SYNTHESIS OF PHOSPHONO- AND PHOSPHINO-SUBSTITUTED SIX-MEMBERED HETEROCYCLES

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Abstract - 3,6-Dihalopyridazines react with the sodium salts of cyanomethylphosphonic acid dialkyl esters or phenylphosphinic acid ethyl ester to yield phosphono- and phosphino-substituted pyridazines. The constitution of one reaction product is proved by an X-ray crystal structure analysis.

Many pyridazines exhibit biological activity and some are used as drugs.[1,2] That's the reason why the research in new derivatives has been stimulated during the last four decades. The syntheses of phosphono- and phosphino-substituted pyridazines should be of great interest, because organophosphorus compounds often possess antibiotic, antineoplastic, antibacterial or antiviral attributes.[3]

Fosfomycine[4] has e. g. a broad sphere of activity, phosphinothricine[5] from streptomyces *viridochromogenes* has antibacterial and excellent herbicidal activities by inhibition of the enzyme glutaminic acid synthetase: the trisodium salt of phosphonoformic acid[3] could be important as an

inhibitor of transcriptase of "retrovires" in the AIDS-therapy.

Aminophosphonic acids are also of biological interest.[3,6] The replacement of amino acids in peptides by phosphono-analogues — aminoalkylphosphonic acids, 2-aminoethylphosphonic acid and substituted derivatives — is an important aspect of peptides research. In pantothenic acid there is a peptide linkage between (2*R*)-2,4-dihydroxy-3,3-dimethylbutyric acid and the amino group of ß-alanine and in pantetheine there is a second peptide linkage between the ß-alanine and cysteamine. The syntheses of phosphono- and phosphino-analogues of pantothenic acid ethyl ester, where the ß-alanine is replaced by the 2-aminoethylphosphonic acid diethyl ester and the 2-aminoethylmethylphosphonic acid ethyl ester, respectively, and the syntheses of the phosphono-analogue of pantetheine, where the ß-alanine is replaced by 2-aminoethylphosphonic acid, are in youngest past described by us.[9,10,13]

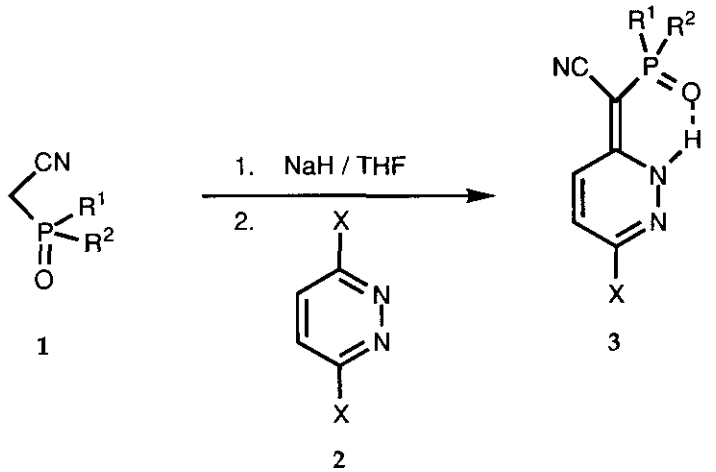
Furthermore the syntheses of phosphono- and phosphino-substituted heterocycles, alkyloximino-phosphonates, diastereomeric 1,3,2-oxazaphospholidines and diastereomeric 1,3,2-dioxa-phosphorinanes, are also known by our scientific work.[6-18]

T. Kealy[19] reported the reaction of 3,6-dichloropyridazine (**2a**) with the sodium salt of malononitrile to give 2-(6-chloro-2*H*-pyridazin-3-ylidene)malononitrile. We studied the reactions of 3,6-dihalopyridazines (**2**) with the sodium salts of cyanomethylphosphonic acid esters (**1.1-3**) and phenylphosphinic acid ethyl ester (**1.4**) as well as the constitution of the products (**3**).

3,6-Dichloropyridazine (**2a**) was caused to react with hydriodic acid to yield the 3,6-diiodo-pyridazine (**2c**).[20] 3,6-Dibromopyridazine (**2b**) was available by the reaction of 1,2-dihydro-pyridazine-3,6-dione with phosphorus pentabromide.[21]

The cyanomethylphosphonic acid dialkyl esters (**1.1-3**) and cyanomethylphenylphosphinic acid ethyl ester (**1.4**) were obtained in good yields from the corresponding trialkyl phosphite or dialkylphenyl phosphonite by treatment with chloroacetonitril (4 h reflux).[22]

The sodium salts of the activated methylene compounds (**1.1-4**) were prepared by reaction with sodium hydride (THF, reflux temperature) and were treated with the pyridazines (**2**) (Scheme 1).



Compound	X	R^1	R^2
3.1a	Cl	OMe	OMe
3.2a	Cl	OEt	OEt
3.2b	Br	OEt	OEt
3.2c	I	OEt	OEt
3.3a	Cl	O^{i}Pr	O^{i}Pr
3.3b	Br	O^{i}Pr	O^{i}Pr
3.4a	Cl	OEt	Ph

Scheme 1: Synthesis of pyridazines **3**

Only one isomer of the respective (6-halo-2*H*-pyridazin-3-ylidene)cyanomethylphosphonic acid dialkyl esters (**3**) and the phenylphosphinic acid ethyl ester (**3.4a**) were isolated. The phosphono- and phosphino-substituted compounds (**1**) were used in the fourfold molar excess based on the corresponding pyridazines (**2**), otherwise the yields of the resulting products (**3**) decrease drastically.

To confirm the proposed structure of **3** and to obtain further structural information an X-ray crystal structure analysis of **3.1a** was performed.

By recrystallization from diethyl ether yellow triclinic crystals of **3.1a** with the space group $P\bar{1}$ (# 2 Int. Tables) were obtained: $C_8H_9N_3O_3ClP$, mol. weight = 261.61 g mol^{-1}. The unit cell parameters were: a = 5.810 (1) Å, b = 9.923 (3) Å, c = 11.055 (3) Å, α = 106.71 (2) °, β = 102.19 (2) °, γ = 104.35 (2) °, V = 563.2 (7) $Å^3$, Z = 2, μ = 4.716 cm^{-1} (Mo Kα), F_{000} = 268 e. Intensity data were collected using a graphite-monochromated Mo-Kα (λ = 0.7107 Å) radiation (Enraf-Nonius CAD 4) and applying ω-2Θ-scan technique. Up to sin Θ/λ = 0.62 $Å^{-1}$ 2202 symmetry independent reflections were measured out of which 1433 reflections with $I \geq 3.0\ \sigma(I)$ were graded as observed. The structure was solved by the conventional direct method (SIR) and refined by full matrix least squares technique using anisotropic temperature factors for the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms (R = 0.037, R_w = 0.043).

(The atomic coordinates and equivalent isotropic thermal parameters of non-hydrogen atoms are given in Table 1; the bond distances are summarized in Table 2 and the bond angles are listed in Table 3).

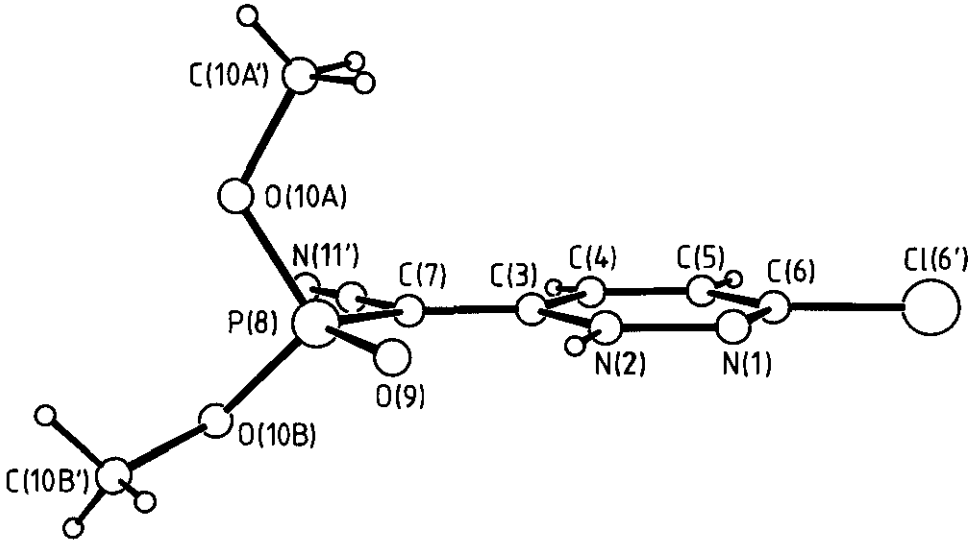


Figure 1: Perspective view and atom labelling of the crystal structure of **3.1a**

In the crystalline form of compound (**3.1a**) (Figure 1) the *Z*-configuration is established. The molecule is nearly planar with the exception of the methoxy groups of the phosphono-substituent. The distance between N2 ··· O9 is 2.737 (3) Å and shows a typical value for NH ··· O hydrogen bonds.[23] The bond lengths N1-N2, N2-C3, C3-C4 and C4=C5 of the pyridazine ring system are in accordance with those of 6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid amide.[24] The C5-C6 distance (1.420 (3) Å) corresponds to that of a Csp^2-Csp^2 bond in comparison with the pyrazole C_3-C_4 distance (1.410 Å).[25] The N1=C6 bond (1.278 (3) Å) shows the typical value for a Csp^2=N bond (1.279 Å)[25] and the exocyclic C3=C7 distance (1.404 (4) Å) is somewhat longer than comparable values described in the literature.[25]

In the case of **3.2a** the configuration at the exocyclic double bond was examined by selective heteronuclear nOe experiments, which were also useful for the assignment of the ^{13}C nmr signals. The irradiation of the NH-proton (13.36 ppm) resulted only in the enhancement of the C7-doublet (52.7 ppm) and the C3-doublet (155.8 ppm). Irradiation of the H4-proton (7.56 ppm) produced an nOe at the C7-doublet (52.7 ppm), the CN-doublet (117.5 ppm) and the C3-doublet (155.8 ppm), indicating the syn-configuration of the H4-proton and the nitrile group.

In summary phosphono- and phosphino-substituted six-membered heterocycles (**3**) were prepared by a simple one-pot reaction and were isolated exclusively in the *Z*-configuration.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer ir-spectrophotometer 283 or 1600 (FTir) using potassium bromide and are given as cm^{-1}. ^1H- and ^{13}C-Nmr spectra were recorded on either a Bruker WM-250 (^1H-Nmr: 250.13 MHz, ^{13}C-Nmr: 62.89 MHz) or a Varian XL 300 (^1H-Nmr:

299.95 MHz, ^{13}C-Nmr: 75.43 MHz) spectrometer in $CDCl_3$. The chemical shifts are reported in parts per million (ppm) downfield from internal tetramethylsilane; coupling constants J are given in Hz. ^{31}P-Nmr spectra were measured with the Varian XL 300 (^{31}P-Nmr: 121.42 MHz) spectrometer using H_3PO_4 as external standard. Ultraviolet spectra were recorded with a Perkin-Elmer 320 uv-spectrophotometer in acetonitrile and are given as λ_{max} (lg ϵ). Elementary analyses were performed on a Heraeus Vario EL CHNS apparatus. P-, Cl-, Br-, and I-analyses were conducted by the Department of Chemistry of the University of Heidelberg.

General procedure for the preparation of pyridazines (**3**)

Either cyanomethylphosphonic acid dialkyl ester (**1.1-3**) or cyanomethylphenylphosphinic acid ethyl ester (**1.4**) (26.8 - 376 mmol) was slowly added at room temperature to a stirred suspension of sodium hydride (26.8 - 376 mmol, washed with pentane) in anhydrous tetrahydrofuran (60 - 400 ml) under argon. Vigorous evolution of hydrogen was observed. After the addition was completed, the suspension was refluxed until all sodium hydride reacted (45 min). A solution of 3,6-disubstituted pyridazine (**2a-c**) (6.71 - 94.0 mmol) in anhydrous tetrahydrofuran (10 - 100 ml) was added and the resulting brown suspension was refluxed for 13 - 30 h. Tetrahydrofuran was removed and the residue was solved in water (50 - 300 ml). The brown aqueous solution was acidified with 10 % HCl (pH 5 - 6) and extracted with four portions (200 - 400 ml) of dichloro methane. The combined organic layers were dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated and the resulting brown oil was chromatographed on silica gel (hexane / ethyl acetate (3:2 - 3:1) as eluant). The semisolid yellow product (**3.1a - 3.4a**) was recrystallized (hexane or hexane / ethyl acetate (9:1 - 4:3)).

(6-Chloro-2*H*-pyridazin-3-ylidene)cyanomethylphosphonic acid dimethyl ester (**3.1a**)

Cyanomethylphosphonic acid dimethyl ester (**1.1**) (4.00 g, 26.8 mmol) was treated in tetrahydrofuran (60 ml) with sodium hydride (0.64 g, 27 mmol). A solution of 3,6-dichloropyridazine (**2a**) (1.00 g, 6.71 mmol) in tetrahydrofuran (10 ml) was added and the suspension was refluxed for 22 h. The crude product was purified by chromatography (silica gel, hexane / ethyl acetate (2:1)).

0.39 g (22 %) **3.1a**, yellow crystals, mp 130 °C (hexane / ethyl acetate (4:3)). ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 3.82 (d, $^3J_{PH}$ = 11.7 Hz, 6H, OCH_3), 7.11 (dd, $^3J_{HH}$ = 9.7 Hz, $^5J_{PH}$ = 2.5 Hz, 1H, H-5), 7.57 (ddd, $^3J_{HH}$ = 9.7 Hz, $^4J_{HH}$ = 2.5 Hz, $^4J_{PH}$ = 0.9 Hz, 1H, H-4), 13.32 (br, 1H, NH). ^{13}C-Nmr (75.43 MHz, $CDCl_3$, {1H}) δ = 51.1 (d, $^1J_{PC}$ = 210 Hz, C-7), 53.4 (d, $^2J_{PC}$ = 6 Hz, OCH_3), 117.2 (d, $^2J_{PC}$ = 7 Hz, CN), 130.9 (s, C-5), 131.3 (d, $^3J_{PC}$ = 14 Hz, C-4), 142.8 (s, C-6), 156.1 (d, $^2J_{PC}$ = 9 Hz, C-3). ^{31}P-Nmr (121.42 MHz, $CDCl_3$) δ = 23.4 (s). Ir (KBr, tablet) ν = 3400 (broad, w), 3070 (m), 2950 (m), 2180 (m), 1720 (w), 1620 (m), 1560 (s), 1500 (m), 1455 (w), 1400 (s), 1330 (m), 1240 (w), 1190 (m), 1175 (m), 1155 (m), 1140 (m), 1085 (m), 1020 (s), 955 (m), 840 (m), 785 (s), 730 (m), 630 (m), 595 (m), 575 (m), 550 (m), 520 (m). Uv (MeCN) λ_{max} (lg ε) = 232 (3.84), 298 (4.34), 389 (3.35). *Anal.* Calcd for $C_8H_9N_3O_3ClP$: C, 36.73; H, 3.47; N, 16.06; Cl, 13.55; P, 11.84. Found: C, 36.99; H, 3.41; N, 15.97; Cl, 13.58; P, 11.90.

Table 1: Atomic Coordinates and Equivalent Isotropic *Thermal Parameters of Non-Hydrogen-Atoms of* **3.1a**

Atom	x	y	z	$U_{eq} \cdot \frac{10^4}{Å^2}$
N(1)	0.4851(4)	0.1621(2)	0.8594(2)	441(6)
N(2)	0.3440(4)	0.2445(2)	0.8296(2)	428(6)
C(3)	0.1162(4)	0.1933(3)	0.7388(2)	364(7)
C(4)	0.0196(5)	0.0351(3)	0.6722(3)	436(8)
C(5)	0.1526(5)	-0.0500(3)	0.6991(3)	488(8)
C(6)	0.3913(5)	0.0216(3)	0.7955(3)	441(7)
C(7)	-0.0118(5)	0.2901(3)	0.7139(3)	389(7)
P(8)	0.1139(1)	0.48456(8)	0.78622(7)	418(2)
O(9)	0.3516(3)	0.5335(2)	0.8918(2)	458(5)
O(10A)	0.1348(3)	0.5482(2)	0.6728(2)	527(6)
O(10B)	-0.1054(3)	0.5308(2)	0.8285(2)	615(6)
C(10A')	0.3156(6)	0.5227(4)	0.6067(3)	660(9)
C(10B')	-0.0667(5)	0.6832(4)	0.9039(4)	700(9)
C(11)	-0.2556(5)	0.2293(3)	0.6209(3)	435(8)
N(11')	-0.4511(4)	0.1875(3)	0.5476(3)	614(8)
Cl(6')	0.5717(2)	-0.08306(8)	0.83617(9)	676(2)

$U_{eq} = \frac{1}{3} \sum \sum U_{ij} \boldsymbol{a}_i \cdot \boldsymbol{a}_j \boldsymbol{a}_i^* \boldsymbol{a}_j^*$

Table 2: Bond Distances (in Å) of **3.1a**

N(1) – N(2)	1.350(4)	C(7) – P(8)	1.750(2)
N(1) – C(6)	1.278(3)	C(7) – C(11)	1.426(3)
N(2) – C(3)	1.353(3)	P(8) – O(9)	1.472(2)
C(3) – C(4)	1.430(3)	P(8) – O(10A)	1.571(2)
C(3) – C(7)	1.404(4)	P(8) – O(10B)	1.572(2)
C(4) – C(5)	1.330(5)	O(10*A*) – C(10*A'*)	1.431(5)
C(5) – C(6)	1.420(3)	O(10*B*) – C(10*B'*)	1.435(4)
C(6) – Cl(6')	1.729(3)	C(11) – N(11')	1.142(3)

In parentheses *e.s.d.'s* in units of the least significant digits.

Table 3: Bond Angles (in °) of **3.1a**

N(2) – N(1) – C(6)	116.1(2)	C(3) – C(7) – C(11)	119.2(2)
N(1) – N(2) – C(3)	126.6(2)	P(8) – C(7) – C(11)	116.9(2)
N(2) – C(3) – C(4)	114.7(3)	C(7) – P(8) – O(9)	111.8(1)
N(2) – C(3) – C(7)	121.7(2)	C(7) – P(8) – O(10*A*)	108.1(1)
C(4) – C(3) – C(7)	123.7(2)	C(7) – P(8) – O(10*B*)	103.3(1)
C(3) – C(4) – C(5)	120.6(2)	O(9) – P(8) – O(10*A*)	113.5(1)
C(4) – C(5) – C(6)	117.7(2)	O(9) – P(8) – O(10*B*)	116.6(1)
N(1) – C(6) – C(5)	124.3(3)	O(10*A*) – P(8) – O(10*B*)	102.5(1)
N(1) – C(6) – Cl(6')	115.7(2)	P(8) – O(10*A*) – C(10*A'*)	118.3(2)
C(5) – C(6) – Cl(6')	119.9(2)	P(8) – O(10*B*) – C(10*B'*)	120.3(2)
C(3) – C(7) – P(8)	123.9(2)	C(7) – C(11) – N(11')	176.7(3)

In parentheses *e.s.d.'s* in units of the least significant digits.

(6-Chloro-2*H*-pyridazin-3-ylidene)cyanomethylphosphonic acid diethyl ester (**3.2a**)

Cyanomethylphosphonic acid diethyl ester (**1.2**) (66.6 g, 376 mmol) was treated in tetrahydrofuran (400 ml) with sodium hydride (9.02 g, 376 mmol). A solution of 3,6-dichloropyridazine (**2a**) (14.0 g, 94.0 mmol) in tetrahydrofuran (100 ml) was added and the suspension was refluxed for 14 h. The crude product was purified by chromatography (silica gel, hexane / ethyl acetate (3:2)). 18.5 g (68 %) **3.2a**, yellow crystals, mp 61 °C (hexane / ethyl acetate (9:1)). ^{1}H-Nmr (250.13 MHz, $CDCl_3$) δ = 1.39 (dt, $^{3}J_{HH}$ = 7.1 Hz, $^{4}J_{PH}$ = 0.8 Hz, 6H, $OCH_2C\underline{H}_3$), 4.09 - 4.23 (m, 4H, $OC\underline{H}_2CH_3$), 7.10 (dd, $^{3}J_{HH}$ = 9.7 Hz, $^{5}J_{PH}$ = 2.5 Hz, 1H, H-5), 7.56 (dd, $^{3}J_{HH}$ = 9.7 Hz, $^{4}J_{PH}$ = 0.7 Hz, 1H, H-4), 13.36 (br, 1H, NH). ^{13}C-Nmr (62.89 MHz, $CDCl_3$, {1H}) δ = 16.1 (d, $^{3}J_{PC}$ = 7 Hz, $OCH_2\underline{C}H_3$), 52.7 (d, $^{1}J_{PC}$ = 208 Hz, C-7), 63.1(d, $^{2}J_{PC}$ = 6 Hz, $O\underline{C}H_2CH_3$), 117.5 (d, $^{2}J_{PC}$ = 7 Hz, CN), 130.7 (s, C-5), 131.4 (d, $^{3}J_{PC}$ = 14 Hz, C-4), 142.6 (s, C-6), 155.8 (d, $^{2}J_{PC}$ = 9 Hz, C-3). ^{31}P-Nmr (121.42 MHz, $CDCl_3$) δ = 19.6 (s). Ir (KBr, tablet) ν = 3440 (broad, w), 3100 (m), 2990 (m), 2930 (m), 2180 (m), 1655 (w), 1620 (m), 1560 (s), 1500 (m), 1410 (m), 1225 (s), 1170 (m), 1030 (s), 965 (s), 835 (m), 805 (m), 760 (m), 730 (w), 630 (w), 585 (m), 560 (w), 545 (w), 520 (w). Uv (MeCN) λ_{max} (lg ε) = 236 (3.82), 300 (4.33), 398 (3.32). *Anal. Calcd for* $C_{10}H_{13}N_3O_3ClP$: C, 41.47; H, 4.52; N, 14.51; Cl, 12.24; P, 10.69. Found: C, 41.68; H, 4.51; N, 14.33; Cl, 12.04; P, 10.90.

(6-Bromo-2*H*-pyridazin-3-ylidene)cyanomethylphosphonic acid diethyl ester (**3.2b**)

Cyanomethylphosphonic acid diethyl ester (**1.2**) (11.9 g, 67.2 mmol) was treated in tetrahydrofuran (80 ml) with sodium hydride (1.61 g, 67.2 mmol). A solution of 3,6-dibromopyridazine (**2b**) (4.00 g, 16.8 mmol) in tetrahydrofuran (20 ml) was added and the suspension was refluxed for 13 h. The crude product was purified by chromatography (silica gel, hexane / ethyl acetate (2:1)). 2.74 g (49 %) **3.2b**, yellow crystals, mp 71 °C (hexane). ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.39 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, $OCH_2C\underline{H}_3$), 4.05 - 4.26 (m, 4H, $OC\underline{H}_2CH_3$), 7.17 (dd, $^{3}J_{HH}$ = 9.8 Hz, $^{5}J_{PH}$ = 2.2 Hz, 1H, H-5), 7.44 (d, $^{3}J_{HH}$ = 9.8 Hz, 1H, H-4), 13.43 (br, 1H, NH). ^{13}C-Nmr (75.43 MHz, $CDCl_3$, {1H}) δ = 16.1 (d, $^{3}J_{PC}$ = 7 Hz, $OCH_2\underline{C}H_3$), 52.7 (d, $^{1}J_{PC}$ = 208 Hz, C-7), 63.1(d, $^{2}J_{PC}$ = 6 Hz, $O\underline{C}H_2CH_3$), 117.3 (d, $^{2}J_{PC}$ = 8 Hz, CN), 130.6 (d, $^{3}J_{PC}$ = 14 Hz, C-4), 131.6 (s, C-6), 133.2 (s, C-5), 155.6 (d, $^{2}J_{PC}$ = 9 Hz, C-3). ^{31}P-Nmr (121.42 MHz, $CDCl_3$) δ = 19.5 (s). Ir (KBr, tablet) ν = 3480 (broad, w),

3100 (m), 3060 (m), 2990 (w), 2910 (w), 2180 (m), 1615 (m), 1545 (s), 1495 (m), 1405 (m), 1385 (m), 1325 (w), 1220 (m), 1200 (m), 1160 (m), 1145 (w), 1130 (m), 1045 (s), 1015 (s), 960 (s), 820 (m), 800 (m), 760 (m), 715 (m), 705 (m), 620 (m), 600 (m), 585 (m), 560 (m), 505 (w). Uv (MeCN) λ_{max} (lg ε) = 239 (3.81), 299 (4.34), 388 (3.32). *Anal.* Calcd for $C_{10}H_{13}N_3O_3BrP$: C, 35.95; H, 3.92; N, 12.58; Br, 23.92; P, 9.27. Found: C, 36.20; H, 4.01; N, 12.64; Br, 24.12; P, 9.14.

Cyano-(6-iodo-2*H*-pyridazin-3-ylidene)methylphosphonic acid diethyl ester (**3.2c**)

Cyanomethylphosphonic acid diethyl ester (**1.2**) (6.40 g, 36.1 mmol) was treated in tetrahydrofuran (80 ml) with sodium hydride (0.87 g, 36 mmol). A solution of 3,6-diiodopyridazine (**2c**) (3.00 g, 9.04 mmol) in tetrahydrofuran (20 ml) was added and the suspension was refluxed for 30 h. The crude product was purified by chromatography (silica gel, hexane / ethyl acetate (3:1)). 1.90 g (55 %) **3.2c**, yellow crystals, mp 98 °C (hexane). ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.38, 1.39 (2 • t, $^3J_{HH}$ = 7.0 Hz, 6H, $OCH_2C\underline{H}_3$), 4.09 - 4.20 (m, 4H, $OC\underline{H}_2CH_3$), 7.22 - 7.31 (m, 2H, H-4, H-5), 13.49 (br, 1H, NH). ^{13}C-Nmr (75.43 MHz, $CDCl_3$, {1H}) δ = 16.1 (d, $^3J_{PC}$ = 5 Hz, $OCH_2\underline{C}H_3$), 52.5 (d, $^1J_{PC}$ = 208 Hz, C-7), 63.1(d, $^2J_{PC}$ = 5 Hz, $O\underline{C}H_2CH_3$), 104.0 (s, C-6), 117.2 (d, $^2J_{PC}$ = 7 Hz, CN), 129.4 (d, $^3J_{PC}$ = 14 Hz, C-4), 137.9 (s, C-5), 155.5 (d, $^2J_{PC}$ = 9 Hz, C-3). ^{31}P-Nmr (121.42 MHz, $CDCl_3$) δ = 19.5 (s). Ir (KBr, tablet) ν = 3470 (broad, w), 2990 (w), 2910 (w), 2180 (m), 1615 (s), 1555 (s), 1540 (m), 1490 (w), 1405 (m), 1385 (m), 1320 (w), 1220 (m), 1195 (w), 1165 (m), 1120 (m), 1040 (m), 1020 (s), 960 (m), 860 (w), 825 (m), 795 (w), 760 (m), 710 (w), 630 (m), 580 (m), 560 (m), 550 (w), 505 (w). Uv (MeCN) λ_{max} (lg ε) = 241 (3.67), 304 (4.42), 387 (3.39). *Anal.* Calcd for $C_{10}H_{13}N_3O_3IP$: C, 31.52; H, 3.44; N, 11.03; I, 33.30; P, 8.13. Found: C, 31.76; H, 3.54; N, 10.93; I, 33.18; P, 8.20.

(6-Chloro-2*H*-pyridazin-3-ylidene)cyanomethylphosphonic acid diisopropyl ester (**3.3a**)

Cyanomethylphosphonic acid diisopropyl ester (**1.3**) (13.8 g, 67.3 mmol) was treated in tetrahydrofuran (80 ml) with sodium hydride (1.62 g, 67.3 mmol). A solution of 3,6-dichloropyridazine (**2a**) (2.50 g, 16.8 mmol) in tetrahydrofuran (20 ml) was added and the suspension was refluxed for 18 h. The crude product was purified by chromatography (silica gel, hexane /

ethyl acetate (3:1)). 2.07 g (39 %) **3.3a**, yellow crystals, mp 56 °C (hexane). ^{1}H-Nmr (250.13 MHz, $CDCl_3$) δ = 1.38, 1.39 (2 • d, $^3J_{HH}$ = 6.2 Hz, 12H, OCH(C<u>H</u>$_3$)$_2$), 4.65 (dseptet, $^3J_{HH}$ = 6.2 Hz, $^3J_{PH}$ = 8.1 Hz, 2H, OC<u>H</u>(CH$_3$)$_2$), 7.03 (dd, $^3J_{HH}$ = 9.7 Hz, $^5J_{PH}$ = 2.4 Hz, 1H, H-5), 7.52 (dd, $^3J_{HH}$ = 9.7 Hz, $^4J_{PH}$ = 1.9 Hz, 1H, H-4), 13.42 (br, 1H, NH). ^{13}C-Nmr (62.89 MHz, $CDCl_3$, {1H}) δ = 23.7, 23.8 (2 • d, $^3J_{PC}$ = 5 Hz, OCH(<u>C</u>H$_3$)$_2$), 54.6 (d, $^1J_{PC}$ = 208 Hz, C-7), 72.2 (d, $^2J_{PC}$ = 6 Hz, O<u>C</u>H(CH$_3$)$_2$), 117.6 (d, $^2J_{PC}$ = 7 Hz, CN), 130.5 (s, C-5), 131.5 (d, $^3J_{PC}$ = 14 Hz, C-4), 142.2 (s, C-6), 155.3 (d, $^2J_{PC}$ = 9 Hz, C-3). ^{31}P-Nmr (121.42 MHz, $CDCl_3$) δ = 17.4 (s). Ir (KBr, tablet) ν = 3430 (broad, w), 3090 (w), 2980 (m), 2930 (w), 2190 (m), 2180 (m), 1735 (w), 1700 (w), 1685 (w), 1655 (w), 1625 (m), 1560 (s), 1505 (w), 1470 (w), 1410 (m), 1395 (m), 1375 (m), 1330 (w), 1235 (w), 1190 (m), 1160 (m), 1140 (m), 1105 (w), 1085 (w), 985 (s), 950 (m), 885 (w), 830 (w), 775 (m), 755 (w), 735 (w), 630 (w), 595 (w), 570 (m), 555 (w), 520 (w). Uv (MeCN) λ_{max} (lg ε) = 233 (3.85), 298 (4.31), 392 (3.32). *Anal.* Calcd for $C_{12}H_{17}N_3O_3ClP$: C, 45.37; H, 5.39; N, 13.23; Cl, 11.16; P, 9.75. Found: C, 45.55; H, 5.28; N, 13.25; Cl, 11.32; P, 9.92.

<u>(6-Bromo-2*H*-pyridazin-3-ylidene)cyanomethylphosphonic acid diisopropyl ester (**3.3b**)</u>

Cyanomethylphosphonic acid diisopropyl ester (**1.3**) (10.3 g, 50.4 mmol) was treated in tetrahydrofuran (80 ml) with sodium hydride (1.21 g, 50.4 mmol). A solution of 3,6-dibromo-pyridazine (**2b**) (3.00 g, 12.6 mmol) in tetrahydrofuran (20 ml) was added and the suspension was refluxed for 21 h. The crude product was purified by chromatography (silica gel, hexane / ethyl acetate (3:1)). 2.18 g (48 %) **3.3b**, yellow crystals, mp 57 °C (hexane). ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.38, 1.39 (2 • d, $^3J_{HH}$ = 6.2 Hz, 12H, OCH(C<u>H</u>$_3$)$_2$), 4.64 (dseptet, $^3J_{HH}$ = 6.2 Hz, $^3J_{PH}$ = 8.1 Hz, 2H, OC<u>H</u>(CH$_3$)$_2$), 7.13 (dd, $^3J_{HH}$ = 9.7 Hz, $^5J_{PH}$ = 2.5 Hz, 1H, H-5), 7.42 (ddd, $^3J_{HH}$ = 9.7 Hz, $^4J_{HH}$ = 2.5 Hz, $^4J_{PH}$ = 0.9 Hz, 1H, H-4), 13.62 (br, 1H, NH). ^{13}C-Nmr (75.43 MHz, $CDCl_3$, {1H}) δ = 23.8, 23.9 (2 • d, $^3J_{PC}$ = 5 Hz, OCH(<u>C</u>H$_3$)$_2$), 54.5 (d, $^1J_{PC}$ = 208 Hz, C-7), 72.2 (d, $^2J_{PC}$ = 6 Hz, O<u>C</u>H(CH$_3$)$_2$), 117.6 (d, $^2J_{PC}$ = 7 Hz, CN), 130.7 (d, $^3J_{PC}$ = 14 Hz, C-4), 131.3 (s, C-6), 133.0 (s, C-5), 155.2 (d, $^2J_{PC}$ = 9 Hz, C-3). ^{31}P-Nmr (121.42 MHz, $CDCl_3$) δ = 17.3 (s). Ir (KBr, tablet) ν = 3460 (broad, w), 3080 (w), 2990 (m), 2940 (w), 2190 (m), 2180 (m), 1620 (m), 1565 (m), 1500 (w), 1470 (w), 1410 (m), 1390 (m), 1375 (m), 1335 (w), 1235 (w), 1200 (m), 1180 (m), 1170 (w), 1145 (w), 1135 (m), 1105 (m), 1080 (w), 980 (s), 940 (m), 900 (w), 885 (w), 825 (w), 765 (m),

755 (m), 710 (m), 630 (w), 600 (w), 590 (m), 570 (w), 565 (w), 555 (w), 510 (w), 505 (w). Uv (MeCN) λ_{max} (lg ε) = 240 (3.83), 299 (4.35), 391 (3.32). *Anal.* Calcd for $C_{12}H_{17}N_3O_3BrP$: C, 39.80; H, 4.73; N, 11.60; Br, 22.06; P, 8.55. Found: C, 39.79; H, 4.80; N, 11.65; Br, 22.23; P, 8.49.

(6-Chloro-2*H*-pyridazin-3-ylidene)cyanomethylphenylphosphinic acid ethyl ester (**3.4a**)

Cyanomethylphenylphosphinic acid ethyl ester (**1.4**) (8.42 g, 40.3 mmol) was treated in tetrahydrofuran (80 ml) with sodium hydride (0.97 g, 40 mmol). A solution of 3,6-dichloropyridazine (**2a**) (1.50 g, 10.1 mmol) in tetrahydrofuran (20 ml) was added and the suspension was refluxed for 22 h. The crude product was purified by chromatography (silica gel, hexane / ethyl acetate (2:1)). 1.52 g (47 %) **3.4a**, yellow crystals, mp 106 °C (hexane). ^{1}H-Nmr (299.95 MHz, $CDCl_3$) δ = 1.46 (t, $^3J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.20 - 4.26 (m, 2H, $OC\underline{H}_2CH_3$), 7.00 - 7.93 (m, 7H, H_{ar}, H-4, H-5), 13.87 (br, 1H, NH). ^{13}C-Nmr (75.43 MHz, $CDCl_3$, {1H}) δ = 16.3 (d, $^3J_{PC}$ = 7 Hz, $OCH_2\underline{C}H_3$), 55.7 (d, $^1J_{PC}$ = 150 Hz, C-7), 61.8 (d, $^2J_{PC}$ = 7 Hz, $O\underline{C}H_2CH_3$), 118.0 (d, $^2J_{PC}$ = 10 Hz, CN), 128.4 - 132.5 (m, C-4, C-5, C-1' - C-6'), 142.3 (s, C-6), 155.9 (d, $^2J_{PC}$ = 7 Hz, C-3). ^{31}P-Nmr (121.42 MHz, $CDCl_3$) δ = 34.9 (s). Ir (KBr, tablet) ν = 3480 (broad, w), 3080 (w), 3000 (w), 2190 (m), 1630 (s), 1570 (s), 1510 (m), 1450 (m), 1400 (s), 1335 (m), 1180 (s), 1150 (m), 1125 (m), 1105 (w), 1090 (m), 1040 (s), 1000 (w), 960 (m), 945 (m), 855 (w), 835 (m), 785 (m), 755 (m), 745 (s), 715 (m), 695 (m), 635 (m), 580 (m), 560 (m), 520 (m), 510 (w). Uv (MeCN) λ_{max} (lg ε) = 216 (4.10), 234 (3.96), 304 (4.37), 397 (3.41). *Anal.* Calcd for $C_{14}H_{13}N_3O_2ClP$: C, 52.27; H, 4.07; N, 13.06; Cl, 11.02; P, 9.63. Found: C, 52.19; H, 4.16; N, 13.32; Cl, 11.29; P, 9.36.

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Dedicated on memory of the late Yoshio Ban, Hokkaido University, Sapporo / Japan.

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