—	128.8 [12.8]
C3′/C5′	—	133.0 [9.8]	—	—	—	133.0 [10.1]	—	132.4 [10.6]
C4′	—	131.8 [2.9]	—	—	—	132.4 [2.9]	—	132.4 [2.9]
P	—	+17.7	—	—	—	+18.2	—	+9.3

[a] In parenthesis, $^{3}J(^{1}H, ^{1}H)$ couplings; in square brackets, $^{n}J(^{31}P,^{1}H)$, $^{n}J(^{31}P,^{13}C)$ and $^{n}J(^{31}P,^{15}N)$ couplings in Hz.

[b] $\delta(^{1}H)$ of phenyl group: 7.39–7.43 ppm (6H), 7.47–7.50 ppm (3H), 7.79–7.84 ppm (6H).

[c] $\delta(^{15}N)$ in DMSO-d_6.

[d] $\delta(^{13}C)$ of CN group: 123.5 ppm; $\delta(^{15}N)$ of CN group: −168.2 ppm; $^{1}J(^{15}N, ^{13}C) = 3.0$ Hz.

[e] $\delta(^{1}H)$ of NH group: 13.2 ppm; $\delta(^{1}H)$ of NH_2 group: 7.35 and 7.67 ppm; $\delta(^{13}C)$ of $CONH_2$ group: 153.2 ppm; $\delta(^{15}N)$ of $CONH_2$ group: −297.9 ppm; $^{1}J(^{15}N, ^{1}H) = 95.2$ Hz.

[f] $\delta(^{1}H)$ of phenyl group: 7.47–7.50 ppm (6H), 7.55–7.58 ppm (3H), 7.83–7.89 (6H) ppm.

[g] $\delta(^{1}H)$ of phenyl group: 7.48–7.51 ppm (6H), 7.57–7.61 ppm (3H), 7.71–7.75 ppm (6H).

[h] Degenerate.

[i] $^{1}J(^{13}C, ^{13}C)$ couplings (Hz).

[j] Not observed in ^{1}H–^{15}N gradient selected HMBC experiment.

[k] Assignment can be reversed.

[l] Not observed because of low solubility of this compound in $CDCl_3$.

[m] Labeled atoms.

[n] Not observed in ^{15}N inverse gated decoupling spectrum.

Table 3. ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR chemical shifts of *N*-ethyl salts **14**–**25** in acetone at 298 K

	14	**15**	**16**[a]	**17**[a]	**18**[b,c]	**19**[b,c]	**20** = **21**	**22**[b,d]	**24**[e]	**25**[e]
% of N-salt	77%	23%	74%	26%	74%	26%	100%	100%	~60%	~40%
H4	9.21 (9.5)	9.14 (10.0)	9.06 (10.0)	8.96 (10.0)	9.06 [0.8] (9.9)	8.93 [1.0] (10.0)	8.74 (9.5)	8.41 (9.3)	—	—
H5	8.65 (9.5)	8.46 (10.0)	8.08 (10.0)	7.91 (10.0)	8.41 (9.9)	8.26 (10.0)	8.85 (9.5)	8.63 [1.2] (9.4)	—	—
CH_2	5.10	5.33	5.06	5.30	4.97	5.08	5.11	4.50	5.03	5.05
CH_3	1.78	1.88	1.78	1.88	1.69	1.72	1.73	1.00	1.68	1.69
C3	139.0	146.7	138.3	146.1	137.2	145.0	157.5	157.0 [3.4]	149.1	149.6
C4	124.4	128.7	124.2	128.3	123.5	127.8	140.7	131.6 [7.8]	134.7	138.0
C5	136.1	134.1	129.0	127.2	128.9 [8.4]	127.1 [8.2]	141.2	140.2	147.2	146.6
C6	156.6	159.0	159.5	161.2	155.8 [3.1]	157.4 [3.5]	155.7	150.8	155.9	153.9
CH_2	48.3	55.9	48.0	55.3	47.7	54.9	61.3	59.9	61.8	62.3
CH_3	13.6	13.7	13.6	13.7	13.5	13.4	13.2	12.6	13.3	13.4
N1′	−150.2	−74.5	−150.6	−75.2	−150.8	−75.8	—	−308.0	—[f,g]	—[f,g]
N2′	−16.2	−86.3	−18.4	−90.2	−19.0	−91.4	—	—	−153.0[f]	−152.4[f]
N3′	—[f]	−35.1	—[f]	−37.4	—[f]	−37.6	—	—	−129.5[f]	−129.4[f]
N1	−79.6	−82.5	−109.1	−110.1	−117.1	−112.3	−121.4	−131.1	−137.5	−52.8
N2	−103.7	−107.2	−107.0	−112.3	−109.2	[f]	−36.3	−74.1	−44.3	−126.7
N1″	—	—	−272.7	−270.2	−308.9	−306.0	—	—	—	—
C1′	—	—	—	—	118.0 [102.9]	118.1 [102.7]	—	118.4 [103.0]	—	—
C2′ = C6′	—	—	—	—	131.1 [14.1]	131.2 [14.1]	—	131.3 [14.1]	—	—
C3′ = C5′	—	—	—	—	134.8 [12.1]	[h]	—	134.9 [12.1]	—	—
C4′	—	—	—	—	136.8 [3.0]	[h]	—	136.9 [3.2]	—	—
P	—	—	—	—	+38.0	+38.2	—	+37.8	—	—

[a] Signals of N2″ and N3″ nuclei of both *N*-ethyl salts not observed in ^{1}H–^{15}N gradient selected HMBC experiment.
[b] In parentheses, $^{3}J(^{1}H, ^{1}H)$ couplings; in square brackets, $^{n}J(^{31}P,^{1}H)$, $^{n}J(^{31}P,^{13}C)$ couplings in Hz.
[c] ^{1}H chemical shifts of phenyl protons of both *N*-ethyl salts: 7.77–7.82 ppm, 7.94–8.00, 8.06–8.12 ppm.
[d] ^{1}H chemical shifts of phenyl protons: 7.81–7.85 ppm (6H), 7.97–8.00, 8.07–8.12 ppm.
[e] Assignment of ^{1}H, ^{13}C and ^{15}N signal of both *N*-ethyl salts can be reversed.
[f] Not observed in ^{1}H–^{15}N gradient selected HMBC experiment.
[g] Not observed in ^{15}N NMR inverse gated decoupling experiment.
[h] Overlaps with signals of *N*1-ethyl salt.

may exhibit prototropic tautomerism, **7A**–**7B** (Fig. 1). Although both compounds **6** and **7** were prepared previously,[4] their structures are still doubtful. In order to establish the structures of these compounds, reactions of selectively ^{15}N-labeled **5TA*** (Fig. 2) with potassium cyanide leading to **6*** and subsequent hydrolysis of **6*** to amide **7*** were carried out.

Analysis of the ^{1}H–^{15}N gradient selected HMBC experiment and inverse gated decoupling ^{15}N NMR spectra of **6**/**6*** and **7**/**7*** in DMSO-d_6 indicates the presence of only one form for each compound. Selective labeling with ^{15}N isotope allows us not only to assign the N3″ signals of compounds **6** and **7**, but also to recognize unambiguously the position of the proton in the triazene part of **7**. The

Table 4. ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR chemical shifts (in TFA) of compounds **3**—**5**, **8** and **12**–**13** at 298 K

	3[a] (TFA)	**4**[b,c] (TFA)	**5** (TFA)	**8**[b,d] (TFA)	**12** (TFA)	**13**[b,e] (TFA)
H4	8.61 (9.6)	7.92 [—] (9.5)	8.40 (9.7)	8.50 (9.5)	—	—
H5	7.76 (9.6)	7.85 [0.9] (9.5)	7.25 (9.7)	7.80 (9.5)	—	—
C3	141.9	154.9 [2.4]	140.5	140.1	149.0	148.0
C4	125.3	128.0[g] [br]	124.2	125.7	142.5	147.3
C5	130.2	134.8	123.4	122.6 [8.2]	131.2	—[h]
C6	154.6	149.7	157.2	152.9 [3.1]	154.7	140.7
N1′	−90.0[f]	−308.8	−96.8[f]	−90.0[f]	−279.8[f]	−285.6[f]
N2′	−4.0[f]	—	−10.6[f]	−7.7[f]	−153.4[f]	—
N3′	−27.9[f]	—	−29.7[f]	−30.0[f]	−133.2[f]	—
N1	−80.8	−108.9	−110.4	−116.8 [2.6]	−41.1[f,g]	−175.8[f]
N2	−104.6	−67.6	−108.1	−111.2	−41.1[f,g]	−51.1[f]
N1″	—	—	−275.8	−310.0	—	—
N2″	—	—	−150.2	—	—	—
N3″	—	—	−135.7[f]	—	—	—
C1′	—	116.0 [103.5]	—	116.3 [103.5]	—	124.1 [108.8]
C2′ = C6′	—	129.3 [14.1]	—	129.9 [14.2]	—	128.3 [8.8]
C3′ = C5′	—	132.5 [11.8]	—	133.3 [11.8]	—	131.4 [11.3]
C4′	—	135.4 [3.0]	—	136.1 [3.1]	—	133.5 [2.6]
P	—	+39.6	—	+40.3	—	+50.8

[a] ^{1}H and ^{13}C NMR chemical shifts in TFA taken from Ref. 13.

[b] In parentheses, $^{3}J(^{1}H,^{1}H)$ couplings; in square brackets, $^{n}J(^{31}P,^{1}H)$, $^{n}J(^{31}P,^{13}C)$ and $^{n}J(^{31}P,^{15}N)$ couplings in Hz.

[c] ^{1}H chemical shifts of phenyl protons: 7.47–7.51 ppm (6H), 7.59–7.68 ppm (9H).

[d] ^{1}H chemical shifts of phenyl protons: 7.47–7.50 ppm (6H), 7.55–7.59 ppm (3H), 7.84–7.89 (6H).

[e] ^{1}H chemical shifts of phenyl protons: 7.42–7.58 ppm (15H).

[f] Not observed in ^{1}H–^{15}N gradient selected HMBC experiment.

[g] Broad signal.

[h] Probably overlaps with TFA signal.

$^{1}J(^{15}N,^{1}H) = 93.5$ Hz observed in the ^{1}H and also in the ^{15}N NMR spectra indicates that the tautomeric proton is bound to the N3″ atom and that in DMSO-d_6 solution only tautomer **7A** exists. The assignment of all remaining ^{15}N NMR signals is based on analysis of the ^{15}N NMR data obtained for triazene structures, presented previously[17,18] (Table 2). A negative charge in **6** (Fig. 1) significantly distorts the electronic structure and probably causes the N3″ nucleus to be deshielded by ca 70 ppm compared with the same nucleus of **7**. At the same time, the N2″ nucleus of **6** is deshielded by ca 70 ppm as compared with **7**. A strong decrease in shielding of the N2″ nucleus is the most significant difference between **5TA** and **6**/**7** observed in the ^{15}N NMR spectra.

Reaction of **5TA** with triphenylphosphine in ethanol, at room temperature, gives derivative **8** (Fig. 1) as a white solid.[19] Analysis of the ^{1}H and ^{13}C NMR data for **8** (Table 2) implies an unsymmetrical monoiminophosphorane structure of this compound, but still does not explain the type of tautomer present. In order to distinguish between two possible forms (**T** and **A**) ^{1}H–^{15}N gradient-selected HMBC and inverse gated decoupling ^{15}N NMR spectra were measured. Additionally, the values of ^{31}P, X couplings were analyzed in order to assign the ^{1}H, ^{13}C and ^{15}N NMR signals properly. The presence of typical ^{15}N NMR tetrazole signals (at −68, +4 and −29 ppm; Table 2) confirms that **8** exists only in the tetrazole form **8T**.

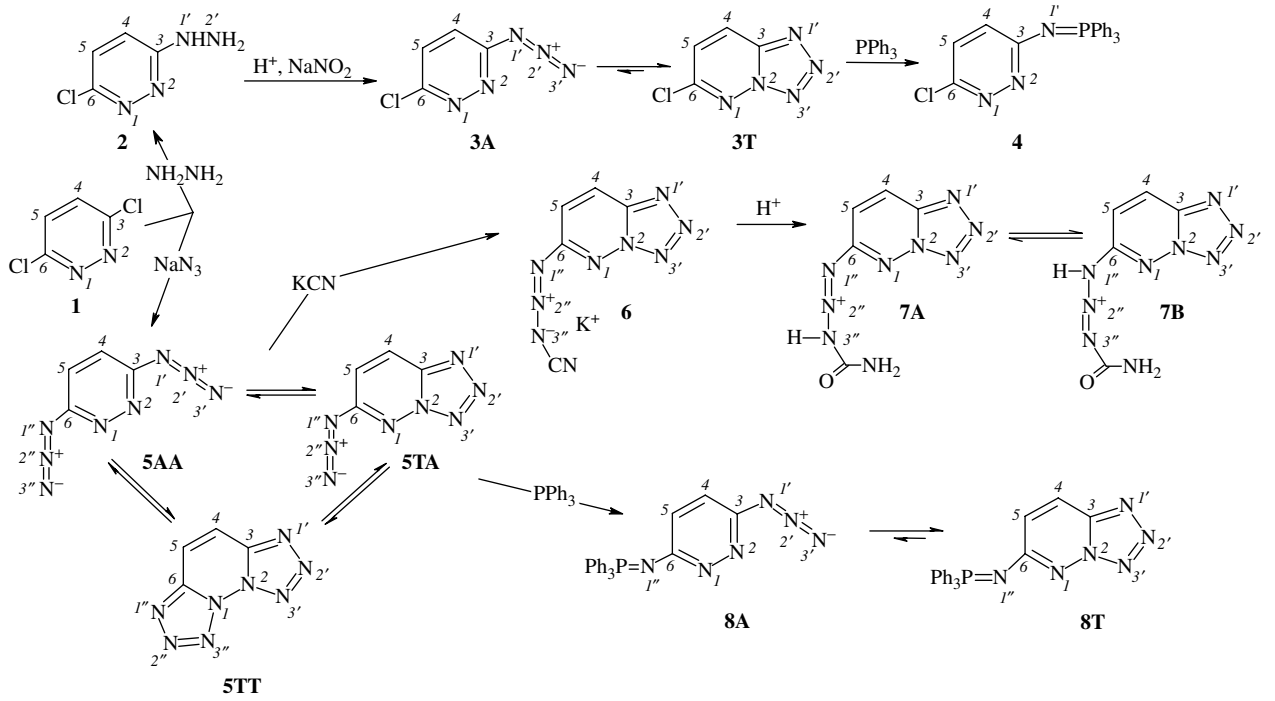

Figure 1. Scheme of the reactions leading to different derivatives of 3,6-dichloropyridazine (**1**) being in azide–tetrazole equilibrium. Atoms of all compounds are numbered in accordance with the pyridazine ring.

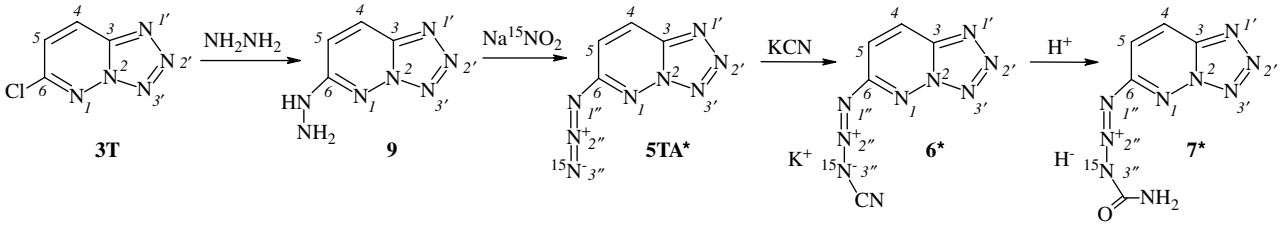

Figure 2. Scheme of reactions leading to selectively ^{15}N-labeled compounds **5TA**, **6** and **7**.

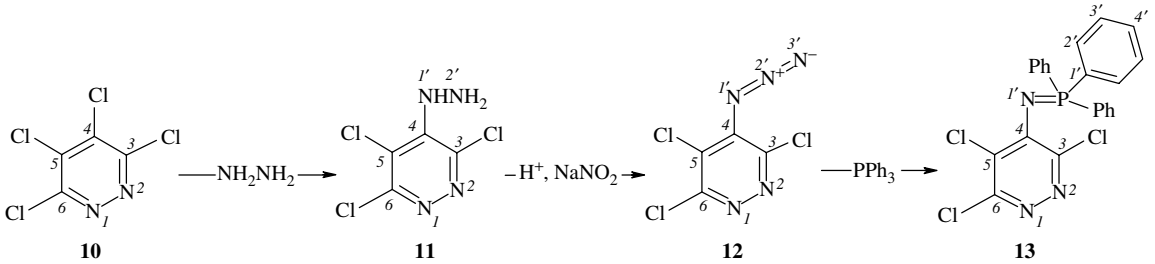

Figure 3. Scheme of different reactions of 3,4,5,6-tetrachloropyridazine (**10**).

Derivatives of 3,4,5,6-tetrachloropyridazine (10)

3,4,5,6-Tetrachloropyridazine (**10**), like 3,6-dichloropyridazine (**1**), reacts with hydrazine hydrate and yields one hydrazinotrichloropyridazine derivative (Fig. 3). However, analysis of a ^{1}H–^{13}C gradient selected HMBC correlation spectrum of the product obtained, suggests the presence of a structure other than the expected 3-hydrazino-4,5,6-trichloropyridazine. Three correlation cross peaks at δ (^{13}C) 113.5, 141.1 and 142.9 ppm caused by interaction between the NH proton of the $NHNH_2$group and three ^{13}C nuclei (C3, C4, C5; see Fig. 3) of the pyridazine ring confirm the existence of 4-hydrazino-3,5,6-trichloropyridazine (**11**). The path of the reaction of **10** with hydrazine is in agreement with kinetic data obtained by Chambers *et al.*[6] for the reaction of **10** with ammonia, leading to 4-amino-3,5,6-trichloropyridazine. This path has also been confirmed by the following results of analysis of NMR data (Table 2) obtained for compounds **12** and **13** (Fig. 3):

1. The lack of $^{3}J(^{31}P,^{15}N)$ couplings as observed in **4** and **8** implies a structure other than 3-iminophosphorane-4,5,6-trichloropyridazine.
2. The increase in the N1 and N2 shieldings of the pyridazine ring after introduction of the azide group is too small compared with the increases observed in azidopyridine

derivatives (the N2 shielding should increase by ca 30 ppm[8–10] in such a case).

3. The shielding of nucleus N1′ in **12** is different (ca 10 ppm) from those observed for other azidoazines with the azido group in the *ortho* position to the ring nitrogen atom (Table 2). For several 2-azidopyridines the values of the ^{15}N NMR chemical shifts of the N1′ nucleus fall within the range −270 to −280 ppm.[8–10]

The values of the ^{31}P,^{13}C couplings are different from those observed in the case of compounds **4** and **8**. The decrease in $^{2}J(^{31}P,^{13}C)$ to ca 3 Hz and increase in $^{3}J(^{31}P,^{13}C)$ to ca 10 and 12 Hz in the case of compound **13** probably originate from the different substitution patterns connected with the other positions of $NPPh_3$ in the pyridazine ring, and also from different orientations of the $NPPh_3$ group to the pyridazine ring plane. Both differences are caused by the bulky chlorine atoms at positions 3 and 5.

Alkylation of the compounds studied

Since all compounds studied contain at least three nitrogen atoms and each nitrogen atom has at least one lone electron pair, they fairly easily undergo alkylation reactions. In this study, ethylation reactions of **1**, **3**–**5**, **8**, **12** and **13** using triethyloxonium tetrafluoroborate were carried out.

Analysis of the ^{1}H and ^{13}C NMR data for the reaction mixtures after ethylation (Fig. 4) shows that in the case of compounds **3**, **5**, **8**, **12** and **13** two *N*-ethyl salts are obtained (two sets of NMR signals), whereas **1** and **4** give only one type of *N*-ethyl salt.

It is known from our previous work that alkylation of tetrazolo[1,5-*a*]pyridine derivatives leads to two types of *N*-ethyl products: *N*1-ethyl- and *N*2-ethyltetrazolo[1,5-*a*] pyridinium salts.[20] In comparison with tetrazolo[1,5-*a*]pyridines, compounds **3**, **5** and **8** contain one additional nitrogen atom, hence alkylation is theoretically possible at three sites: N1 atom of the pyridazine ring and both N1′ and N2′ atoms of the tetrazole moiety. In the case of compounds **1**, **4**, **12** and **13**, there are two potentially possible ethylation sites: N1 and N2 atoms of the pyridazine ring.

In order to evaluate the results of ethylation qualitatively, ^{1}H–^{15}N gradient selected HMBC correlation experiments were applied to assess the presence of the *N*-ethyl salts in the mixtures, whereas quantitative estimations of the content of the *N*-ethyl salts were made using integrals of the ^{1}H NMR spectra.

Comparison of the ^{1}H–^{15}N gradient selected HMBC results for mixtures of ethyl salts **14**/**15**, **16**/**17** and **18**/**19** (Fig. 4, Table 3) with data for *N*-ethyl salts of tetrazolo[1,5-*a*]pyridines[20] excludes the N1 atom of the pyridazine ring as an ethylation site. Only *N*1′-ethyl and *N*2′-ethyl salts are present in the mixtures after ethylation. The increase in shielding of the alkylated nitrogen nuclei by ca 100 ppm compared with neutral molecules is the most characteristic phenomenon observed in the NMR spectra of the compounds obtained after the alkylation reactions (Table 3). Other ^{1}H, ^{13}C and ^{15}N nuclei in the neighborhood of the alkylation site also experience a shielding increase, but these changes are smaller than the above-mentioned ones and were described in detail in our previous paper.[20]

Using ^{1}H NMR integrals of mixtures **14**/**15**, **16**/**17** and **18**/**19**, the contents of *N*1′-ethyl salts were estimated. Regardless of the nature of the substituent in position 6, the content of *N*1′-ethyl salt is ca 75% and constant for all three ethylation mixtures.

Ethylation of **1** leads to **20** = **21** owing to the substrate symmetry, whereas derivative **4** yields only one of two possible *N*-ethyl salts **22**/**23**. The presence of a bulky $NPPh_3$ group at position 3 of **4** probably hinders access of ethyl group to the N2 atom, and therefore ethylation occurs at the N1 atom. This is confirmed by analysis of the ^{1}H–^{15}N and ^{1}H–^{13}C gradient selected HMBC correlation spectra and also by the strong nitrogen shielding increase of about ca 130–140 ppm after ethylation of **4**. Ethylation also influences N2 shieldings of compounds **1** and **4** but this effect is smaller, ca 45–50 ppm.

In the ^{1}H NMR spectra of mixtures of the monocyclic salts **24**/**25** and **26**/**27** derived from **12** and **13**, respectively, two sets of appropriate NMR signals are observed. This implies

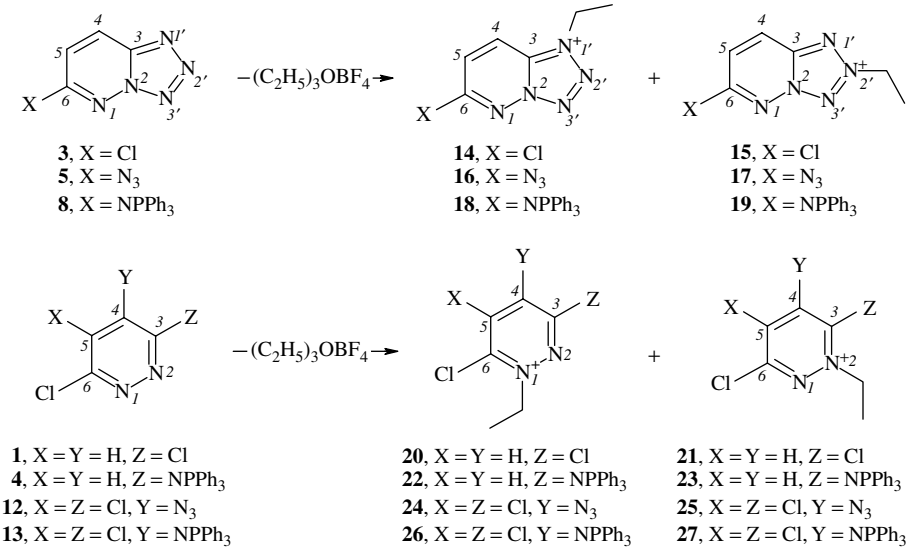

Figure 4. Scheme of ethylation of compounds **1**, **3**–**5**, **8**, **12** and **13**.

the presence of two different types of salts: *N*1-ethyl and *N*2-ethyl.

The presence of azido and iminophosphoro groups at position 4 of chloropyridazines **12** and **13** causes only a slight differentiation of the basicity of the ring nitrogen atoms, and therefore the amounts of both *N*-ethyl salts are almost the same. Accurate estimation of the ratio of the two *N*-salts in the case of mixtures **24**/**25** and **26**/**27** is difficult since the ^{1}H NMR signals of appropriate CH_2 and CH_3 groups partially overlap.

It is very difficult to assign ^{13}C signals in case of the *N*-ethyl salts of **12** and **13** (the mixture of salts **26/27** in acetone is not stable enough to be measured by ^{13}C and ^{15}N NMR methods and the results of such NMR measurements are not listed in Table 3) because there are no protons attached to ring carbons and *N*-ethyl protons do not correlate with ring carbon nuclei. In the case of ^{15}N NMR chemical shifts this task seems to be much easier. On the basis of differences in ^{15}N NMR chemical shifts between **1** and **20** = **21**, ^{1}H NMR signals at 1.68, 5.03 ppm and ^{15}N NMR signals at −44.3, −137.5 ppm belong to *N*1-ethyl salt **24**, whereas those at 1.69, 5.05, −52.8 and −126.7 ppm, respectively, correspond to the second isomer **25** (Table 3). The estimated content of *N*1-salts for both cases **24**/**25** and **26**/**27** is ca 60%.

Protonation of the compounds studied

Downing *et al*., using magnetic circular dichroism, examined tetrazolo[1,5-*b*]pyridazine and a few other compounds containing several nitrogen atoms in order to determine the site of protonation.[21] They suggested protonation of unsubstituted tetrazolo[1,5-*b*]pyridazine at the N1 atom but, as was reported previously for three tetrazolo[1,5-*b*]pyridazines substituted at position 6, protonation occurred at the N1′ atom of the tetrazole ring.[13]

Application of ^{15}N NMR spectroscopy is more effective for the identification of the protonation site. For the wide group of nitrogen-containing compounds the preferred site of protonation can be found on the basis of ^{15}N NMR chemical shifts and their changes caused by protonation. An increase in shielding of the nitrogen nucleus of ca 100 ppm and more indicates that such an atom interacts strongly with a proton; however, smaller values of such an increase do not exclude the phenomenon of protonation.

In the case of **3**, **5** and **8**, the increase in N1′ shielding after protonation is 27, 33 and 21 ppm, respectively. Such results indicate that in all three cases proton–nitrogen interaction occurs but is rather weak.

In contrast to the bicyclic compounds **3**, **5** and **8**, after protonation of the monocyclic compounds **1**, **4**, **12** and **13** the increase in ^{15}N shielding is 63, 100, 38 and 135 ppm, respectively. This suggests a strong dependence of the protonation effect on the nature, position and size of the substituent attached to the pyridazine ring. The latter statement is additionally confirmed by the results of protonation of compounds **12** and **13**. The increase in ^{15}N shielding of the N1 and N2 nuclei in **12** is smaller (ca 35 ppm) than in **13**, where the bulky $NPPh_3$ group at position 4 not only causes a strong N1 shielding increase but also favors the N1 atom as the protonation site (Tables 2 and 3).

In the case of the monocyclic compounds **1**, **4**, **12** and **13** and the bicyclic compounds **3**, **5** and **8**, for which both alkylation and protonation reactions were carried out, the changes in ^{15}N chemical shifts are smaller after protonation than the changes observed after ethylation (Tables 3 and 4). This observation undoubtedly confirms that proton–nitrogen interaction is of completely different nature than the nitrogen–carbon bond in the *N*-ethylated tetrazolo[1,5-*b*]pyridazine derivatives.

CONCLUSIONS

Application of NMR spectral parameters such as ^{1}H, ^{13}C, ^{15}N and ^{31}P chemical shifts and various coupling constants proves unquestionably that the reaction of 3,6-dichloropyridazine and 3,4,5,6-tetrachloropyridazine with hydrazine hydrate yields derivatives in which the chlorine atom is substituted in two different positions. As a consequence, two different types of azides are produced, from which 4-azido-3,5,6-trichloropyridazine cannot exist in the tetrazole–azide equilibrium, whereas azide derivatives of 3,6-dichloropyridazine exist exclusively in the tetrazole form.

NMR data [^{1}H, ^{13}C, ^{15}N and ^{31}P chemical shifts and ^{1}J(^{13}C, ^{13}C) and in some cases ^{31}P, X couplings, where X = ^{1}H, ^{13}C and ^{15}N nuclei] provide sufficient evidence to assess the tautomeric form of the azidopyridazines investigated in solution and to determine the structure of other compounds synthesized.

Especially the large shielding sensitivity of ^{15}N nuclei to different changes (tetrazole–azide equilibrium, ethylation, protonation) allows one not only to distinguish between tautomeric forms, existing in solution, but also to establish ethylation and protonation sites of the compounds containing more than one nitrogen nucleus.

The strong shielding increase of the nitrogen nucleus (ca 100 ppm and more) after ethylation precisely indicates the site of ethylation. By the same rule, the strong nitrogen shielding increase after protonation of monocyclic compounds undoubtedly proves the site of protonation. In case of the protonation of bicyclic compounds, the increase in shielding after protonation is not so large but still sufficient to assess the protonation site.

EXPERIMENTAL

Synthesis

The compounds studied were prepared according to schemes presented in Figs 1–3.

3-Chloro-6-hydrazinopyridazine (2) and
4-hydrazino-3,5,6-trichloropyridazine (11)

Hydrazine hydrate (2.0 ml) was added to the solution of 3,6-dichloropyridazine (**1**) (1.2 g, 8.1 mmol) or 3,4,5,6-tetrachloropyridazine (**10**) (1.0 g, 4.59 mmol) in ethanol (20 ml). The reaction mixtures were heated under reflux for 6 or 2 h, respectively, and upon cooling the separated products were collected. Both hydrazines were used in the next step without further purification. The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts of **2** and **11** in DMSO-d_6 are collected in Table 1.

6-Hydrazinotetrazolo[1,5-b]pyridazine (9)
This was prepared according to the literature.[22] The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in DMSO-d_6 are collected in Table 1.

6-Tetrazolo[1,5-b]pyridazine (3)
Obtained according to literature method.[11] MS: *m/z* 157, 155, 101, 99, 65, 64 (100%), 63, 52. IR (KBr): 3098.0 (m), 3067.0 (m), 3050.0 (m), 1531.3 (s), 1459.0 (s), 1449.0 (s), 1354.4 (s), 1291.6 (s), 1274.5 (s), 1172.7 (s), 1147.0 (s), 1128.6 (s), 1067.0 (s), 991.9 (m), 932.4 (m), 847.1 (s), 796.7 (m), 728.7 (s), 588.2 (m) cm^{-1}. Analysis: found, H 1.10, C 30.54, N 44.67%; calculated for $C_4H_2N_5Cl$, H 1.21, C 30.87, N 45.02%. The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in acetone-d_6 are collected in Table 2.

(6-Chloropyridazin-3-yl)(triphenyl-λ^5-phosphanylidene)amine (4)
Obtained according to the literature.[14] MS: *m/z* 392, 391, 390 (10.1%), 389 (19.4%), 388 (16.7%), 363, 362, 361, 360, 326 (12.1%), 262 (16.9%), 261, 260, 186, 185 (25.8), 184, 183 (45.6%), 172, 157, 154, 153, 152, 149, 139, 128, 125, 123, 111, 109, 108 (17.5%), 107, 97, 95, 89, 88 (25.8%), 86 (100%), 85, 84 (80.8%), 83 (10.2%), 81, 77, 71 (11.6%), 70, 69 (11.4%), 57 (23.9%). IR (KBr): 3060.8 (w), 1577.9 (m), 1512.8 (m), 1484.0 (w), 1410.0 (s), 1337.7 (m), 1276.6 (m), 1133.7 (m), 1113.9 (s), 987.3 (s), 841.4 (m), 797.2 (w), 753.2 (m), 722.9 (s), 693.4 (s), 549.3 (m), 524.1 (m) cm^{-1}. Analysis: found, H 4.28, C 67.62, N 10.42%; calculated for $C_{22}H_{17}N_3PCl$, H 4.36, C 67.78, N 10.58%. The ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR chemical shifts in $CDCl_3$ are presented in Table 2.

6-Azidotetrazolo[1,5-b]pyridazine (5)
Obtained according to the literature.[19] MS: *m/z* 162, 153, 136, 134, 108, 107, 106, 89, 80, 79, 78 (100%), 77 (42.6%), 76, 64, 63, 53 (15.9%), 52, 51 (84.3%), 49. IR (KBr): 3110.8 (w), 3071.2 (m), 2148.5 (s), 2089.0 (s), 1610.6 (m), 1549.6 (s), 1472.7 (s), 1381.9 (s), 1367.4 (s), 1330.8 (s), 1295.4 (s), 1242.6 (s), 1163.2 (m), 1126.2 (m), 1081.2 (m), 977.7 (m), 965.6 (m), 869.8 (m), 850.7 (s), 756.9 (m), 669.5 (m), 590.6 (s), 540.6 (m) cm^{-1}. The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in acetone-d_6 are presented in Table 2.

Tetrazolo[1,5-b]pyridazine-6-yl(triphenyl-λ^5-phosphanylidene)amine (8)
Obtained according to the literature.[19] MS: *m/z* 396, 288, 264, 263 (19.4%), 262 (100.0%), 261, 186, 185, 184 (10.3%), 183 (44.3%), 170, 157, 154, 108 (20.6%), 107, 78, 77, 51. IR (KBr): 3057.9 (w), 1605.3 (m), 1546.7 (s), 1451.4 (s), 1435.2 (s), 1392.3 (s), 1337.9 (m), 1235.8 (s), 1176.8 (w), 1113.7 (s), 1020.6 (m), 997.7 (m), 920.9 (s), 859.4 (m), 829.3 (s), 749.7 (m), 721.7 (s), 694.2 (s), 600.0 (m), 576.7 (s), 528.8 (s), 503.3 (m) cm^{-1}. Analysis: found, H 4.18, C 66.24, N 21.05%; calculated for $C_{22}H_{17}N_6P$, H 4.29, C 66.57, N 21.21%. The ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR chemical shifts in $CDCl_3$ are presented in Table 2.

4-Azido-3,5,6-trichloropyridazine (12)
To a stirred mixture at 0 °C containing **11** (0,64 g, 3 mmol) in water (25 ml with 5 ml of concentrated HCl) a solution of sodium nitrite (0.215 g, 3.12 mmol) in water (5 ml) was added dropwise. The reaction mixture was left at room temperature for 1 h and thereafter extracted with chloroform. Upon evaporation of the solvent, the residue was purified by chromatography [C_6H_{14}–$CHCl_3$ (40 : 10)]. MS: *m/z* 227, 225, 223 (13.7%), 199, 197, 195, 138, 136 (35.2%), 135, 134 (57.4%), 132, 120, 118, 110, 108, 106, 101 (21.4%), 99 (68.2%), 98, 97, 96 (11.0%), 94, 87 (11.0%), 86, 85 (16.6%), 84 (26.7%), 83, 82 (75.3%), 76, 75 (42.7%), 73 (100.0%), 71 (15.4%), 64, 62, 61. IR (KBr): 2167.1 (s), 2137.9 (s), 1501.8 (s), 1482.1 (m), 1402.5 (s), 1306.8 (s), 1282.8 (m), 1241.2 (m), 1193.0 (m), 1115.4 (s), 914.9 (s), 812.0 (m), 744.6 (m), 717.3 (w), 514.3 (m) cm^{-1}. Analysis: found C 21.14, N 30.95%; calculated for $C_4N_5Cl_3$, C 21.38, N 31.18%. The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in $CDCl_3$ are presented in Table 2.

(3,5,6-Trichloropyridazin-4-yl)(triphenyl-λ^5-phosphanylidene)amine (13)
To a stirred solution of **12** (1.09 g, 5 mmol) in ethanol (30 ml) was added triphenylphosphine (1.40 g, 5.34 mmol) in small portions. Nitrogen evolution started instantly, and the yellow solution became clear. The reaction mixture was concentrated and the residue purified by chromatography [C_6H_{14}–$CHCl_3$ (60 : 10). MS: *m/z* 463, 462, 461, 460 (17.5%), 459 (28.4%), 458 (20.4%), 457 (46.5%), 456 (13.8%), 426, 425, 424 (32.5%), 423, 422 (50.2%), 352, 288, 277, 263, 262 (25.5%), 261 (14.6%), 260, 259, 245, 228, 220, 186, 185 (25.5%), 184 (18.7%), 183 (100.0%), 170, 157, 154, 153, 152 (13.1%), 143, 141, 139, 133, 131, 115, 108 (25.9%), 107, 78, 77 (12.2%), 51. IR (KBr): 3058.1 (w), 1576.4 (m), 1539.2 (s), 1484.5 (m), 1436.2 (s), 1342.6 (m), 1229.2 (s), 1172.6 (m), 1112.4 (s), 1078.4 (m), 1051.9 (m), 1021.3 (w), 996.9 (w), 804.1 (m), 757.4 (m), 719.8 (s), 693.0 (s), 626.8 (m), 553.0 (m), 534.6 (s) cm^{-1}. Analysis: found, H 3.09, C 56.98, N 8.89%; calculated for $C_{22}H_{15}N_3Cl_3P$, H 3.17, C 57.38, N 9.06%. The ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR chemical shifts in $CDCl_3$ are collected in Table 2.

General procedure for the preparation of N-ethyl salts (14–27)
A mixture of the appropriate compound (**1**, **3**–**5**, **8**, **12** and **13**) (2 mmol) and triethyloxonium tetrafluoroborate (2.1 mmol) in dichloromethane (25 ml) was stirred overnight. Diethyl ether was added and the mixture allowed to stand at 0 °C for 2–4 h. The precipitated salts were collected, washed with diethyl ether and dried in vacuum. All *N*-salts are stable as solids but decompose in solution. The ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR chemical shifts of the prepared *N*-salts are collected in Table 4.

Spectra

The ^{1}H, ^{13}C, ^{15}N and ^{31}P NMR spectra were measured at 298 K on a Bruker DRX 500 spectrometer operating at 500.133, 125.773, 50.690 and 202.456 MHz for ^{1}H, ^{13}C, ^{15}N and ^{31}P nuclei, respectively. Typical conditions were as follows: for ^{1}H spectra, ca. 32 transients, relaxation delay 2.0 s, pulse width 2.5 μs (ca 30°), 32 K data points zero filled to 64 K, spectral width 6000 Hz, digital resolution 0.2 Hz; for ^{13}C spectra, 256–600 transients, relaxation delay 2.0 s, pulse width 4.0 μs (ca 30°), 32 K data points zero filled to 64 K, spectral width 20 000–24 000 Hz, digital resolution 0.2–0.5 Hz and power gated decoupling sequence; for ^{15}N spectra, 1000–3000 transients, relaxation delay 15 s, pulse width 7.0 μs (ca 30°), 32K data points zero filled to 64K, spectral width 15 000–20 000 Hz, digital resolution 0.4 Hz and inverse gated decoupling sequence; for ^{31}P spectra, 64–128 transients, relaxation delay 2.0 s, pulse width 6.0 μs (ca 30°), 32 K data points zero filled to 64 K, spectral width 15 000 Hz, digital resolution 0.3 Hz and power gated decoupling sequence. The $^{1}J(^{13}C, ^{13}C)$ spin couplings were obtained using the INADEQUATE sequence with parameters as follows: ca 5000 transients, relaxation delay 2.0 s, pulse widths 7.0 μs (90°), 14.0 μs (180°), 64 K zero filled to 128 K, spectral width ca 6000 Hz.

Two-dimensional ^{1}H–^{13}C gradient selected HSQC (heteronuclear single quantum coherence) (C, H correlation via double INEPT transfer in the phase sensitive mode) and ^{1}H–^{13}C as well as ^{1}H–^{15}N gradient selected HMBC (heteronuclear multiple bond coherence) (long-range correlations experiments) were performed using standard Bruker software and the following parameters: spectral widths in F_2 and F_1 were ca 2–10 ppm for ^{1}H, 80–160 ppm for ^{13}C and 200–400 ppm for ^{15}N. The relaxation delay was usually ca 2.0 s, the refocusing delay in HSQC experiment was ca 1.3 ms, whereas delays for long-range evolutions were ca 80 and 80–320 ms for $^{1}H/^{13}C$ HMBC and $^{1}H/^{15}N$ experiments, respectively. The 2D spectra were acquired as 2048 × 512 or 1024 × 256 hypercomplex files, with 4–8 transients for each 512 or 256 time increments, using appropriate 90° and 180° pulse widths for ^{1}H, ^{13}C and ^{15}N channels.

For ^{1}H and ^{13}C spectra, internal TMS was used as the chemical shift standard, whereas external nitromethane and 85% H_3PO_4 in a capillary were applied as standard for ^{15}N and ^{31}P measurements, respectively. In the case of TFA

solutions, ^{1}H and ^{13}C spectra were calibrated using DMSO-d_6 as an external standard. IR spectra were recorded on an FT Spectrum 2000 (Perkin-Elmer) and mass spectra were measured using an AMD-604 spectrometer.

REFERENCES

1. Shin MS, Kang YJ, Chung HA, Park JW, Kweon DH, Lee WS, Yoon YJ, Khim SK. *J. Heterocycl. Chem.* 1999; **36**: 1135, and references cited therein.
2. Holdoń B, Laskowska H, Sloderbach A, Melzer E. *Pol. J. Pharmacol.* 1997; **49**: 471.
3. Rubat C, Coudert P, Couguelet J, Tronche P, Bastide J, Bastide P. *Farmaco* 1990; **45**: 332.
4. Kamiya S, Tanno M. *Chem. Pharm. Bull.* 1980; **28**: 529.
5. Fox MA, Lemal DM, Johson DW, Hohman JR. *J. Org. Chem.* 1982; **47**: 398.
6. Chambers RD, Martin PA, Waterhouse JS, Williams DLH, Anderson B. *J. Fluorine Chem.* 1982; **20**: 507.
7. Klauke E, Oehlmann L, Baasner B. *J. Fluorine Chem.* 1983; **23**: 301.
8. Cmoch P, Stefaniak L, Webb GA. *Magn. Reson. Chem.* 1997; **35**: 237, and references cited therein.
9. Cmoch P, Korczak H, Stefaniak L, Webb GA. *J. Phys. Org. Chem.* 1999; **12**: 470.
10. Cmoch P, Wiench JW, Stefaniak L, Webb GA. *J. Mol. Struct.* 1999; **510**: 165.
11. Kovačič A, Stanovnik B, Tišler M. *J. Heterocycl. Chem.* 1968; **5**: 351.
12. Sasaki T, Kanematsu K, Murata M. *Tetrahedron* 1971; **27**: 5121.
13. Cmoch P, Stefaniak L, Melzer E, Bałoniak S, Webb GA. *Magn. Reson. Chem.* 1999; **37**: 493.
14. Sasaki T, Kanematsu K, Murata M. *Tetrahedron* 1972; **28**: 2383.
15. Katrusiak AS, Gdaniec M, Katrusiak AA. *Pol. J. Chem.* 1997; **71**: 488.
16. Krivopalov VP, Baram SG, Denisov A Yu, Mamatyuk VI. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1989; **9**: 2002.
17. Witanowski M, Stefaniak L, Webb GA. *Annu. Rep. NMR Spectrosc.* 1993; **25**: 375.
18. Jollimore JV, Vaughan K, Hopper DL. *J. Org. Chem.* 1996; **61**: 210.
19. Deeb A, Sterk H, Kappe T. *Liebigs Ann. Chem.* 1991; 1225.
20. Cmoch P, Wiench JW, Stefaniak L, Sitkowski J. *J. Mol. Struct.* 1999; **477**: 119.
21. Downing JD, Waluk J, Stanovnik B, Tišler M, Vercek B, Michl J. *J. Org. Chem.* 1985; **50**: 302.
22. Katrusiak AA, Bałoniak S, Katrusiak AS. *Pol. J. Chem.* 1996; **70**: 1279.