# SYNTHESIS OF 3-(4-PYRIDINYL)-, 3-(2-CHLORO-4-PYRIDINYL)- AND 3-(2-AMINO-4-PYRIDINYL)PROPOXYMETHANEPHOSPHONIC ACID

Marcela KRECMEROVA, Antonin HOLY and Milena MASOJIDKOVA

*Institute of Organic Chemistry and Biochemistry,*
*Academy of Sciences of the Czech Republic, 166 10 Prague 6, The Czech Republic*

Received February 14, 1995
Accepted February 24, 1995

Reaction of sodium salt of 4-(3-hydroxypropyl)pyridine (*I*) with diisopropyl *p*-toluenesulfonyloxymethanephosphonate (*II*) afforded diisopropyl ester of the corresponding phosphonomethyl derivative (*III*), together with 4-cyclopropylpyridine (*IV*). The ester *III* was converted into free 3-(4-pyridinyl)propoxymethanephosphonic acid (*V*). The synthesis of 3-(2-amino-4-pyridinyl)propoxymethanephosphonic acid (*XVI*) started from 4-(3-benzoyloxypropyl)pyridine (*VII*) via the *N*-oxide *VIII* which on heating with phosphoryl chloride afforded the 2-chloro derivative *IX*. Compound *IX* was debenzoylated with sodium methoxide to give 2-chloro-4-(3-hydroxypropyl)pyridine (*XI*). Condensation of sodium salt of *XI* with tosylate *II* afforded diisopropyl 3-(2-chloro-4-pyridinyl)propoxymethanephosphonate (*XIII*) and 2-chloro-4-cyclopropylpyridine (*XIV*). Deprotection of the ester groups in *XIII* with bromotrimethylsilane gave 3-(2-chloro-4-pyridinyl)propoxymethanephosphonic acid (*XV*). The chlorine atom in position 2 was replaced by reaction of compound *XV* with aqueous ammonia at 200 °C under catalysis with copper(II) sulfate. This gave 3-(2-amino-4-pyridinyl)propoxymethanephosphonic acid (*XVI*) as the final product.

This study represents a continuation of our previous investigation devoted to the preparation of phosphonomethyl derivatives of acyclic nucleoside analogs. Particularly important in this group of compounds proved to be certain adenine derivatives such as 9-(2-phosphonomethoxyethyl)adenine and (*S*)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine[1,2], exhibiting high in vitro and in vivo antiviral activity[2–6]. Great number of related phosphonomethoxy compounds were prepared, modified in the aliphatic[7–9] as well as the heterocyclic[10,11] part of the molecule, and their structure–activity relationships were studied.

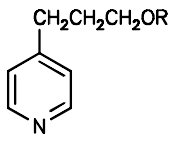
We focused our attention, inter alia, to the preparation of phosphonomethyl derivatives formally derived from acyclic nucleoside analogs in which, however, the nucleobase is replaced by a simple heterocyclic system containing an amino group. Recently, a related paper appeared dealing with the preparation of such derivatives of guanine with an open imidazole ring[12]. Also our preceding paper concerns the synthesis of phosphonomethyl ethers derived from aminophenethyl alcohols[13]. The present communi-

cation describes derivatives containing a phosphonomethoxy- propyl group attached to a pyridine system.

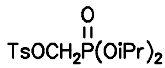
As the starting compound we have chosen 3-(4-pyridinyl)propanol (*I*) which was prepared in high yield by the reaction of 4-picoline with ethylene oxide in the presence of sodium amide[14]. Sodium salt of 3-(4-pyridinyl)propanol reacted with diisopropyl *p*-toluenesulfonyloxymethanephosphonate (*II*, ref.[15]) to give the desired phosphonomethyl derivative in the form of diisopropyl ester *III*. The yield of this product was significantly reduced by formation of 4-cyclopropylpyridine (*IV*) which represented the principal product (the ratio *IV* to *III* was about 3 : 1). Although the ratio of *IV* to *III* could be somewhat improved by modification of the reaction conditions, e.g. by working at lower temperature, the cyclopropyl derivative still remained the main reaction product. Reaction of the diisopropyl ester *III* with bromotrimethylsilane afforded free 3-(4-pyridinyl)propoxymethanephosphonic (*V*).

Our main goal, however, was the synthesis of a phosphonomethyl derivative analogous to compound *V* which would contain an amino group in the position 2 of the pyridine ring. The simplest approach seemed to be the Chichibabin amination of alcohol *I* protected with a suitable alkali-stable group. To this end, we synthesized trityl derivative *VI* by reaction of compound *I* with trityl chloride in pyridine. Whereas various 4-alkylpyridines, such as 4-propylpyridine, undergo the Chichibabin reaction affording the corresponding 2-amino derivatives in high yields[16], in our case heating the trityl derivative *VI* with sodium amide in xylene in the presence of *N*,*N*-dimethylaniline gave 4-cyclopropylpyridine (*IV*) as the sole reaction product.

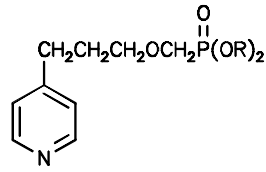
An alternative approach to the 2-amino derivatives consists in the introduction of a suitable substituent into the position 2, which subsequently could be transformed into the amino group. Such a substituent might be e.g. a halogen or azido group. Therefore, we first converted the starting 3-(4-pyridinyl)propanol (*I*) into benzoyl derivative *VII* which on heating with peroxyacetic acid afforded 4-(3-benzoyloxypropyl)pyridine *N*-oxide (*VIII*). The obtained *N*-oxide *VIII* reacted with phosphoryl chloride to give 4-(3-benzoyloxypropyl)-2-chloropyridine (*IX*). The reaction was accompanied with chlorination of the side chain under formation of 4-(3-benzoyloxy-1-chloropropyl)-pyridine (*X*). The products were obtained in the ratio 1 : 1, however, they could be easily separated by chromatography. The formation of the side chain-chlorinated derivative is analogous to the situation described for reactions of other alkylpyridine *N*-oxides with phosphoryl chloride[17,18]. Our attempts to find other methods leading to the 2-chloro derivative *IX* without formation of the compound *X* were unsuccessful. The recommended method, consisting in heating pyridine *N*-oxides with sulfuryl chloride[19,20] in a pressure vessel, in our case gave only negligible yield of the 2-chloro derivative *IX*. Most of the compound underwent deep degradation to a complex mixture of polar products. Unsuccessful was also the reaction of *N*-oxide *VIII* with phosphorus trichloride and an attempted preparation of the 2-bromo derivative by reaction of *VIII*



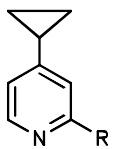
| | R |
|---|---|
| *I* | H |
| *VI* | Trt |
| *VII* | Bz |



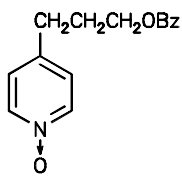
*II*



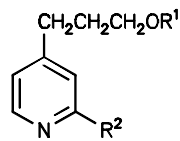
| | R |
|---|---|
| *III* | iPr |
| *V* | H |



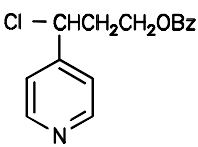
| | R |
|---|---|
| *IV* | H |
| *XIV* | Cl |



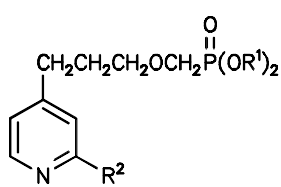
*VIII*



| | $R^1$ | $R^2$ |
|---|---|---|
| *IX* | Bz | Cl |
| *XI* | H | Cl |
| *XII* | H | $NH_2$ |



*X*



| | $R^1$ | $R^2$ |
|---|---|---|
| *XIII* | iPr | Cl |
| *XV* | H | Cl |
| *XVI* | H | $NH_2$ |

with bromotrimethylsilane. In both cases the reaction mixture contained only the unchanged *N*-oxide even after several hours of heating.

As an alternative approach, we tried to introduce an azido group into position 2 and to reduce it to the amine. However, attempts to prepare the azido derivative from *N*-oxide *VIII* by reaction with sodium azide or trimethylsilyl azide were also without success. Similarly, attempted replacement of chlorine with the azido group in compound *IX* by prolonged heating with sodium or lithium azide in dimethylformamide gave no product.

The only successful procedure leading to the 2-amino derivative *XII* was direct substitution of the chlorine atom with ammonia under conditions described by Wibaut and Nicolai[21] for 2-chloropyridine: the benzoylated 2-chloro derivative *IX* on reaction with sodium methoxide was converted into 2-chloro-4-(3-hydroxypropyl)pyridine (*XI*) which was then heated with concentrated aqueous ammonia under high pressure and temperature in the presence of copper(II) sulfate to afford the desired 2-amino-4-(3-hydroxypropyl)pyridine (*XII*). Because of instability of this compound due to easy oxidation of the amino group, it was better to prepare the phosphonomethyl derivative not from the compound *XII* but to synthesize first the 2-chloro substituted phosphonate and to replace the chlorine atom by the amino group only in the free phosphonomethyl derivative as the last synthetic step.

Reaction of sodium salt of 2-chloro-4-(3-hydroxypropyl)pyridine (*XI*) with diisopropyl *p*-toluenesulfonyloxymethanephosphonate (*II*) gave the desired phosphonate in the form of its diisopropyl ester *XIII*, together with 2-chloro-4-cyclopropylpyridine (*XIV*). The presence of the chlorine atom in position 2 enhanced strongly the propensity to formation of the cyclopropyl derivative. Whereas the analogous reaction with unsubstituted 4-(3-hydroxypropyl)pyridine (*I*) can be performed at room temperature, with the 2-chloro derivative *XI* the reaction mixture must be cooled (−20 to −10 °C) and the reaction has to be monitored by thin-layer chromatography. At temperatures higher than −5 °C the cyclopropyl derivative *XIV* was practically the sole reaction product. Reaction of the ester *XIII* with bromotrimethylsilane afforded free 3-(2-chloro-4-pyridinyl)propoxymethanephosphonic acid (*XV*). The replacement of the chlorine atom by amino group was carried out analogously as described for compound *XI*, i.e., by copper(II) sulfate-catalyzed reaction with aqueous ammonia at high temperature and pressure. In this way, we obtained 3-(2-amino-4-pyridinyl)propoxymethanephosphonic acid (*XVI*) as the final product in a relatively high yield (57%).

The structure of the compounds was determined by $^{1}H$ and $^{13}C$ NMR spectra and further confirmed by elemental analysis or mass spectrometry. The $^{13}C$ NMR spectra of the individual compounds are listed in Table I.

The antiviral activity and cytotoxicity of free phosphonomethyl derivatives was tested in cell cultures. Compound *V* was inactive to herpes simplex viruses (HSV-1, HSV-2), vesicular stomatitis virus (VSV), vaccinia virus (VV) and RNA viruses. The

compound is not cytotoxic[22]. The biological assays of compounds *XV* and *XVI* are still under way.

## EXPERIMENTAL

Unless stated otherwise, solvents were evaporated at 40 °C/2 kPa and compounds were dried over phosphorus pentoxide at 13 Pa. Thin-layer chromatography was performed on Silufol UV 254 foils (Kavalier, The Czech Republic). The solvent systems are specified in the text. Spots were detected by UV light at 254 nm or by spraying with 0.5% solution of 4-(4-nitrobenzyl)pyridine in ethanol with subsequent heating and exposure to ammonia vapours. Preparative column chromatography was carried out on silica gel (30 – 60 μm, Service Laboratories of the Institute), reversed-phase chromatography on octadecyl-silica gel (20 μm, Laboratorni Pristroje, Prague) with a gradient of methanol; detection with a Uvicord 4701 A (LKB, Sweden) instrument at 254 nm. Electrophoresis was performed on a Whatman No 3MM paper in 0.1 M triethylammonium hydrogen carbonate for 1 h at 20 V/cm. The electrophoretic mobilities given in the text ($E_{AMP}$) are referenced to adenosine 5′-phosphate. $^1$H NMR spectra (δ, ppm; *J*, Hz) were measured on Varian UNITY-200 (200.01 MHz) and Varian

TABLE I
$^{13}$C NMR chemical shifts (δ, ppm) of compounds *III* – *XVI*

| Compound | C-2 | C-3 | C-4 | C-5 | C-6 | C-1′ | C-2′ | C-3′ |
|---|---|---|---|---|---|---|---|---|
| *III*[a] | 149.73 | 124.18 | 150.80 | 124.18 | 149.73 | 30.95 | 29.72 | 71.69 |
| *IV* | 149.41 | 120.84 | 153.61 | 120.84 | 149.41 | 14.65 | 10.71 | – |
| *V*[b] | 144.02 | 125.47 | 158.14 | 125.47 | 144.02 | 30.98 | 28.41 | 71.29 |
| *VI* | 149.54 | 124.11 | 150.65 | 124.11 | 149.54 | 29.93 | 31.18 | 62.08 |
| *VII* | 149.72 | 124.06 | 150.31 | 124.06 | 149.72 | 31.04 | 28.77 | 64.08 |
| *VIII* | 138.50 | 126.62 | 139.64 | 126.62 | 138.50 | 30.11 | 28.80 | 64.03 |
| *IX* | 150.67 | 124.27 | 154.84 | 123.57 | 149.85 | 30.87 | 28.55 | 64.13 |
| *X* | 150.33 | 122.21 | 149.58 | 122.21 | 150.33 | 58.63 | 37.13 | 61.87 |
| *XI* | 150.59 | 124.25 | 155.73 | 123.62 | 149.80 | 30.76 | 32.95 | 59.90 |
| *XIII*[c] | 150.65 | 124.26 | 155.13 | 123.61 | 149.86 | 30.65 | 29.37 | 71.50 |
| *XIV* | 150.66 | 120.94 | 158.21 | 120.20 | 149.53 | 14.70 | 11.28 | – |
| *XV*[d] | 150.58 | 124.22 | 155.43 | 123.67 | 149.76 | 30.74 | 29.65 | 70.90 |
| *XVI*[e] | 155.05 | 111.25 | 155.01 | 112.93 | 145.77 | 30.73 | 28.95 | 71.85 |

Other data: [a] 71.69 d, *J*(P,C) = 11.7 (C-3′); 70.34 d, *J*(P,C) = 5.9 (POC); 64.89 d, *J*(P,C) = 165.0 (PC); 24.05 d, *J*(P,C) = 3.9 ($CH_3$); 23.95 d, *J*(P,C) = 4.9 ($CH_3$). [b] 71.29 d, *J*(P,C) = 10.7 (C-3′); 66.63 d, *J*(P,C) = 155.3 (PC). [c] 71.50 d, *J*(P,C) = 10.7 (C-3′); 70.26 d, *J*(P,C) = 5.8 (POC); 64.83 d, *J*(P,C) = 164.1 (PC); 24.01 d, *J*(P,C) = 3.9 ($CH_3$); 23.91 d, *J*(P,C) = 4.9 ($CH_3$). [d] 70.90 d, *J*(P,C) = 10.7 (C-3′); 68.18 d, *J*(P,C) = 159.2 (PC). [e] 71.85 d, *J*(P,C) = 11.0 (C-3′); 68.42 d, *J*(P,C) = 149.4 (PC).

UNITY-500 (499.8 MHz) instruments in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. NMR spectra of compounds *V* and *XVI* were taken in deuterium oxide with sodium 3-(trimethylsilyl)-1-propanesulfonate (DSS) as reference. The carbon signals were referenced to the solvent signal ($\delta^{13}$C (DMSO) = 39.7) or to dioxane as external standard ($\delta$ $^{13}$C (dioxane) = 66.86) for solutions in deuterium oxide. Mass spectra were taken on a ZAB-EQ (VG Analytical) spectrometer using EI (electron energy 70 eV) or FAB (xenone, 8 kV) techniques with glycerol (G) or thioglycerol (TG) as matrices.

Bis(2-propyl) 3-(4-Pyridinyl)propoxymethanephosphonate (*III*)

Sodium hydride (60% suspension in oil; 1.76 g, 44 mmol) was added to a solution of alcohol *I* (2.04 g, 14.9 mmol) in dimethylformamide (70 ml) and the mixture was stirred at room temperature for 30 min. Tosylate *II* (7.82 g, 22.3 mmol) was added to the formed suspension of the sodium salt and the stirring at room temperature was continued for 1.5 h. The mixture was neutralized by addition of acetic acid (2 ml), the solvent was evaporated and the residue was partitioned between water (400 ml) and ethyl acetate (600 ml). The organic layer was dried over magnesium sulfate, taken down and the residue was chromatographed on silica gel (750 ml) in ethyl acetate–acetone–ethanol–water (18 : 3 : 1 : 1), $R_F$ 0.40. Yield 1.19 g (25%) of phosphonate *III*. For $C_{15}H_{26}NO_4P$ (315.4) calculated: 57.13% C, 8.31% H, 4.44% N, 9.82% P; found: 56.86% C, 8.60% H, 4.14% N, 9.55% P. Mass spectrum (FAB, $CHCl_3$), *m/z*: 316 (M + H). $^1$H NMR spectrum: 1.24 d, 6 H and 1.25 d, 6 H, $J(CH_3,CH)$ = 6.1 ($CH_3$); 1.82 m, 2 H (2′-$CH_2$); 2.62 dd, 2 H, $J(1',2')$ = 6.3 and 8.5 (1′-$CH_2$); 3.50 t, 2 H, $J(3',2')$ = 6.3 (3′-$CH_2$); 3.71 d, 2 H, $J$(P,CH) = 8.3 ($PCH_2$); 4.60 d sept, 2 H, $J(CH,CH_3)$ = 6.1, $J$(P,OCH) = 7.8 (POCH); 7.23 d, 2 H, $J$ = 6.1 (H-3 and H-5 pyridine); 8.44 d, 2 H, $J$ = 6.1 (H-2 and H-6, pyridine).

4-Cyclopropylpyridine (*IV*)

This compound was obtained as the chromatographically more mobile product in the preparation of diester *III*. Yield 1.3 g (73%), $R_F$ 0.70 (ethyl acetate–acetone–ethanol–water 18 : 3 : 1 : 1). Mass spectrum (FAB, G + dimethyl sulfoxide), *m/z*: 120 (M + H). $^1$H NMR spectrum: 0.77 m, 2 H and 1.04 m, 2 H (2′-$CH_2$); 1.90 tt, 1 H, $J(1',2'$-*trans*) = 5.1, $J(1',2'$-*cis*) = 8.3 (1′-CH); 7.06 d, 2 H, $J$ = 6.1 (H-3 and H-5, pyridine); 8.36 d, 2 H, $J$ = 6.1 (H-2 and H-6, pyridine).

3-(4-Pyridinyl)propoxymethanephosphonic Acid (*V*)

Bromotrimethylsilane (4.5 ml, 34 mmol) was added in an argon atmosphere to a solution of diisopropyl ester *III* (1.14 g, 3.6 mmol) in acetonitrile (15 ml) and the mixture was stirred for 24 h in the dark. The reaction mixture was adjusted to neutrality with 1 M triethylammonium hydrogen carbonate and the solvent was evaporated. The residue was codistilled with water (50 ml), dissolved in water (5 ml) and applied onto a column of DEAE-Sephadex A-25 (300 ml; $HCO_3^-$ form). The column was washed with water (1 000 ml) and then with a gradient of triethylammonium hydrogen carbonate (0 – 0.4 mol/l; 1 000 ml). The product was eluted at buffer concentration 0.2 – 0.3 mol/l. The product fractions were evaporated, the residue was codistilled with water (3 × 100 ml) and then purified by chromatography on a reversed phase (C-18). The pure product was eluted with water, the product fractions were concentrated to 3 ml and applied onto a column of Dowex 50 ($Li^+$ form; 50 ml). The column was washed with water. Fractions containing the lithium salt of phosphonate *V* were evaporated, the solid residue was triturated with a methanol–acetone mixture, collected on filter and dried in vacuo. Yield 400 mg (42%), $R_F$ 0.18 (2-propanol–25% aqueous ammonia–water 7 : 1 : 2); $E_{AMP}$ 1.18. For $C_9H_{12}Li_2NO_4P \cdot H_2O$ (261.1) calculated: 41.41% C, 5.40% H, 5.36% N, 11.86% P; found: 41.11% C, 5.52% H, 5.23% N, 11.75% P. Mass spectrum (FAB, $H_2O$), *m/z*: 244 (M + H, dilithium

salt), 238 (M + H, monolithium salt), 232 (M + H, free acid). $^1$H NMR spectrum: 1.96 m, 2 H (2′-$CH_2$); 2.84 bt, 2 H, $J$(1′,2′) = 7.6 (1′-$CH_2$); 3.60 d, 2 H, $J$(P,CH) = 8.7 ($PCH_2$); 3.61 t, 2 H, $J$(3′,2′) = 6.4 (3′-$CH_2$); 7.56 d, 2 H, $J$ = 5.5 (H-3 and H-5, pyridine); 8.48 d, 2 H, $J$ = 5.5 (H-2 and H-6, pyridine).

4-(3-Triphenylmethoxypropyl)pyridine (*VI*)

Trityl chloride (20.4 g, 73 mmol) was added to a solution of alcohol *I* (8.76 g, 63.86 mmol) in dry pyridine (110 ml) and the solution was stirred at room temperature for 48 h. Crystalline pyridine hydrochloride separated during the reaction. The reaction mixture was slowly added into ice-cold water (1.5 l). After standing in a refrigerator for 16 h, the solid product was collected and dissolved in chloroform (1 l). The chloroform solution was washed with water (2 × 500 ml), dried over magnesium sulfate, the solvent was evaporated and the residue crystallized from 2-propanol–methanol. Yield 20.6 g (85%) of crystalline trityl derivative *VI*, m.p. 110 °C, $R_F$ 0.33 (toluene–ethyl acetate 3 : 1). For $C_{27}H_{25}NO$ (379.5) calculated: 85.45% C, 6.64% H, 3.69% N; found: 85.47% C, 6.62% H, 3.60% N. Mass spectrum (FAB, $CHCl_3$), *m*/*z*: 380 (M + H), 243 (trityl). $^1$H NMR spectrum: 1.87 m, 2 H (2′-$CH_2$); 2.67 t, 2 H, $J$(1′,2′) = 7.5 (1′-$CH_2$); 2.96 t, 2 H, $J$(3′,2′) = 6.3 (3′-$CH_2$); 7.14 d, 2 H, $J$ = 6.1 (H-3 and H-5, pyridine); 7.20 – 7.40 m, 15 H (H-trityl); 8.38 d, 2 H, $J$ = 6.1 (H-2 and H-6, pyridine).

3-(4-Pyridinyl)propyl Benzoate (*VII*)

Benzoyl chloride (21 ml, 181 mmol) was added at 0 °C to a solution of alcohol *I* (20.48 g, 149.3 mmol) in pyridine (100 ml). The mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h. Ethanol (30 ml) was added and the solvent evaporated. The residue was partitioned between water (400 ml) and ethyl acetate (750 ml), the organic phase was washed with water (2 × 400 ml), dried over magnesium sulfate and taken down. The thus-obtained liquid benzoate *VII* (40 g) was used in the preparation of *N*-oxide *VIII* without further purification. For characterization, a sample (200 mg) was chromatographed on silica gel (40 ml) in ethyl acetate ($R_F$ 0.46) to give 150 mg of pure benzoate *VII* as a yellowish liquid. For $C_{15}H_{15}NO_2$ (241.3) calculated: 74.67% C, 6.27% H, 5.80% N; found: 74.49% C, 6.45% H, 5.65% N. Mass spectrum (FAB, dimethyl sulfoxide), *m*/*z*: 242 (M + H). $^1$H NMR spectrum: 2.06 m, 2 H (2′-$CH_2$); 2.76 dd, 2 H, $J$(1′,2′) = 7.0 and 8.2 (1′-$CH_2$); 4.28 t, 2 H, $J$(3′,2′) = 6.4 (3′-$CH_2$); 7.28 d, 2 H, $J$ = 5.8 (H-3 and H-5, pyridine); 7.48 – 7.72 m, 3 H and 7.91 m, 2 H (H-benzoyl); 8.46 d, 2 H, $J$ = 5.8 (H-2 and H-6, pyridine).

4-(3-Benzoyloxypropyl)pyridine *N*-Oxide (*VIII*)

The benzoate *VII* from the preceding preparation was dissolved in a mixture of acetic acid (55 ml) and 30% hydrogen peroxide (10 ml). The solution was heated at 75 °C for 8 h; during the heating further portions of hydrogen peroxide (2 × 6 ml) were added. The reaction mixture was diluted with water (500 ml) and the solvent was evaporated. The residue was codistilled with water (3 × 400 ml) and ethanol (100 ml) and chromatographed on silica gel (1 500 ml) in ethyl acetate–acetone–ethanol–water 18 : 3 : 2 : 2 ($R_F$ 0.36). Yield 16 g (42%, based on compound *I*); in addition, the starting benzoate *VII* (13 g; 36%) was also obtained. The product *VII* was a white crystalline hygroscopic compound. Mass spectrum (FAB, chloroform), *m*/*z*: 258 (M + H). $^1$H NMR spectrum: 2.02 m, 2 H (2′-$CH_2$); 2.73 t, 2 H, $J$(1′,2′) = 7.7 (1′-$CH_2$); 4.27 t, 2 H, $J$(3′,2′) = 6.3 (3′-$CH_2$); 7.30 d, 2 H, $J$ = 6.8 (H-3 and H-5, pyridine); 7.52 t, 2 H, 7.65 t, 1 H and 7.94 d, 2 H (H-benzoyl); 8.12 d, 2 H, $J$ = 6.8 (H-2 and H-6, pyridine).

3-[4-(2-Chloropyridinyl)]propyl Benzoate (*IX*)

Phosphoryl chloride (70 ml) was added to *N*-oxide *VIII* (11.7 g, 45.5 mmol) and the mixture was refluxed for 3 h. After cooling, the excess phosphoryl chloride was distilled off in vacuo and the residue was neutralized with a mixture of ice and 25% aqueous ammonia. The product was taken up in ethyl acetate (500 ml), the organic layer was dried over magnesiun sulfate and the solvent was evaporated. The residue was chromatographed on a column of silica gel (500 ml) in toluene–ethyl acetate 2 : 1 ($R_F$ of benzoate *IX* 0.69). Yield 3.84 g (31%), slightly yellow liquid. For $C_{15}H_{14}ClNO_2$ (275.7) calculated: 65.34% C, 5.12% H, 12.86% Cl, 5.08% N; found: 64.99% C, 5.03% H, 12.98% Cl, 5.12% N. Mass spectrum (FAB, $CHCl_3$), *m/z*: 276 (M + H). $^1$H NMR spectrum: 2.06 m, 2 H (2′-$CH_2$); 2.78 t, 2 H, *J*(1′,2′) = 7.6 (1′-$CH_2$); 4.28 t, 2 H, *J*(3′,2′) = 6.3 (3′-$CH_2$); 7.32 dd, 1 H, *J*(5,3) = 1.0, *J*(5,6) = 5.1 (H-5, pyridine); 7.44 bs, 1 H (H-3, pyridine); 7.50 t, 2 H, 7.65 t, 1 H and 7.91 d, 2 H (H-benzoyl); 8.28 bd, 1 H, *J*(6,5) = 5.1 (H-6, pyridine).

3-Chloro-3-(4-pyridinyl)propyl Benzoate (*X*)

The title compound was obtained as the chromatographically less mobile side product in the preparation of benzoate *IX*. Yield 5.14 g (41%); slightly yellow, light-sensitive liquid. $R_F$ 0.45 (ethyl acetate–toluene 2 : 1). Mass spectrum (FAB, $CHCl_3$), *m/z*: 276 (M + H). $^1$H NMR spectrum: 2.54 m, 2 H (2′-$CH_2$); 4.36 pent, 1 H, *J*(3′a,2′) = 5.6, *J*(gem) = 12.2 (H-3′a); 4.40 ddd, 1 H, *J*(3′b,2′) = 5.6 and 7.1, *J*(gem) = 12.2 (H-3′b); 5.40 dd, 1 H, *J*(1′,2′) = 6.6 and 7.1 (1′-$CH_2$); 7.49 t, 2 H (H-benzoyl); 7.54 d, 2 H, *J* = 6.1 (H-3 and H-5, pyridine); 7.65 t, 1 H and 7.91 d, 2 H (H-benzoyl); 8.20 d, 2 H, *J* = 6.1 (H-2 and H-6, pyridine).

2-Chloro-4-(3-hydroxypropyl)pyridine (*XI*)

A solution of the benzoyl derivative *IX* (3.30 g, 12 mmol) was stirred with 0.1 M methanolic sodium methoxide (200 ml) at room temperature for 2 h. The solution was neutralized with Dowex 50 ($H^+$ form) to pH 7, the ion-exchanger was removed by filtration and washed on the filter with methanol containing 1% of triethylamine until the UV absorption of the filtrate disappeared. The combined filtrates were taken down and the residue was chromatographed on silica gel (260 ml) in ethyl acetate ($R_F$ 0.46). Yield 1.87 g (91%) of alcohol *XI* (colourless sirup). Mass spectrum (FAB, T + G, methanol), *m/z*: 172 (M + H). $^1$H NMR spectrum: 1.72 m, 2 H (2′-$CH_2$); 2.65 t, 2 H, *J*(1′,2′) = 7.7 (1′-$CH_2$); 3.39 td, 2 H, *J*(3′,2′) = 6.3, *J*(3′,OH) = 5.1 (3′-$CH_2$); 4.55 t, 1 H, *J*(OH,3′) = 5.1 (OH); 7.26 dd, 1 H, *J*(5,3) = 1.5, *J*(5,6) = 5.1 (H-5, pyridine); 7.37 d, 1 H, *J*(3,5) = 1.5 (H-3, pyridine); 8.27 d, 1 H, *J*(6,5) = 5.1 (H-6, pyridine).

2-Amino-4-(3-hydroxypropyl)pyridine (*XII*)

A mixture of 2-chloro derivative *XI* (268 mg, 1.6 mmol), 25% ammonium hydroxide (30 ml) and copper(II) sulfate (50 mg) was heated in an autoclave at 220 °C for 17 h. After cooling, the solution was taken down and the residue was mixed with a small amount (about 1 – 2 ml) of the solvent system ethyl acetate–acetone–ethanol–water 18 : 3 : 2 : 2. The soluble portion was applied onto a column of silica gel (25 ml) and chromatographed in the above-mentioned system. Yield 100 mg (42%) of amorphous aminopyridine *XII*, $R_F$ 0.4. Mass spectrum (FAB, T + G, $CH_3OH$), *m/z*: 153 (M + H). $^1$H NMR spectrum: 1.65 m, 2 H (2′-$CH_2$); 2.41 t, 2 H, *J*(1′,2′) = 7.5 (1′-$CH_2$); 3.39 t, 2 H, *J*(3′,2′) = 6.4 (3′-$CH_2$); 4.50 br, 1 H (OH); 6.0 br, 2 H ($NH_2$); 6.03 d, 1 H, *J*(5,6) = 5.0 (H-5, pyridine); 6.15 s, 1 H (H-3, pyridine); 7.26 d, 1 H, *J*(6,5) = 5.0 (H-6, pyridine).

Bis(2-propyl) 3-(2-Chloro-4-pyridinyl)propoxymethanephosphonate (*XIII*)

Tosylate *II* (4.59 g, 13 mmol) was added to a solution of alcohol *XI* (1.5 g, 8.74 mmol) in dimethylformamide (20 ml), the solution was cooled to −20 °C and sodium hydride (60% dispersion; 1.05 g, 26 mmol) was added. The suspension was stirred at −20 °C for 15 min and then the temperature was increased from −20 °C to −10 °C during 1 h. The reaction mixture was neutralized with acetic acid (3.5 ml) and the solvent was evaporated. The residue was partitioned between water (200 ml) and ethyl acetate (300 ml). The organic phase was dried over magnesium sulfate, the solvent was evaporated and the residue was chromatographed on silica gel (200 ml) in ethyl acetate. The elution afforded successively: cyclopropyl derivative *XIV* ($R_F$ 0.80), minor amount of unreacted starting alcohol *XI* ($R_F$ 0.46; 205 mg, 14%), and then phosphonate *XIII* ($R_F$ 0.36). Yield of pure product *XIII* 800 mg (26%). For $C_{15}H_{25}ClNO_4P$ (349.8) calculated: 51.51% C, 7.20% H, 10.14% Cl, 4.00% N, 8.85% P; found: 51.23% C, 6.96% H, 9.92% Cl, 3.79% N, 8.56% P. Mass spectrum (FAB, T + G, chloroform), *m/z*: 350 (M + H). $^1$H NMR spectrum: 1.23 d, 6 H and 1.24 d, 6 H, $J(CH_3,CH)$ = 6.1 ($CH_3$); 1.83 m, 2 H (2′-$CH_2$); 2.65 t, 2 H, $J(1',2')$ = 7.7 (1′-$CH_2$); 3.49 t, 2 H, $J(3',2')$ = 6.3 (3′-$CH_2$); 3.71 d, 2 H, $J$(P,CH) = 8.1 ($PCH_2$); 4.59 d sept, 2 H, $J(CH,CH_3)$ = 6.1, $J$(P,OCH) = 7.5 (POCH); 7.28 dd, 1 H, $J$(5,3) = 1.5, $J$(5,6) = 5.1 (H-5, pyridine); 7.38 d, 1 H, $J$(3,5) = 1.5 (H-3, pyridine); 8.29 bd, 1 H, $J$(6,5) = 5.1 (H-6, pyridine).

2-Chloro-4-cyclopropylpyridine (*XIV*)

This compound was isolated as the side product in the preparation of phosphonate *XIII*; yield 0.4 g (30%). $^1$H NMR spectrum: 0.85 m, 2 H and 1.08 m, 2 H (2′-$CH_2$); 1.97 tt, 1 H, $J(1',2'$-*trans*) = 4.9, $J(1',2'$-*cis*) = 8.3 (1′-CH)); 7.09 dd, 1 H, $J$(5,3) = 1.5, $J$(5,6) = 5.1 (H-5, pyridine); 7.23 d, 1 H, $J$(3,5) = 1.5 (H-3, pyridine); 8.19 d, 1 H, $J$(6,5) = 5.1 (H-6, pyridine).

3-(2-Chloro-4-pyridinyl)propoxymethanephosphonic Acid (*XV*)

Bromotrimethylsilane (3.3 ml, 25 mmol) was added in an argon atmosphere to a solution of compound *XIII* (900 mg, 2.6 mmol) in acetonitrile (15 ml) and the solution was stirred in the dark for 20 h. The reaction was quenched by addition of 1 M triethylammonium hydrogen carbonate to neutrality. The solvent was evaporated, the residue was codistilled with water (2 × 40 ml), dissolved in water (4 ml) and applied onto a column of DEAE-Sephadex A-25 ($HCO_3^-$ form; 300 ml). The column was washed with water (600 ml) and then with a gradient of triethylammonium hydrogen carbonate (0 – 0.5 mol/l; 1 000 ml). The product was eluted at concentration 0.3 – 0.4 mol/l. The product fractions were combined, the solvent was evaporated and the residue was codistilled several times with water until the decomposition of triethylammonium hydrogen carbonate was complete. The final purification was performed by chromatography on a reversed phase (C-18); the product was eluted with a gradient of methanol (0 – 100%). The pure phosphonate *XV* was eluted with 30% methanol. Yield 650 mg (82%, about 1/3 of the compound as the bis(triethylammonium) salt), $R_F$ 0.20 (2-propanol–25% aqueous ammonia–water 7 : 1 : 2); $E_{AMP}$ 1.25. Mass spectrum (FAB, T + G, methanol), *m/z*: 468 (M + H, bis(triethylammonium) salt), 367 (M + H, triethylammonium salt), 266 (M + H, free acid). $^1$H NMR spectrum: 1.15 t, 6 H, $J(CH_3,CH_2)$ = 7.3 ($CH_3$); 1.78 m, 2 H (2′-$CH_2$); 2.65 t, 2 H, $J(1',2')$ = 7.8 (1′-$CH_2$); 2.94 q, 4 H, $J(CH_2,CH_3)$ = 7.3 ($CH_2$); 3.36 d, 2 H, $J$(P,CH) = 9.0 ($PCH_2$); 3.41 t, 2 H, $J(3',2')$ = 6.3 (3′-$CH_2$); 7.28 dd, 1 H, $J$(5,3) = 1.5, $J$(5,6) = 5.1 (H-5, pyridine); 7.37 bs, 1 H (H-3, pyridine); 8.27 d, 1 H, $J$(6,5) = 5.1 (H-6, pyridine).

3-(2-Amino-4-pyridinyl)propoxymethanephosphonic Acid (*XVI*)

Copper(II) sulfate (120 mg) was added to a solution of compound *XV* (500 mg, 1.1 mmol) in 25% aqueous ammonia (30 ml) and the mixture was heated at 200 °C for 18 h. After cooling, the solution was saturated with hydrogen sulfide for 15 min. The precipitated copper sulfide was filtered through Celite and the filtrate was taken down. The residue was chromatographed on a reversed phase (C-18) in water. Because of the presence of small amounts of impurities (arising by oxidation of the amino group) the chromatography was repeated under the same conditions. Yield 150 mg (57%) of white solid, $R_F$ 0.16 (2-propanol–25% aqueous ammonia–water); $E_{AMP}$ 1.21. Mass spectrum (FAB, G + water), *m/z*: 247 (M + H). $^1$H NMR spectrum ($D_2O$ + NaOD): 1.88 m, 2 H (2′-$CH_2$); 2.54 t, 2 H, *J*(1′,2′) = 7.6 (1′-$CH_2$); 3.48 d, 2 H, *J*(P,CH) = 8.5 ($PCH_2$); 3.60 t, 2 H, *J*(3′,2′) = 6.8 (3′-$CH_2$); 6.30 bs, 1 H (H-3, pyridine); 6.48 dd, 1 H, *J*(5,3) = 1.5, *J*(5,6) = 5.6 (H-5 pyridine); 7.72 d, 1 H, *J*(6,5) = 5.6 (H-6, pyridine).

*The authors are indebted to Professor E. De Clercq, Rega Institute, Catholic University, Leuven, Belgium, for the antiviral tests. Their thanks are also due to Mrs A. Sterecova for the technical assistance, to the staff of the Analytical Laboratory of the Institute (Dr V. Pechanec, Head) for the elemental analyses and to the staff of the Central Laboratory of Mass Spectroscopy (Dr K. Ubik, Head) for the mass spectra. This work was supported by Grant No. 203/93/0118 of the Czech Grant Agency, Grant No. 455407 of the Grant Agency of the Czech Academy of Sciences, and by Gilead Sciences (California, U.S.A.).*

**REFERENCES:**

1. De Clercq E., Holy A., Rosenberg I., Sakuma T., Balzarini J., Maudgal P. C.: Nature *323*, 464 (1986).
2. Holy A., Rosenberg I.: Collect. Czech. Chem. Commun. *52*, 2801 (1987).
3. Holy A., Votruba I., Merta A., Cerny J., Vesely J., Vlach J., Sediva K., Rosenberg I., Otmar M., Hrebabecky H., Travnicek M., Vonka V., Snoeck R., De Clercq E.: Antiviral Res. *13*, 295 (1990).
4. De Clercq E., Holy A., Rosenberg I.: Antimicrob. Agents Chemother. *33*, 185 (1989).
5. Bronson J. J., Kim C. U., Ghazzouli I., Hitchcock M. J. M., Kern E., Martin J. C. in: *Nucleotides as Antiviral Agents* (J. C. Martin, Ed.), p. 72. American Chemical Society, Washington D.C. 1989.
6. Pauwels R., Balzarini J., Schols D., Baba M., Desmyter J., Rosenberg I., Holy A., De Clercq E.: Antimicrob. Agents Chemother. *32*, 1025 (1988).
7. Holy A.: Collect. Czech. Chem. Commun. *54*, 446 (1989).
8. Jindrich J., Holy A., Dvorakova H.: Collect. Czech. Chem. Commun. *58*, 1645 (1993).
9. Dvorakova H., Holy A., Rosenberg I.: Collect. Czech. Chem. Commun. *59*, 2069 (1994).
10. Holy A., Rosenberg I., Dvorakova H.: Collect. Czech. Chem. Commun. *54*, 2470 (1989).
11. Holy A., Rosenberg. I.: Nucleosides Nucleotides *8*, 673 (1989).
12. Eger K., Klunder E. M., Schmidt M.: J. Med. Chem. *37*, 3057 (1994).
13. Krecmerova M., Holy A.: Collect. Czech. Chem. Commun. *60*, 659 (1995).
14. Cislak F. E.: U.S. 2,789,982 (1957); Chem. Abstr. *51*, 12985 (1957).
15. Holy A.: Collect. Czech. Chem. Commun. *58*, 649 (1993).
16. Solomon W.: J. Chem. Soc. *1946*, 934.
17. Barnes J. H., Hartley F. R., Jones C. E. L.: Tetrahedron *38*, 3277 (1982).
18. Ash M. L., Pews R. G.: J. Heterocycl. Chem. *18*, 939 (1981).

19. Gilman H., Edward J. T.: Can. J. Chem. *31*, 457 (1953).
20. Bobranski B., Kochanska L., Kowalewska A.: Chem. Ber. *71*, 2385 (1938).
21. Wibaut J. P., Nicolai J. R.: Rec. Trav. Chim. *58*, 709 (1939).
22. De Clercq E.: Unpublished results.