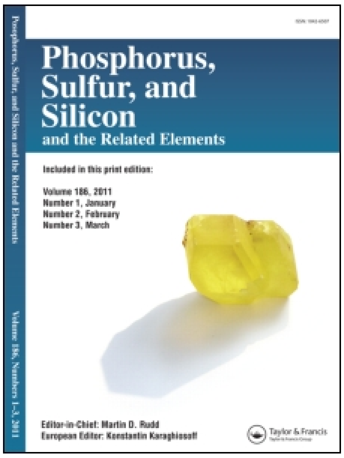

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1-PHTHALAZINEPHOSPHONIC ACID -AN UNEXPECTED PRODUCT OF THE REACTION BETWEEN DIISOPROPYLPHOSPHITE AND O-PHTHALAZINE

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1-PHTHALAZINEPHOSPHONIC ACID -AN UNEXPECTED PRODUCT OF THE REACTION BETWEEN DIISOPROPYLPHOSPHITE AND O-PHTHALAZINE

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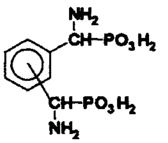
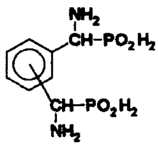
The unexpected nucleophilic substitution in phthalazine and formation of 1- phthalazinephosphonic acid is presented. The structure of the compound was proven by ^{1}H, ^{31}P, ^{13}C, H-H and H-C cosy experiments as well as by X-ray analysis.

Keywords: 1- Phthalazinephosphonic acid; NMR and X-ray analysis

Recently we have described our attempts for the synthesis of phenylene 1,2–1 bis(aminomethane)phosphonic acid[1] and found that all the standard procedures used for the synthesis of these aminophosphonates were unseccessfull.





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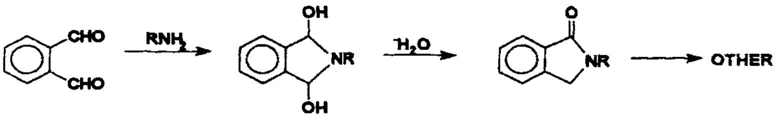
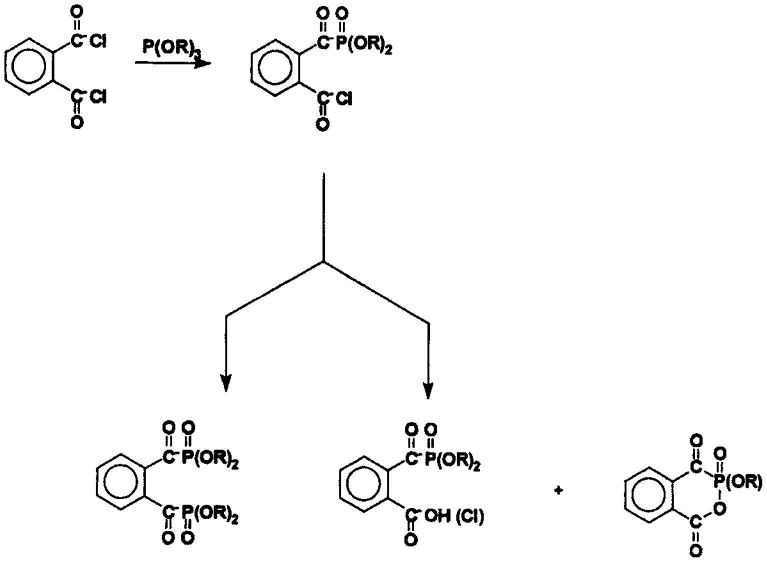
* Corresponding Author.

Thus, o-phthalic aldehyde reacted with amine and instead of imine a mixture of unidentified coloured compounds were formed, whereas in the case where intermediate hydroxyaminal is formed, its intramolecular cyclisation is faster than the desired reaction with a second amine molecule[2].

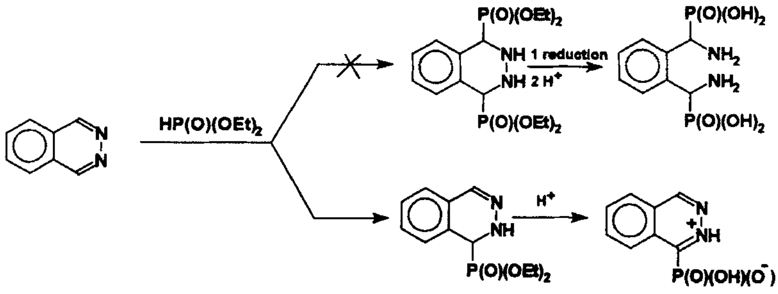


Also the synthesis via bisamides was not successfull since the starting bisamides were unavailable by standard procedures. The reaction of methyl o-phthalaldehyde acetal with phosphorus trichloride and benzyl carbamate in acetic acid also did not lead to the desired compound[3].

A complicated mixture of mostly insoluble compounds was obtained in the reaction of ortho-phthalate bishalides and trialkyl phosphites, and the following products were detected in the reaction mixture:



Finally, we tried to adapt the method published by Rachoń[4] in which an aldazine was used as a substrate.



Heating the mixture of phthalazine with different phosphites in the presence of metallic sodium as a base yielded in all cases a complicated mixture from which it was difficult to isolate products. Fortunately, in the case when an excess of diisopropyl phosphite was used followed by hydrolysis of the mixture with acetic acid and concentrated hydrochloric acid 1:1 the reaction resulted in isolation of a crystalline product containing phosphorus and nitrogen in the ratio close to 1:2 (in yield of 24%). In this paper we describe the NMR and crystalographic studies, which showed that the isolated compound unexpectedly is 1-phthalazinephosphonic acid (Fig. 1).

THE NMR STUDIES

Although elemental analysis were in good agreement with the monoaddition product, the carefull analysis of IR, ^{1}H, ^{31}P, ^{13}C as well as H,H COSY and H,C COSY- NMR spectra led to the conclusion that this is neither the target compound, i.e the product of addition of two phosphite molecules to phthalazine nor the product of monoaddition. The high downfield signals in the ^{1}H-NMR and ^{13}C-NMR spectra indicate that the product has only aromatic protons. The ^{31}P signal at 3.47 ppm strongly suggest an ionic structure. Final assignment of the ^{1}H and^{13}C spectra were done after crystallographic analysis and 2D NMR spectra interpretation. The high downfield doublets at 9.41 and 8.91 come from H4 and H8 respectively. The signal between 7.97–8.04 is a second order multiplet of the remaining aro-

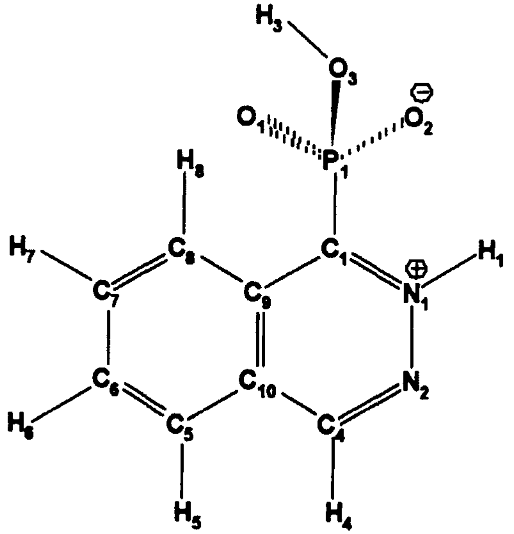


FIGURE 1 The structure of 1-phthalazinephosphonic acid

matic protons. The exact chemical shift values and coupling constants were found by simulation of the original spectrum (Fig. 2). Both original and simulated spectra are presented below and show good correlation supporting the proposed structure (Fig. 1).

TABLE I Calculated and observed ^{1}H-NMR parameters

			Calculated		
Index	4H	5H	H6	H7	8H
Shielding	13.7	15.05	15.14	15.07	14.2
Shift	9.41	8.06	7.97	8.04	8.91
			Found		
Shift	9.38 (d,J_{HH}=2.57Hz)		8.20–7.80 (complex)		8.87 (d,J_{HH}=8.10Hz)

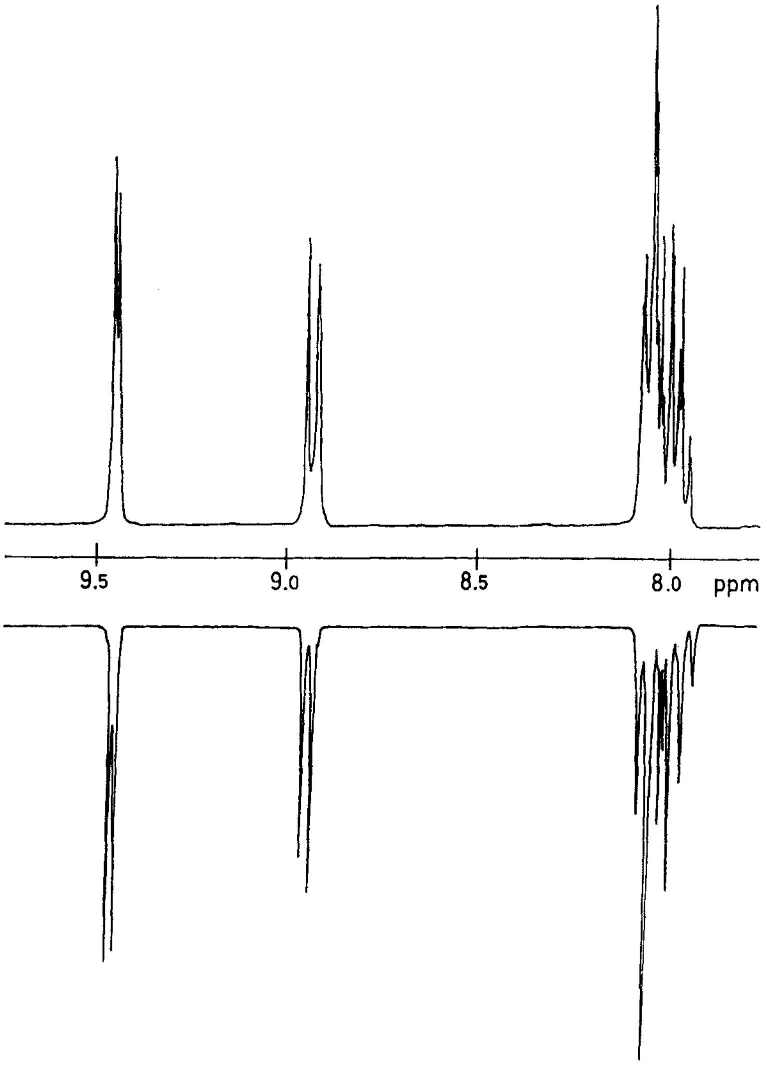


FIGURE 2 The calculated (lower) and observed (upper) ^{1}H-NMR spectrum of 1-phthalazinephosphonic

CRYSTAL STRUCTURE STUDIES

The structure of the studied compound was finally proven by X-Ray studies. Selected bond distances and angles are given in Table II. The molecular structure and atom numbering of 1-phthalazinephosphonic acid is ilustrated on Fig 3. It shows the phthalazine N(1) atom to be protonated and the phosphonic acid group ionized.

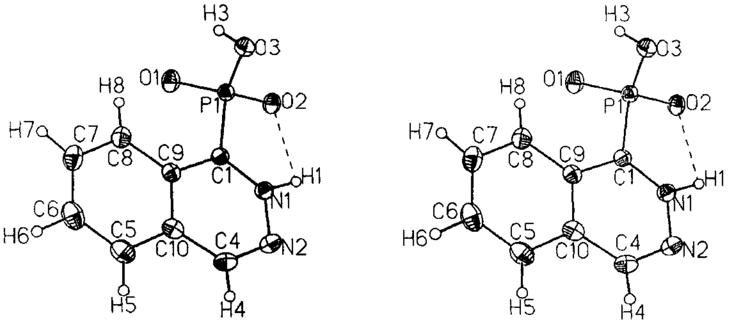


FIGURE 3 A stereoview of the 1-phthalazinephosphonic acid showing the atom labeling scheme. Displacement elleipsoids are drawn at 35% probability level

The positive charge resulting from the protonation of N(1) is somewhat delocalised over the C(1)-N(1)-N(2)-C(4) fragment. Bond distances and angles within the phthalazine ring are comparable to that found in the literature for similar compounds[5–7].

The C(1)-N(1) bond [1.314(3)Å] is slightly longer than the N(2)-C(4) one [1.305(3)Å] and they are shorter than the values observed in other pyridazine derivatives. The benzene and pyridazine rings are esentially planar, with maximum deviation from the calculated mean plane of 0.018(2) Å and 0.015(1) Å, respectively.

The dihedral angle between the best planes through the benzene ring and pyridazine ring is 2.6(1)° indicating that the whole molecule is almost planar. The phosphonic oxygen atoms O(1), O(2), O(3), and P(1) atoms are displaced out ofthe plane formed by the pyridazine ring by –0.936(4), –0.499(4), 1.402(4) and 0.088(3) Å, respectively, while the amine hydrogen atom H(1) is almost coplanar with the pyridazine ring within 0.003 (37) Å.

TABLE II Selected bond lengths (Å) and selected angles (°) for 1-phthalazinephosphonic acid

P(1)-O(1)	1.486(2)
P(1)-O(2)	1.483(2)
P(1)-O(3)	1.559(2)
P(1)-C(1)	1.855(2)
N(1)-C(1)	1.314(3)
N(1)-N(2)	1.362(3)
N(2)-C(4)	1.305(3)
C(1)-C(9)	1.424(3)
C(4)-C(10)	1.414(3)
C(5)-C(6)	1.361(4)
C(5)-C(10)	1.405(3)
C(6)-C(7)	1.410(4)
C(7)-C(8)	1.375(4)
C(8)-C(9)	1.416(3)
C(9)-C(10)	1.414(3)
N(1)-H(1)	0.93(4)
O(3)-H(3)	0.85(3)
O(1)-P(1)-O(3)	111.2(1)
O(2)-P(1)-O(1)	119.7(1)
O(2)-P(1)-O(3)	109.9 (1)
O(2)-P(1)-C(1)	105.0(1)
O(1)-P(1)-C(1)	107.0(1)
O(3)-P(1)-C(1)	102.3(1)
C(1)-N(1)-N(2)	126.6(2)
C(4)-N(2)-N(1)	115.3(2)
N(1)-C(1)-C(9)	118.9(2)
N(1)-C(1)-P(1)	115.3(2)
C(9)-C(1)-P(1)	125.8(2)
N(2)-C(4)-C(10)	125.1(2)
C(6)-C(5)-C(10)	119.3(2)
C(5)-C(6)-C(7)	120.8(2)
C(8)-C(7)-C(6)	121.3(2)
C(7)-C(8)-C(9)	118.7(2)
C(10)-C(9)-C(8)	119.4(2)
C(10)-C(9)-C(1)	116.8(2)
C(8)-C(9)-C(1)	123.8(2)
C(5)-C(10)-C(4)	122.3(2)
C(5)-C(10)-C(9)	120.4 (2)
C(4)-C(10)-C(9)	117.3(2)

The X-Ray studies[8] show that all pyridazine rings deviate sligthly from planarity adapting distorted boat conformation. In the present structure the nearly planar conformation of the title molecule is stabilized by a network of the intermolecular and intramolecular hydrogen bonds (Table III). As depicted in Fig. 4 the molecules around the twofold axis are linked by N(1)ˉH(1)···O(2^{I}) hydrogen bonds to form a dimer [N(1)···O(2); 2.630(4)Å, H(1)···O(2); 1.72(5) Å, N(1)ˉH(1)···O(2); 163(4)°]. Additionally, the amine hydrogen H(1) participates in an intramolecular hydrogen bond involving the oxygen atom O(2) of the phosphonic group. The distances N(1)···O(2); and H(1)···(O2) are 2.830(3), 2.42(4) Å, and the angle is 107(3)°. Thus it forms a five membered pseudoring which has an envelope conformation with O(2) displaced from the plane of the remaining four atoms by 0.373(2) Å.

TABLE III Hydrogen bond lengths (Å) and angles (°) for 1-phthalazinephosphonic acid

D-H...A	*D...A*	*H...A*	*D-H...A*
N(1)-H(1)...O(2)	2.830 (3)	2.42 (4)	107 (3)
N(1)-H (1)...O (2^{I})	2.630 (2)	1.72 (5)	163 (4)
O(3)-H(3)...O (1^{II})	2.527 (3)	1.65 (5)	174 (5)
C(4)-H(4)...O (3^{III})	3.514 (4)	2.67 (4)	165 (4)
C(5)-H(5)...O (1^{III})	3.480 (4)	2.69 (5)	146 (4)
C(6)-H(6)...O(3^{IV})	3.391 (4)	2.51 (5)	148 (4)
C(7)-H(7)...N(2^{V})	3.562 (5)	2.64 (4)	172 (3)
C(8)-H(8)...O (1)	3.086 (4)	2.42 (4)	125 (3)

Symmetry code: (I))2-x,y,1.5-z; (II) 1.5-x,-0.5+y,1.5-z: (III) x,-y,-0.5+z; (IV)-0.5+x,-0.5-y,-0.5+z (V) -0.5+x,-0.5+y,z.

Furthemore, the O(3) atoms (as donors) form infinite hydrogen-bond chains with O(1) [1½-x,-½+y, 1½-z] parallel to the b direction (Fig. 5). Apart from that, five short contacts between hydrogen from the phthalazine ring and other atoms were found in the molecule (Table III). The H(4)···O(3), H(5)···O(1), H(6)···O(3), H(7)···N(2) and H(8)···O(1) are 2.67(4), 2.69(4), 2.51(4), 2.64(4), 2.42(4) Å, respectively. The distances C···O(N) [3.562(5)-3.086(4) Å] and angles [125(3)-172(3)°] suggest some

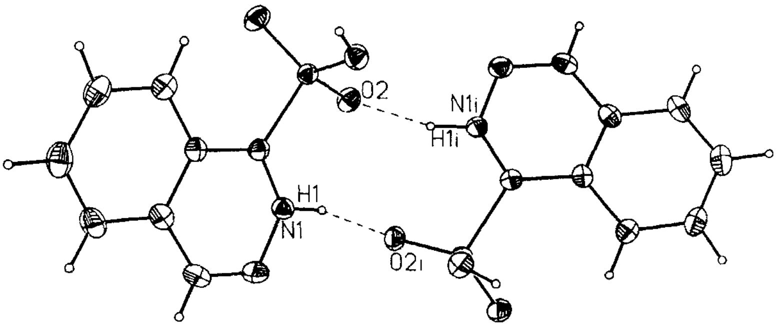


FIGURE 4 Pseudo-dimer in the crystal of 1-phthalazinephosphonic acid. Intramolecular hydrogen bonds are shown by dotted lines and intermolecular hydrogen bonds by dashed lines. Molecule (i) is generated by the symmetry operation [2-x, y, 1½-z]

kind of weak C-H···X hydrogen bond[9], Another intermolecular interaction in the crystal is the stocking between the benzene ring from molecule at x,y,z, and the pyridazine ring from another [1½-x, ½-y, 1-z]. The shortest distance between them is about 3.5 Å.

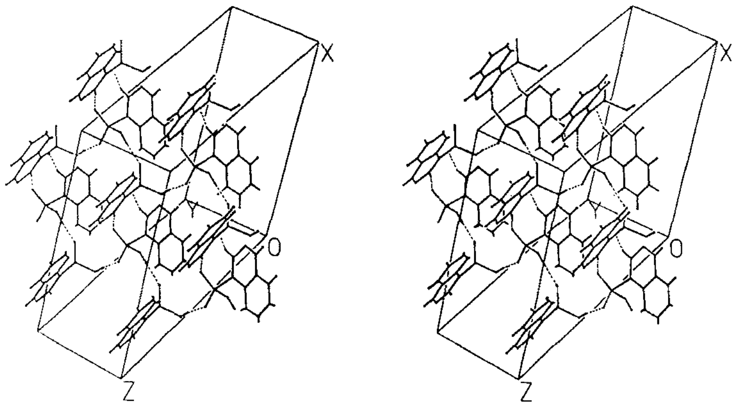


FIGURE 5 Stereoscopic packing diagram. Hydrogen bonds are shown as dashed lines

In the present structure, the phosphonic group is negatively charged, with the charge beeing distributed over the O(1) and O(2) atoms, and the P-O bond lengths are 1.486(2) Å and 1.483(2) Å, respectively. The P-O(3) bond is longer by 0.07 Å from the other two P-O bonds due to the protonation of its oxygen atom. Thus the P-O(3) bond of 1.559(2) Å has a character of a single bond whereas the other two are partially double bound.

The coordination around the P atom is in a form of a distorted tetrahedron (Table I). The O-P-O and O-P-C angles in the phosphonic groups range from 102.3(1) to 119.7(1)°. The smallest angle corresponds to the protonated 0(3) and C(1) while the largest angle derives from the unprotonated O(1) and O(2) atoms. The above values of angles and bond lengths agree well with those found earlier for other aminophosphonic acids.

Based on all available data, we can state that the isolated product is of aromatic structure with the phosphorus attached to the heteroaromatic diazine ring. The phosphorus group is in the ionic form what explains the very downfield shift of the proton doublet at 8.91 ppm, due to the proton H8 attached to carbon C8.

The formation of this product is quite unexpected, because instead of addition we observe the substitution at the heteroaromatic ring. The strongly basic reaction conditions suggest the reaction being similar to the Chichibabin reaction, the standard nucleophilic addition to heteroaromatic systems followed by abstraction of hydride anion.

The formation of 1-phthalazinephosphonic acid was observed only when metallic sodium is added to the reaction mixture. When the typical acidic catalysts – aluminium choride, or boron trifluoride-etherate were used, we have not detected the formation of this compound. We were not able to identify any other product of this reaction so far, and the understanding of the course of this reaction requires more detailed studies.

EXPERIMENTAL

Phthalazine was prepared by the reaction of o-phthalaldehyde with hydrazine hydrate in ethanol at 0°C[10]. All other materials were obtained commercially. NMR spectra were recorded on AMX 300 MHz Brucker instrument, operating at 300.13 MHz (^{1}H) 75.1 (^{13}C), and 121.499 (^{31}P). Measurements were made in D_2O/NaOD. IR spectra and elemental analyses were performed in the Analytical Laboratory of the Institute of Organic Chemistry, Biochemistry and Biotechnology. All commercially available reagents were used as received from the suppliers.

Crystal structure determination of 1-phthalazinephosphonic acid

The single crystal of 1-phthalazinephosphonic acid used for X-ray data collection (aprox. dimensions 0.3× 0.25 × 0.25 mm) was grown by slow evaporation from water:ethyl alcohol (10:2).

Crystal data: $C_8H_7N_2O_3P$, M=210.13, Colourless, block, monoclinic, space group C2/c, (No.15), a=15.293(3), b=7.344(1), c=16.691(3) Å, $\beta = 116.10(3)^o$,V= 1683.9(5)$Å^3$, Z=8, D_c=1.658 g .cm^{-1}, F(000)=864,μ= 2.785 mm^{-1}.

Data collection: The intensity data were colected on an KM4 four-circle diffractometer [temperature 293(2)K],θ range 5–81.5°; $0<h<19$, $0<k<9$, $-21<l<18$ using graphite monochromated Cu-Kα X-radiation (λ =1.5418 Å) and ω-2θ scanning. Of 2100 unique data, 1477 had $F>4\sigma(F)$ .The data were corrected for Lorentz and polarization effects, and extinction [x=0.002(3)], but no absorption correction.

Structure solution. The aproximate positions of the non-hydrogen atoms were determined by direct methods (SHELXS-86[11]). The structure was refined by full-matrix least-squares methods (SHELXL-93[12]) using F^2 data and anisotropic temperature factors for all the non-hydrogen atoms. All the hydrogen atoms were located on Fourier difference maps and included in the refinement with isotropic temperature factors. At convergence, the discrepancy factors R(F) and wR(F^2) were 0.039 and 0.11, respectively. The weighting scheme: $w=1/[\sigma^2(F_o^2)+(a\cdot P)^2+ b\cdot P]$ where $P=[f\cdot \text{Max of } (0 \text{ or } F_o^2)+(1-f)\cdot F_c^2)]$; [a=0.076, b=1.94, f=1/3] was found to give satisfactory analyses of variance. The final difference Fourier map was essentially featureless, with largest difference peak and hole of 0.36 and –0.38 e·$Å^{-3}$, respectively.

Syntheses of 1-phthalazinephosphonic acid

1.62g of phthalazine and 0.11 5g sodium in 25 ml diisopropylphosphite were heated to 80°C for 3 hours with stirring. Then diisopropyl phosphite was stripped off under vacum and the dark brown residue was hydrolyzed with a mixture of 50 ml of acetic acid and 50 ml of concentrated hydrochloric acid for 1 hr. After evaporation to dryness on a rotatory evaporator, the resulting oilly residue was diluted and evaporated several times with water and then with alcohol on a rotatory evaporator. The residue was dissolved in ethanol and propylene oxide was added to give 0.6g (24%) of product as a white powder $C_8H_9N_2O_3P$ M=214 m.p. 282–284°C, microanal. % calc/found P 14.48/14.58; N 13.08/13.17. ^{1}H-NMR (Table I. Fig. 2)).

Acknowledgements

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