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The Cleavage of 1-Amino-2'-Nitrobenzylphosphonates in a Basic Medium. Formation of the 3-Amino-2,1-Benzisoxazole Derivatives

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Abstract: Treatment of 1-amino-2'-nitrobenzylphosphonic acids with aqueous sodium hydroxide caused a C-P bond cleavage, with formation of 3-amino-2,1-benzisoxazole derivatives (**3**). The leaving phosphorus moiety was identified here as phosphoric acid. In the case of basic hydrolysis of corresponding esters, new cyclic phosphorus compounds (derivatives of benzoxazaphosphorin-3,1,2 P^{V}-one-2) were obtained. The cyclic products were formed as a result of the subsequent reaction of anthranil derivatives with leaving phosphorus fragment, presumably metaphosphate. These benzoxazaphosphorins (compounds **4**) were converted by means of aqueous hydrochloric acid to 3-amino-2,1-benzisoxazole derivatives. © 1997 Elsevier Science Ltd.

INTRODUCTION

Recently, we have found that acidic hydrolysis of some pyridylmethyl(amino)phosphonates led to a C-P bond cleavage and formation of pyridylmethylamines[1]. The splitting of the 2- and 4-pyridylmethyl(amino)-phosphonates and rearrangement to amines was under the control of electronic phenomena, namely mesomeric and inductive effects of protonated nitrogen atoms in the pyridyl phosphonates[1].

In order to determine the scope of this reaction, we have been searching for other aminophosphonate structures demonstrating similar chemical properties.

The nitro group is often considered as an analogue for pyridine nitrogen in many cases, for example: *o*- or *p*-nitrophenyl chlorides or bromides react similarly as corresponding halogenopyridines in nucleophilic substitution reactions. Some years ago, one of the authors had noticed a dephosphorylation of 1-(N-propylamino)-4-nitrobenzylphosphonic acid, in a basic medium[11]. Thus, we turned our attention to some nitro derivatives of 1-aminobenzylphosphonates (phosphonic analogues of nitrophenylglycines), and investigated their behaviour in acidic and basic media.

First, we hydrolysed diethyl 1-amino- 2'-, 3'- and 4'-nitrobenzylphosphonates by means of aqueous hydrochloric acid, likewise as it was carried out earlier for pyridylmethyl derivatives[1], and we obtained the corresponding 1-amino-nitrobenzylphosphonic acids in high yield. Thus, there was no indication that a cleavage of C-P bond occurred.

However, the treatment of 1-amino- 2'-, or 4'-nitrobenzylphosphonic acids by with the excess of dilute aqueous sodium hydroxide, afforded some new products, which resulted from splitting of C-P bond in these acids.

Interestingly, 1-(N-benzylamino)-3'-nitrobenzylphosphonic acid was not affected by base. Thus, treatment of the acid with excess of aqueous NaOH and refluxing the solution for two hours, the above 3-nitro-phosphonic acid afforded unchanged, after neutralization of the mixture with aqueous HCl.

In summation, we are convinced, that the basic cleavage of C-P bond occurred only in the case of 1-amino-2'-nitro-, and 1-amino-4'-nitrobenzylphosphonic acids. This interesting reaction become an object of our more detailed studies.

In this paper, we wish to present some results concerning of the cleavage of 1-amino-2'-nitrobenzylphosphonic acids and esters, in basic conditions. The similar cleavage of 1-amino-4'-nitrobenzylphosphonic derivatives is more complex, and therefore it will be a subject of a separated publication.

RESULTS AND DISCUSSION

Synthesis of 1-amino-2'-nitrobenzylphosphonates

The title compounds were prepared by an addition reaction of diethyl ester of phosphorous acid (diethyl phosphite) to aldimines, which in turn, were obtained from *o*-nitrobenzaldehyde and various amines.

The aldimines were prepared by refluxing a mixture of *o*-nitrobenzaldehyde and amine (butylamine, benzylamine, or *p*-toluidine) in diluted toluene solution. The formed water was removed by addition of anhydrous potassium carbonate. Crude aldimines (in toluene solution) were treated with diethyl phosphite and the mixture was again refluxed to complete reaction. The formed products (the nitro-phosphonates **1c,d**) crystallized out directly from reaction mixture, after cooling. The corresponding N-butylamino derivative (**1b**) was obtained as an oil and therefore it was purified by transformation into oxalate. The free ester **1b** was liberated from the oxalate by treatment with excess of aqueous sodium bicarbonate.

The acidic hydrolysis of esters **1b,c** by means of 20% aqueous HCl afforded corresponding nitro-phosphonic acids **2b,c**. However, hydrolysis of the ester **1d** (*p*-toluidine derivative) led to indefinite dark colored products, and the corresponding acid was not isolated.

Similarly, 1-(N-benzylamino)-3'-nitrobenzylphosphonic acid was prepared.

The acid **2a** (with unsubstituted amino group) was obtained (in *one-pot synthesis*), by treatment of *o*-nitrobenzaldehyde with benzhydrylamine and then with diethyl phosphite in toluene, followed by hydrolysis of formed ester with 20% aqueous HCl, according to the method published in a literature[12].

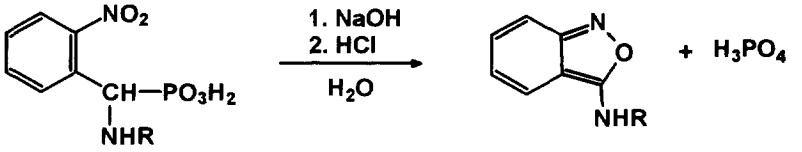
The cleavage of 1-amino-2'-nitrobenzylphosphonic acids (2a,b,c) in a basic medium

The nitro-phosphonic acids **2a,b,c** were dissolved in eight-fold molar excess of aqueous sodium hydroxide and the solution was refluxed for 2 hours. The solution become yellowish after few minutes. Final neutralization of reaction solution with aqueous HCl caused precipitation of a solid (in the case of **2a** and **2c**), or an oil (in the case of **2b**). Analysis of the precipitates proved, that the separated products were 3-amino derivatives of anthranil **3a-c** (Scheme 1).

During basic hydrolysis the phosphorus-carbon bond was cleaved and the product of this cleavage was found in water layer. Analysis of the water layer (after work-up) by means of ^{31}P-NMR spectra, revealed that expelled phosphorus moiety was phosphoric acid.

Formation of anthranil derivatives **3a-c** was rather unexpected result. The unsubstituted 3-amino-anthranil (**3a**) was earlier described in a literature[2,3], and it was helpful in establishing the structures of the formed products **3**. The anthranils **3a-c** were identified also on the basis of ^{1}H-NMR, MS spectra and their comparison with the literature data[2,3].

The anthranils (2,1-benzisoxazoles) are formed usually by the reduction of *o*-nitrobenzoic acids with zinc, tin or tin (II) chloride[4,5], or by the oxidation of anthranilic acids[5]. Also, electrochemical reduction of *o*-nitrobenzonitriles, or their controlled hydrogenation over Ni, gave 3-amino-2,1-benzisoxazoles (3-amino-anthranils)[2,3]. The benzisoxazole is presumed to arise *via* an intermediate hydroxylamine[3,8].



2 a - c 3 a - c

	R
a	H
b	Bu
c	CH_2Ph

Scheme 1

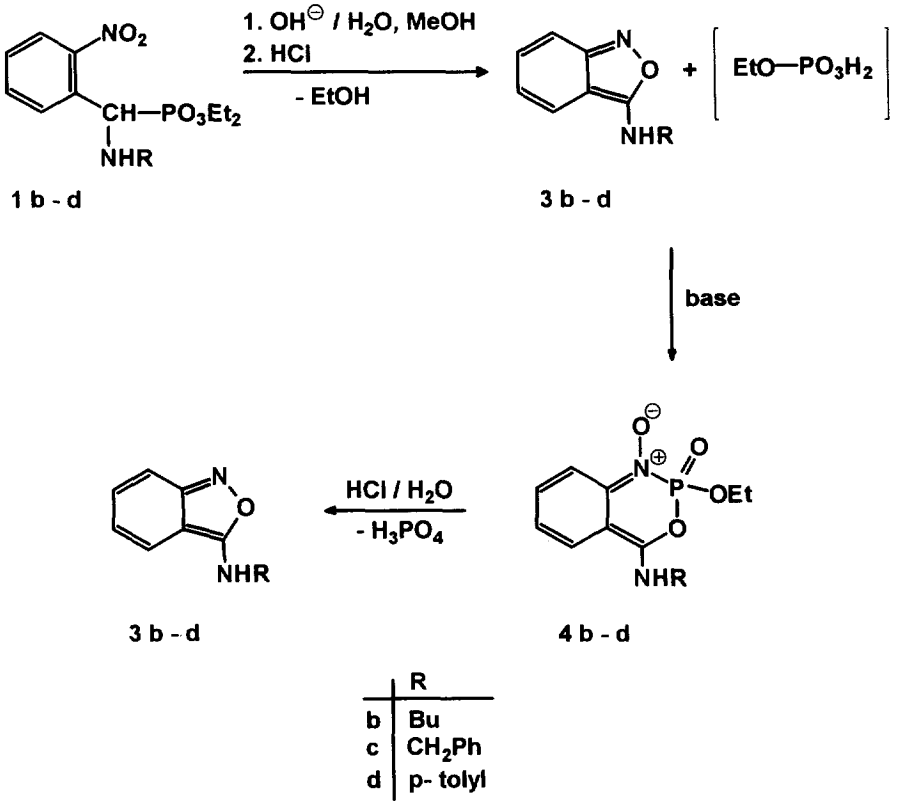
The formation of anthranils from the above aminophosphonates represent in fact, an intramolecular reduction of the *o*-nitro group by phosphonic moiety, which in turn, oxidizes to a phosphate group.

Diethyl 1-amino-2'-nitrobenzylphosphonates (**1b,c,d**) were also splitted by base, similarly as the corresponding acids, but unexpectedly new products containing phosphorus were formed, in this case.

Thus, when the *o*-nitro-phosphonates **1b-d** were heated in aqueous-methanolic solution, containing eight-fold molar excess of NaOH, the ester was also splitted and the anthranils (**3**) were formed, likewise as it was

observed in the case of the hydrolysis of acids. However, the composition of isolated product was dependent on the way of work-up of reaction mixture. Usually, after 2 hours of heating, the reaction mixture was neutralized with aqueous HCl, and the formed products extracted with chloroform. The chloroform extract contained the anthranils (**3**) and additionally the monoethyl ester of removed phosphorus moiety. Upon long standing, or upon drying of the extract with a basic agent (i.e. anhydrous K_2CO_3), new products were formed, which separated spontaneously as a precipitate from chloroform solution. These products (**4b-d**) were collected by filtration, or isolated by reextraction to methanol.

The formation of these products is probably a result of binding of two parts of the splitted ester. The leaving phosphorus group, (according to the results of NMR studies of reaction mixture) was supposedly the mono-ester of phosphoric acid, or ethyl metaphosphate (Et-O-PO_2). Such species was also able to react with anthranil (**3b-d**), to form the derivatives of benzoxazaphosphorins-3,1,2 P^v (**4b,c,d**).



	R
b	Bu
c	CH_2Ph
d	p- tolyl

Scheme 2

Formation of phosphorin derivatives from anthranils was described in a literature. Similar products containing sulfur (benzothiazaphosphorin derivatives), were obtained by thionation of some anthranil derivatives with phosphorus pentasulfide[6,7].

The cyclic products **4b-d**, were easily hydrolysed back to anthranil derivatives **3b-d**, by means of aqueous hydrochloric acid. This is not unexpected, since the P-N bond is unstable in acidic conditions. After removal of phosphorus moiety, the remaining part of molecule was contracted again to an anthranil ring during hydrolysis.

Additionally, interesting side products were isolated during a basic cleavage of the phosphonic esters **1b-d**. When reaction mixture was extracted prior to neutralization with diethyl ether, some N-methylated anthranils **5** were isolated. The alternative structure (**5'b-d**) for these compounds (Scheme 3) is less probable, on the basis of MS data (EI mode at 70 eV).The fragmentation pattern of these compounds usually shows the departure of a fragment containing N-methylated amine derivative, what indicates that the first structure is more preferable.

The yield of **5b-d** was low, (never exceeding 20%) even in the case, when the reaction was carried out in pure methanol. The way of formation of N-methylated anthranils **5b-d** seems to be unclear. 3-Aminoanthranils exist in two tautomeric forms[2,3], and one of the tautomeric forms is a weak acid, which can be ionized by a strong base, giving an anion localized on anthranil nitrogen atom[8]. But it seems to be very unlikely, that the N-methylated anthranils were formed as a result of a nucleophilic attack of such anion on methanol molecule. Another possibility is, that a *nitrene* intermediate could be formed during basic cleavage of the ester, or the formed anthranil was splitted to a *nitrene* in the reaction conditions[9]. But the *nitrene* mechanism seems to be also unlikely, because a *nitrene* usually undergoes CH or OH insertion, in preference to CO insertion. However, there is no doubt, that the solvent (methanol) is involved in the process of formation of N-methylated anthranils. It was proved, by carrying out of a separated experiment, in which the acid **2c** was splitted by aqueous-methanolic solution of NaOH, in the same conditions, as it was carried out in the case of esters. After work-up, the product **5c** was also isolated, with low yield (about 15%).

Much of the interpretation of formation of the **5b-d**, presented herein, is highly speculative. Anyway, the **5b-d** are significant products in a basic cleavage of *o*-nitrobenzyl(amino)phosphonates, carried out in methanol.

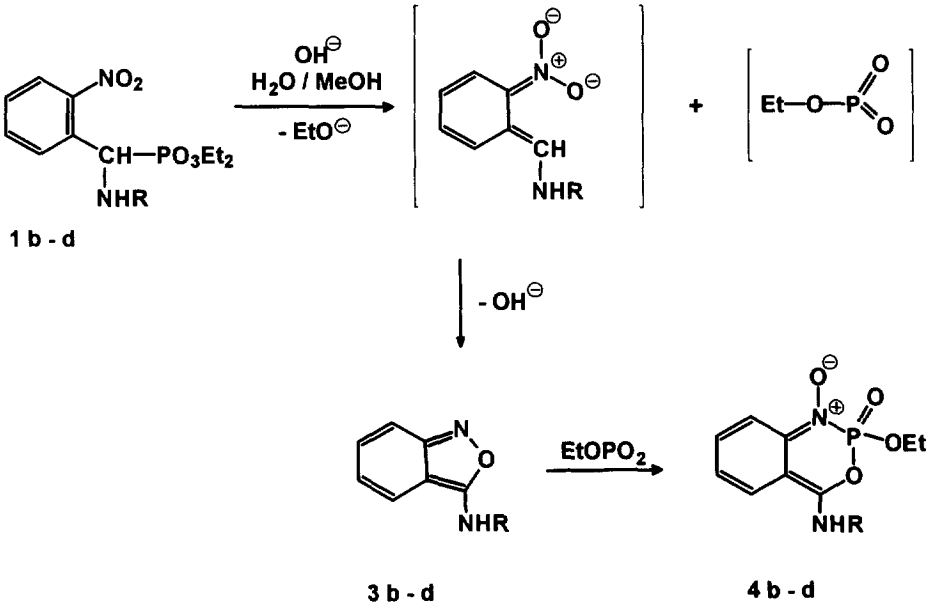
5 b - d **5 ' b - d**

Scheme 3

Proposed Mechanism of the Cleavage of 1-Amino-2'-nitrobenzylphosphonic Acids

Many mechanisms of anthranil formation from corresponding *o*-nitrophenyl derivatives had been described[4,5]. The intermediacy of an *aci*-nitro compound has been proposed for most of them. The *aci*-nitro intermediate can be formed in basic, as well as in acidic conditions. For example; *o*-nitrophenylacetic acid heated in concentrated sulfuric acid gave a mixture of 2,1-benzisoxazole and 2,1-benzisoxazole-3-carboxylic acid[10]. According to described mechanism[10], the formed *aci* intermediate oxidized α hydrogen atoms to water and also the carboxylic group to carbon dioxide. In the first case, when the leaving groups were water and CO_2, the final product was unsubstituted anthranil. In the second case, when only water was removed, the 3-carboxyanthranil was produced.

We postulate, that the basic cleavage of 1-amino-2'-nitrobenzylphosphonic acids proceeded also *via aci*-nitro intermediate. The *aci*-nitro species forms easily in basic solution, in an ionizable form. The observed cleavage is an intramolecular redox reaction, in which, the *aci*-nitro intermediate oxidizes the phosphonic group to pentavalent phosphorus moiety. The leaving group might be phosphate (in the case of acid cleavage), or probably the metaphosphate ($EtO\text{-}PO_2$) in the case of ester cleavage. After removal of phosphorus moiety, the remaining fragment of molecule is contracted into an anthranil ring.



Scheme 4

The anthranil ring formation appears to involve also an *aci*-nitro species which, by nucleophilic attack of the nitro-oxygen anion on methine carbon atom, undergoes ring closure to give the final product.

In the case of a basic cleavage of diethyl 1-amino-2'-nitrobenzylphosphonates (**1b-d**), formation of the cyclic phosphorus compounds (benzoxazaphosphorins-3,1,2) suggests, that the leaving group might be metaphosphate. It can react with an anthranil, to give six-membered ring, containing phosphorus atom. It is unlikely, that the metaphosphate would be formed during basic cleavage of the acids **2a-c**, and therefore, formation of benzoxazaphosphorins was not observed in this case.

The presence of nitro group in *ortho* or *para* positions in the benzylphosphonate was substantial for an occurrence of the C-P bond cleavage. The nitro group at those positions was able to form conjugate double bonds between benzene ring and side CH group, as a result of mesomeric effect. This effect was responsible for a C-P bond cleavage, because in the case of 1-(N-benzylamino)-3'-nitrobenzylphosphonic acid (where similar mesomeric effect is impossible), such a cleavage was not observed.

Replacement of nitro group at *ortho* position by other electronegative group (for example: Br) leads to stability of such compound towards a base. For example, when 1-(butylamino)-2'-bromobenzylphosphonic acid was heated with excees of aqueous NaOH, lack of a cleavage of C-P bond was observed, and the acid was recovered unchanged, after acidification. It can be explained by the fact, that bromine exhibits a positive mesomeric effect towards benzene ring, in the contrary to the nitro group, which shows a quite opposite effect.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in $CDCl_3$, DMSO-d_6 or D_2O solutions, using 300.13 MHz for ^{1}H-NMR, 75.477 MHz for ^{13}C-NMR and 121.51 MHz for ^{31}P-NMR spectra, respectively. G.C.-M.S. analyses were carried out with a Hewlett Packard HP 5971A apparatus, at an ionization potential of 70 eV, equipped with HP-1 capillary column, 25 m length, and also the M.S. analyses were performed on a Finnigan TSQ 700 instrument (electrospray ionization on mode: ESI -Q1MS, or ESI +Q1MS). Elemental analyses were done in the Laboratory of Instrumental Analysis, in the Institute. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200, and were uncorrected.

All commercially available reagents were used as received from the supplier (Aldrich Company).

Preparation of Diethyl 1-Amino-2'-nitrobenzylphosphonates (1b-d); General Procedure:

To a solution of *o*-nitrobenzaldehyde (3.0g, 20 mmol) in toluene (50 mL) corresponding amine was added (20 mmol). The mixture was refluxed for 1 hr, cooled, and anhydrous potassium carbonate was added (10g). The mixture was shaken for short time, filtered, and diethyl phosphite was added to the filtrate (2.8g, 20 mmol). The obtained solution was refluxed again for 3 hrs and cooled. The precipitated esters **1c** and **1d** were collected

by filtration. The ester **1b** was purified as oxalate salt; thus, the reaction solution was evaporated and remaining oil was dissolved in acetone (20 mL) and treated with acetone solution (30 mL) of oxalic acid (3.8g, 30 mmol). After cooling, the oxalate separated was collected by filtration and dried. Free ester **1b** was liberated from the oxalate by neutralization with aq. sodium bicarbonate, and then extracted with chloroform.

The esters: Diethyl 1-(N-benzylamino)-3'-nitrobenzylphosphonate (**1c^{III}**) and diethyl 1-(N-butylamino)-2'-bromobenzylphosphonate (**1b^{II}**) were obtained similarly.

Diethyl 1-(N-butylamino)-2'-nitrobenzylphosphonate (1b): Oil. Yield: 68%. ^{1}H-NMR($CDCl_3$): 7.77(m, 2H), 7.53(m, 1H), 7.33(m, 1H), 5.06(d, 1H, CH-P, J=22.8 Hz), 4.05-3.80(m, 4H, OCH_2), 2.47(t, 2H, CH_2N), 1.38-1.18(m, 7H, CH_2, CH_3), 1.00(t, 3H, CH_3), 0.81(t, 3H, CH_3). ^{31}P-NMR: 23.009(s). Oxalate: m.p.127-129°C. Anal. calc. for $C_{15}H_{25}N_2O_5P(COOH)_2$: Calc. N, 6.45; P, 7.13; found: N,6.56; P, 7.30.

Diethyl 1-(N-benzylamino)-2'-nitrobenzylphosphonate (1c): Yield: 88%. m.p. 63-64.5°C. ^{1}H-NMR ($CDCl_3$): 7.84(m, 2H), 7.57(m, 1H), 7.36(m, 1H), 7.21(m, 5H, Ph), 5.13(d, 1H, CH-P, J=22.7 Hz), 4.08-3.60(m, 6H, OCH_2, CH_2N), 2.22(bs, 1H, NH), 1.22(t, 3H, CH_3), 1.02(t, 3H, CH_3). ^{31}P-NMR: 22.94(s). Anal. calc. for $C_{18}H_{23}N_2O_5P$: N, 7.40; P, 8.19; found: N, 7.14; P, 8.40. m.p. of oxalate: 132-133°C.

Diethyl 1-(N-*p*-tolylamino)-2'-nitrobenzylphosphonate (1d): Yield:75%. m.p. 163.5-165.5°C. ^{1}H-NMR ($CDCl_3$): 8.30(d, 1H, J=8.04 Hz), 8.05(m, 1H), 7.84(t, 1H, J=7.4 Hz), 7.72(m, 1H), 7.25(d, 2H, J=8.3 Hz), 6.88(d, 2H, J=8.4 Hz), 6.44(d, 1H, CH-P, J=26.1 Hz), 5.2(bs, 1H, NH), 4.5-4.05(m, 4H, OCH_2), 2.50(s, 3H, CH_3), 1.61(t, 3H, J=7.1 Hz, CH_3), 1.40(t, 3H, CH_3, J=7.1 Hz). ^{31}P-NMR: 22.29(s). Anal. calc. for $C_{18}H_{23}N_2O_5P$: N, 7.40; P, 8.19; found: N, 7.20, P, 8.19.

Diethyl 1-(N-butylamino)-2'-bromobenzylphosphonate (1b^{II}): Oil. Yield: 94%. Oxalate: m.p: 129-130°C., ^{1}H-NMR (D_2O): 7.68(d, 1H), 7.54(d, 1H), 7.42(t, 1H), 7.30(t, 1H), 5.21(d, 1H, CH-P, J=18.6 Hz), 4.15-3.87(m, 4H, OCH_2), 2.89(m, 2H, CH_2N), 1.50(m, 2H), 1.22-1.06(m, 8H, CH_2, CH_3), 0.70(t, 3H, CH_3). ^{31}P-NMR: 16.998(s). Anal. calc. for $C_{15}H_{25}NO_3PBr(COOH)_2$: N, 2.99, P, 6.61, Br, 17.06; found: N, 3.48, P, 6.82, Br, 17.38.

Diethyl 1- (N-benzylamino)-3'-nitrobenzylphosphonate (1c^{III}): Oil. Yield: 54%. Oxalate: m.p: 139-140°C., ^{1}H-NMR (D_2O): 8.34(m, 2H), 7.84(m, 2H), 7.50-7.04(m, 5H, Ph), 4.91(d, 1H, CH-P, J=18.4 Hz), 4.44-4.06(m, 6H, OCH_2, CH_2N), 1.35(t, 3H, CH_3), 1.19(t, 3H, CH_3). ^{31}P-NMR: 14.092(s). Anal. calc. for $C_{18}H_{23}N_2O_5P(COOH)_2$: N, 5.98; P, 6.61; found: N, 6.30; P, 6.50.

Preparation of 1-Amino-2'-nitrobenzylphosphonic Acids (2a-c); Hydrolysis of Esters:

The appropriate nitro-ester **1b,c** (10 mmol) was dissolved in 20% aq. HCl (100 mL) and refluxed for 5-6 hrs. After evaporation *in vacuo*, the crude nitro-phosphonic acids **2b,c** were obtained, which were purified by recrystallization from aqueous methanol, or aqueous ethanol.

The esters **1b^{II}** and **1c^{III}** were hydrolysed similarly, as described above.

1-Amino-2'-nitrobenzylphosphonic acid (2a) was obtained according to the method described in[12]. Yield: 34%. m.p. 245-247°C (dec.). lit[13] m.p. 239-240 °C. ^{1}H-NMR (D_2O+D_2SO_4): 8.22(d, 1H), 7.93-7.72(m, 3H), 5.72(d, 1H, CH-P, J=18.6 Hz). ^{31}P-NMR: 10.861(s). Anal. calc. for $C_7H_9N_2O_5P$: N, 12.07; P, 13.34; found: N, 11.64; P, 13.28.

1-(N-butylamino)-2'-nitrobenzylphosphonic acid:(2b): Yield: 60%. m.p. 214-216°C. ^{1}H-NMR (D_2O+D_2SO_4): 8.27(d, 1H), 7.93-7.79(m, 3H), 5.65(d, 1H, CH-P, J=18.8 Hz), 3.20(m, 2H, CH_2N), 1.77(m, 2H), 1.33(m, 2H), 0.90(t, 3H, CH_3). ^{31}P-NMR: 9.259(s). Anal. calc. for $C_{11}H_{17}N_2O_5P$: N, 9.72; P, 10.75; found: N, 9.40, P, 10.82.

1-(N-benzylamino)-2'-nitrobenzylphosphonic acid:(2c): Yield: 53%. m.p. 205-206°C. ^{1}H-NMR (DMSO-d_6): 8.18(m, 1H), 8.00(m, 1H), 7.76(m, 1H), 7.58(m, 1H), 4.99(d, 1H, CH-P, J=17.9 Hz), 4.3-3.9(dd, 2H, CH_2N). ^{31}P-NMR: 8.78(s). Anal. calc. for $C_{14}H_{15}N_2O_5P$: N, 8.69; P, 9.61; found: N, 8.30; P, 9.16.

1-(N-butylamino)-2'-bromobenzylphosphonic acid ($2b^{II}$): Yield: 55%. m.p. 232-233°C. ^{1}H-NMR (D_2O+D_2SO_4): 7.81(d, 1H), 7.71(d, 1H), 7.56(t, 1H), 7.42(t, 1H), 5.18(d, 1H, CH-P, J=17.6 Hz), 3.04(m, 2H, CH_2N), 1.69(m, 2H, CH_2), 1.29(m, 2H, CH_2), 0.85(t, 3H, CH_3). ^{31}P-NMR: 10.839(s). Anal. calc. for $C_{11}H_{17}NO_3BrP$: N, 4.35; P, 9.62; Br, 24.80; found: N, 4.73; P, 9.86; Br, 24.78.

1-(N-benzylamino)-3'-nitrobenzylphosphonic acid ($2c^{III}$): Yield: 48%. m.p. 256-260°C (dec.) ^{1}H-NMR (D_2O+D_2SO_4): 8.35(m, 2H), 7.90-7.75(m, 2H), 7.41(m, 5H, Ph), 4.82(d, 1H, CH-P, J=18.0 Hz), 4.34(dd, 2H, CH_2N). ^{31}P-NMR: 9.459(s). Anal. calc. for $C_{14}H_{15}N_2O_5P$: N, 8.69; P, 9.61; found: N, 8.77; P, 9.45.

The Cleavage of Acids 2a-c; Formation of 3-Amino-2,1-Benzisoxazoles (3a-c):

The acid **2a-c** (3 mmol) was dissolved in aqueous sodium hydroxide solution (50 mL), containing 0.96g NaOH. The solution was refluxed for 2 hrs, cooled and neutralized with 6 M aqueous HCl (5 mL). It caused a precipitation of antranil derivative as a solid (in the case of **3a** and **3c**), or an oil (in the case of **3b**). The solid products were collected by filtration, dried, and recrystallized from benzene. The derivative **3b** was extracted with chloroform, and purified on column chromatography (silicagel, eluant: $CHCl_3$-ethyl acetate 20:1).

3-Amino-2,1-benzisoxazole (3a): Red powder. Yield: 74%. m.p.140-145°C (dec.) lit[2] m.p.110-114°C (dec). lit.[3] m.p.145°C (dec.). ^{1}H-NMR ($CDCl_3$): 7.64-7.57(m, 2H), 7.42(t, 1H, J= 6.9 Hz), 7.14(t, 1H, J= 7.0 Hz). M.S.: ESI -Q1MS: 133.2 (M-1), ESI +Q1MS: 135.1 (M+1). Anal. calc. for $C_7H_6N_2O$: C, 62.68, H, 4.50, N, 20.88; found: C, 62.42, H 4.35, N, 20.30.

3-(N-butylamino)-2,1-benzisoxazole (3b): Yellow oil. Yield: 78%. ^{1}H-NMR ($CDCl_3$): 9.50(bs, 1H, NH), 7.61(d, 1H, J= 7.8 Hz), 7.34(t, 1H, J= 6.9 Hz), 7.12(d, 1H, J= 7.8 Hz), 6.99(t, 1H, J=6.9 Hz), 3.81(t, 2H, CH_2N, J= 7.1 Hz), 1.64(m, 2H), 1.19(m, 2H), 0.76(t, 3H, CH_3, J= 7.2 Hz). M.S. (70 eV): 190 (M, 43.7%), ESI-Q1MS: 189.2 (M-1), ESI +Q1MS: 191.1 (M+1). Anal. calc. for $C_{11}H_{14}N_2O$: C, 69.44, H, 7.36, N, 14.73; found: C, 69.27, H, 7.51, N,14.44.

3-(N-benzylamino)-2,1-benzisoxazole (3c): White powder. Yield: 73%. m.p. 167-169°C. ^{1}H-NMR ($CDCl_3$): 7.82(d, 1H, J= 7.8 Hz), 7.45(t, 1H, J= 7.2 Hz), 7.30(bs, 5H, Ph), 7.23-7.07(m, 3H), 5.00(s, 2H, CH_2N). M.S.: ESI-Q1MS: 223.2 (M-1), ESI +Q1MS: 225.2 (M+1). Anal. calc. for $C_{14}H_{12}N_2O$: C, 74.92, H, 5.35, N, 12.49; found: C, 74.48, H, 5.41, N, 12.80.

The water layer (after collection of antranils) was evaporated to dryness and the residue extracted with methanol or ethanol (in order to extract phosphoric acid). After evaporation of solvent, the remained oily residue was dissolved in D_2O and the NMR spectra were recorded (^{1}H and ^{31}P). The spectra of these samples revealed a presence of phosphoric acid (H_3PO_4), and traces of anthranils. On ^{31}P-NMR spectra, the following singlets of H_3PO_4 were found: 1.10 ppm (cleavage of **2a**), 1.14 ppm (cleavage of **2b**) and 1.13 ppm (cleavage of **2c**). (Pure H_3PO_4 exhibited the singlet at 0.985 ppm, in D_2O).

The Cleavage of Esters 1b-d; Formation of Derivatives of Benzoxazaphosphorin-3,1,2 P^V (4b-d):

The ester **1b-d** (5 mmol) was dissolved in a mixture of methanol (50 mL) and water (50 mL), containing sodium hydroxide (1.6g). The solution was refluxed for 2 hrs, cooled and evaporated to a small volume (30 mL). The mixture was extracted twice with diethyl ether (50mL), in order to remove N-methylated anthranils **5b-d**. The remaining water layer was neutralized with 6 M HCl (8 mL). It caused a precipitation of an oily product, which was extracted with chloroform (100 mL). The extract was dried with a mixture of anhydrous sodium sulfate (5 g) and potassium carbonate (1g). After several hours a white precipitate occurred in the chloroform extract. The formed product (**4b-d**) was collected (together with a drying agent) by filtration, and separated from inorganic salts by reextraction to methanol (100 mL). After evaporation of solvent, crude products **4b-d** were obtained, which were purified by recrystallization from a mixture of toluene, acetone and hexane. Evaporation of remaining chloroform solution to dryness afforded additional amounts of the products **4b-d**, which were mixed with some unreacted anthranils and phosphoric ethyl monoester.

1-Oxo-2-ethoxy-4-(N-butylamino)-benzoxazaphosphorin-3,1,2 P^V-one-2 (4b): White powder. Yield: 56%. m.p. 113-115°C. ^{1}H-NMR (DMSO): 7.92(d, 1H), 7.61(d, 1H), 7.29(m, 2H), 4.61(t, 2H, CH_2N, J= 7.5 Hz), 3.90(m, 2H, OCH_2), 1.77(m, 2H), 1.37(m, 2H), 1.16(t, 3H, CH_3, J=7.0 Hz), 0.86(t, 3H, CH_3, J=7.5 Hz). ^{13}C-NMR: 13.86[s, CH_3 ,(Bu)], 16.48[d, CH_2, (Bu), $^6J_{PC}$=6.8 Hz], 19.70[s, CH_3, (Et)], 30.45[s, CH_2 (Bu)], 45.61(s, CH_2NH), 61.71(d, CH_2O, $^2J_{POC}$=6.04 Hz), 109.58(s, C_{10}), 112.43(s, C_9), 113.08(s, C_6), 121.57(s, C_7), 125.95(s, C_5), 126.65(s, C_8), 128.49(d, C_4, $^2J_{POC}$= 8.31 Hz). ^{31}P-NMR: +0.866(s) ppm. M.S.: ESI-Q1MS: 297.4 (M-1), ESI+Q1MS: 299.2 (M+1). Anal. calc. for $C_{13}H_{19}N_2O_4P$: C, 52.34, H, 6.42, N, 9.39; P, 10.38; found: C, 51.78, H, 6.53, N, 9.68; P, 10.30.

1-Oxo-2-ethoxy-4-(N-benzylamino)-benzoxazaphosphorin-3,1,2 P^V-one-2 (4c): White powder. Yield: 68%. m.p. 84-88°C. ^{1}H-NMR (DMSO): 7.94(m, 1H), 7.62(m, 1H), 7.30(m, 7H, arom.), 5.90(s, 2H, CH_2N), 3.74(m, 2H, OCH_2), 0.98(t, 3H, CH_3). ^{13}C-NMR: 16.24[d, CH_3 (Et), $^3J_{POCC}$= 6.8 Hz], 48.47(s, $PhCH_2N$), 61.70(d, CH_2O, $^2J_{POC}$= 4.53 Hz), 109.44(s, C_{10}), 112.28(s, C_9), 113.32(s, C_6), 121.62(s, C_7), 126.27(s, C_5), 126.79(s,

C_8), 127.97(s, C_m , Ph), 128.02(s, C_p, Ph), 128.28(d, C_4, $^2J_{POC}$= 7.50 Hz), 128.75(s, C_o, Ph), 135.65(s, Ph). ^{31}P-NMR: -3.77(s) ppm. M.S.: ESI -Q1MS: 331.3 (M-1), ESI+Q1MS: 333.2 (M+1). Anal. calc. for $C_{16}H_{17}N_2O_4P$ H_2O: C, 54.86, H, 5.46, N, 7.99; P, 8.84; found: C, 54.46, H, 5.78, N, 7.66; P, 9.05.

1-Oxo-2-ethoxy-4-(N-*p*-tolylamino)-benzoxazaphosphorin-3,1,2 P^v-one-2 (4d): White powder. Yield: 51%. m.p. dec.>200°C. ^{1}H-NMR (DMSO): 8.20(m, 1H, 7.36-6.94(m, 7H, arom.), 3.32(m, 3H, OCH_2, NH), 2.31(s, 3H, Ar-CH_3), 076(t, 3H, CH_3). ^{13}C-NMR: 17.32[d, CH_3 (Et), $^3J_{POCC}$=6.8 Hz], 21.79(s, Ph-CH_3), 59.66[d, OCH_2, $^2J_{POC}$=6.04 Hz], 112.95(s, C_6), 120.75(s, C_{10}), 121.71(s, C_9), 123.73(s, C_7), 125.20(s, C_5), 126.91(s, C_8), 127.93(d, C_4, $^2J_{POC}$=6.80 Hz), 129.34(s, C_m, Ph), 129.71(s, C_o, Ph), 132.53(s, C_p , Ph), 139.85(s, C_p , Ph). ^{31}P-NMR: -4.50(s) ppm. M.S.: ESI-Q1MS: 331.3 (M-1). Anal. calc. for $C_{16}H_{17}N_2O_4P$ H_2O: C, 54.86, H, 5.46, N, 7.99; P, 8.84; found: C, 54.80, H, 5.26, N, 7.52, P, 9.24.

The water layer (after removing of the products **4**) contained some residues, which were analyzed by means of NMR spectroscopy. After work-up (likewise, as it was described for preparation of anthranil derivatives), the ^{1}H and ^{31}P-NMR spectra of the residue were recorded, in D_2O solution. The ^{1}H-NMR spectra showed an existence of the monoethyl ester of phosphoric acid, and traces of the cyclic products **4b,c,d**. The ^{31}P-NMR spectra revealed a presence of the monoester of H_3PO_4 (the corresponding singlets at 5.15, 3.88 and 5.17 ppm were recorded) and some phosphoric acid (singlets at 1.45, 0.93 and 0.97 ppm, respectively).

Hydrolysis of the products 4b-d by means of aqueous HCl:

The benzoxazaphosphorin **4b-d** (2 mmol) and 6 M aqueous HCl (10 mL) was refluxed for 4 hrs and then evaporated to dryness. The residue was neutralized with aqueous $NaHCO_3$ to pH = 7, and extracted with chloroform (50 mL). After evaporation of solvent, the anthranils (**3b-d**) were obtained (data for **3b,c** are given above). The *p*-tolyl derivative of anthranil (**3d**) was unstable, and it partially decomposed to *p*-toluidine and other indefinite products, during recrystallization from a mixture of benzene and hexane.

3-(N-*p*-tolylamino)-2,1-benzisoxazole (3d): Brown solid. Yield: 54% (crude product) m.p. dec.>130°C. ^{1}H-NMR ($CDCl_3$): 7.65-7.08(m, 8H, arom.), 2.39(s, 3H, Ar-CH_3). M.S.: ESI-Q1MS: 223.2 (M-1), ESI+Q1MS: 225.1 (M+1). Anal. calc. for $C_{14}H_{12}N_2O$: C, 74.92, H, 5.35, N, 12.49; found: C, 74.12, H, 5.85, N, 12.09.

Isolation of the Products 5b-d :

The N-methylated anthranils **5b-d** were extracted with diethyl ether (50 mL) from a basic reaction mixture of cleaved esters, prior to neutralization with hydrochloric acid. The extract was dried (anhydrous K_2CO_3), filtered and evaporated to give the products as yellow oils (**5b,c**), or yellow solid (**5d**).

3-(N-Methyl-N-butylamino)-2,1-benzisoxazole (5b): Oil. Yield: 11%. ^{1}H-NMR ($CDCl_3$): 7.58(d, 1H, J=6.7 Hz), 7.43(d, 1H, J=8.8 Hz), 7.11(t, 1H, J=6.6 Hz), 6.81(t, 1H, J=6.6 Hz), 4.21(s, 3H, N-CH_3), 4.15(t, 2H, N-CH_2, J=3.4 Hz), 1.81(m, 2H), 1.26(m, 2H), 0.86(t, 3H, CH_3, J=7.2 Hz). M.S. (70 eV): 204 (M, 31.8%),

189(M-CH_3, 0.6%), 173(M-OCH_3, 47.7%), 161(100%), 147(M-Bu, 54.5%), 133(M-N-Bu, 15.9%), 119[M-N(Me)Bu, 18.2%]. Anal. calc. for $C_{12}H_{16}N_2O$: C, 70.56, H, 7.90, N, 13.71; found: C, 70.39, H, 7.99, N, 13.40.

3-(N-Methyl-N-benzylamino)-2,1-benzisoxazole (5c): Oil. Yield: 20%. ^{1}H-NMR ($CDCl_3$): 7.66-6.94(m, 9H, arom.), 5.43(s, 2H, NCH_2Ph), 4.25(s, 3H, N-CH_3). M.S.: (70 eV): 238(M, 51.9%), 223(M-CH_3, 7.4%), 205(0.8%), 161, 147, 119[M-N(Me)-benzyl, 11%], 104, 91(100%). Anal. calc. for $C_{15}H_{14}N_2O$: C, 75.60, H, 5.92, N, 11,76; found: C, 75.12, H, 6.80, N, 11.60.

3-(N-Methyl-N-*p*-tolylamino)-2,1-benzisoxazole (5d): Solid. Yield: 19%. m.p. 62.4-63.8°C. ^{1}H-NMR ($CDCl_3$): 7.63-6.82(m, 8H, arom.), 4.17(s, 3H, N-CH_3), 2.33(s, 3H, Ar-CH_3). M.S. (70 eV): 238(M, 100%), 223(M-CH_3, 93.5%), 165(48.5%), 152(57.4%), 119[M-N(Me)-tolyl, 22.4%], 104(19.1%), 91(51%). M.S. ESI +Q1MS: 239.2 (M+1).Anal. calc. for $C_{15}H_{14}N_2O$: C, 75.60, H, 5.92, N, 11.76; found: C, 75.56, H, 5.80, N, 11.50.

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