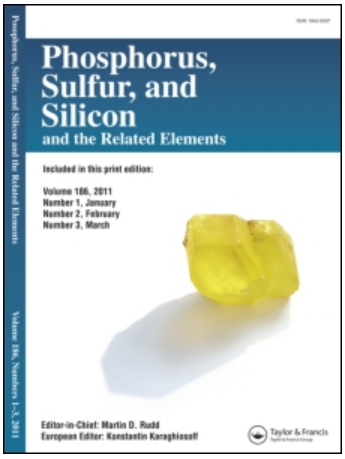

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Insecticidal Activity of Some New Amidophosphoric Acid Esters Containing Substituted Pyridine Moieties

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Insecticidal Activity of Some New Amidophosphoric Acid Esters Containing Substituted Pyridine Moieties

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Some new amidophosphoric acid esters containing substituted pyridine moieties were synthesized by the reaction of O-aryl,O-ethyl phosphoryl chlorides with 3-(aminomethyl)pyridine and 5-(aminomethyl)-2-chloropyridine. Characterization was done by ^{1}H *NMR,* $^{31}P\{^{1}H\}$ *NMR, IR, MS, and elemental analyses. The results of preliminary bioassay showed that the new compounds possess good insecticidal activity against aphides.*

Keywords Amidophosphoric acid esters; insecticidal activity; substituted pyridine

INTRODUCTION

Insecticides that have the structure and mechanism similar to nicotine are called neonicotinoids.[1] Seven neonicotinoids such as imidcaloprid, acetamipyrid, and nitenpyram, which have the pyridine-like moiety, have been commercialized and many SARs (structure-activity relationships) for these neonicotinoids have been reported.[1,2] It was found that most of the biological active nicotinic compounds contain the 3-(aminomethyl)-pyridine moiety.[3] Organic phosphorus insecticides—especially amidophosphoric acid ester insecticides—play an important role in pesticide industry, such as methomidophos, acephate, phenamidphos, fosthiazate, mitemate, etc., have been commercialized; some neonicotinoid derivatives containing phosphorus atom have been reported.[4,5] Herein, we hope to report the synthesis and insecticidal

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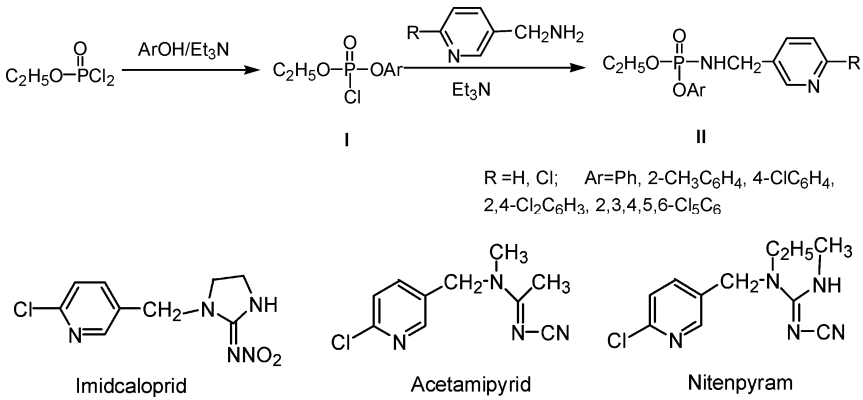

SCHEME 1

activity of amidophosphoric acid esters containing substituted pyridine moieties.

The synthetic route is shown in Scheme 1. Characterization was done by ^{1}H NMR, ^{31}P{^{1}H}NMR, IR, MS, and elemental analyses. The results of preliminary bioassay showed that the new compounds possess good insecticidal activity against aphides.

RESULTS AND DISCUSSION

The Structures of the Title Compounds

All the products were purified by flash column chromatography on a silica gel with a mixture of petroleum ether and acetone (4:1, *v*/*v*) as the eluent, The structures of compounds **IIa**∼**IIi** were confirmed by ^{1}H NMR, ^{31}P{^{1}H}NMR, IR spectra, MS, and elemental analyses.

For ^{1}H NMR spectra, the NH proton appears as a broad singlet with variable chemical shifts, the NCH_2 protons display as a doublet, in some cases as a double doublet due to the coupling with phosphorus atom and with the proton of NH. In some cases, these protons appear with equal chemical shifts with those of OCH_2 and are difficult to be distinguished. The pyridine protons are easily differentiated from the phenyl protons. The ^{31}P{^{1}H}NMR spectra of compounds **IIa**∼**IIi** exhibited a singlet in the range of δ 3.0 to 3.4. Their structures were also supported by correct elemental analysis and by the mass spectra, which exhibited the anticipated molecular ion peaks. The IR spectra of all compounds showed normal stretching absorption bands indicating the existence of the N-H ($\sim$ 3200 cm^{-1}), P=O ($\sim$1250 cm^{-1}), P-O-C ($\sim$950 cm^{-1}) moiety.

Biological Activities

Compounds **IIa**~**IIi** were tested for insecticidal activity against aphides by dipping at various concentrations according to a previously reported method 6. Preliminary bioassay results show that these title compounds possess good insecticidal activity at the different dosages. For example, compounds **IIb**, **IId**, **IIh,** and **IIi** exhibited 100% inhibitory rates against aphides at the dosage of 250 mg/L. Moreover, these four compounds also showed good insecticidal activity at the low concentration (50 mg/L). Table 1 showed that the insecticidal activity of compounds **II** depended on the nature of substituent groups in the benzene rings; compounds containing 4-chloro and 2,4-dichloro groups displayed good insectcidal activities. However, the chloro group in the pyridine moiety has less effect on their biological activities. Further structure-activity relationships are under investigation. The results of insecticidal activities are listed in Table I.

In conclusion, we synthesized some new *O*-aryl, *O*-ethyl, *N*-(substitutedpyridin-methyl) amidophosphoric acid esters. The results of the preliminary bioassays indicated that most of the title compounds possess good insecticidal activity.

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. ^{1}H NMR and ^{31}P{^{1}H} NMR spectra were recorded with a Varian MERCURY-PLUS400 spectrometer with TMS and 85% H_3PO_4 as the internal and external reference, respectively, and $CDCl_3$ as the solvent. Mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method. IR spectra were measured by a Nicolet NEXUS470 spectrometer. Elemental analyses were performed with a Vario EL **III** CHNSO elementary analyzer. The reagents and solvents were available commercially and purified according to conventional methods before use. 5-(aminomethyl)-

TABLE I Insecticidal Activity of IIa~IIi Against Aphides: (Death Rate %)

%Dosage	IIa	IIb	IIc	IId	IIe	IIf	IIg	IIh	IIi
250 mg/L	35.6	100	68.5	100	53.1	40.7	71.3	100	100
50 mg/L	—	95.6	—	100	—	—	—	81.3	76.4

2-chloro-pyridine and *O*-aryl, *O*-ethyl, phosphoryl chloride **I** were prepared according to the reported methods,[7,8] respectively.

General Procedure for the Synthesis of O-aryl, O-ethyl, N-(substitutedpyridin-methyl) Amidophosphoric Acid Esters

Compound **I** (2 mmol), triethylamine (0.3 g, 3 mmol) and dichloromethane (10 mL) were added to a 50 mL three-necked reaction flask, after cooling to 5^{o}C, the solution of 3-(aminomethyl)pyridine or 5-(aminomethyl)-2-chloro-pyridine (2 mmol) in dichloromethane (5 mL) was added dropwise slowly, the mixture was allowed to stir at room temperature for 5–6 h, until the reaction was finished (monitored by TLC). The work-up involved filtration and drying over anhydrous magnesium sulfate, the crude product was purified by flash column chromatography on a silica gel with a mixture of petroleum ether and acetone (4:1, v/v) as the eluent, giving compounds **IIa**∼**IIi** as a yellow oil or solid.

O-ethyl, *O*-phenyl, *N*-(pyridin-3-yl-methyl) amidophosphoric acid ester (**IIa**): an orange oil, yield 73%; IR (KBr) υ: 3216 (N-H), 1560 (C=N), 1390–1566 (C=C), 1236 (P=O), 950 (P-O-C); $\{^1H\}$NMR ($CDCl_3$, 400 MHz) δ:1.30 (t, $J = 6.2$ Hz, 3H, CH_3), 1.72 (sb, 1H, NH), 4.08–4.16 (m, 4H, $2CH_2$), 7.13–7.28 (m, 6H, Ar-H, Py-H), 7.28 (d,$J = 8.4$ Hz, 1H, Py-H), 7.63 (d, $J = 7.6$ Hz, 1H, Py-H), 8.51 (s, 1H, Py-H); $^{31}P\{^1H\}$NMR ($CDCl_3$, 162 MHz) δ:3.05 (s); MS (70eV) *m/z* (%): 294 (22.9), 292 (M^+, 66.9), 263 (34.1), 245 (4.4), 183 (29.1), 107 (100), 92 (55.5); Anal. Calcd. for $C_{14}H_{17}N_2O_3P$: C 57.53, H 5.86, N 9.58; found C 57.26, H 5.65, N 9.37.

O-ethyl, *O*-(4-chlorophenyl), *N*-(2-chloropyridin-5-yl-methyl) amidophosphoric acid ester (**IIb**), an orange oil, yield 68%; IR (KBr) υ: 3219 (N-H), 1589 (C=N), 1393–1569 (C=C), 1233 (P=O), 955 (P-O-C); $\{^1H\}$NMR ($CDCl_3$, 400 MHz) δ: 1.32 (t, $J = 6.8$ Hz, 3H,CH_3), 1.78 (sb, 1H, NH), 4.09–4.15 (m, 4H, $2CH_2$), 7.08–7.28 (m, 5H, Ar-H, Py-H), 7.59 (d, $J = 7.6$ Hz, 1H, Py-H), 8.30 (s, 1H, Py-H); $^{31}P\{^1H\}$NMR ($CDCl_3$, 162 MHz) δ:3.03 (s); MS (70eV) *m/z* (%): 362 (2.2), 360 (M^+, 10.5), 317 (5.3), 238 (4.3), 190 (14.0), 127 (100), 111 (41.5), 99 (86), 75 (45.5); Anal. Calcd. for $C_{14}H_{15}Cl_2N_2O_3P$: C 46.56, H 4.19, N 7.76; found C 46.40, H 4.31, N 7.52.

O-ethyl, *O*-(2-methylphenyl), *N*-(2-chloropyridin-5-yl-methyl) amidophosphoric acid ester (**IIc**), an orange oil, yield 63%; IR (KBr) υ: 3211 (N-H), 1588 (C=N), 1392–1569 (C=C), 1233 (P=O), 947 (P-O-C); ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (t, $J = 6.0$ Hz, 3H, CH_3), 2.21 (s, 3H, Ar-CH_3), 2.60 (sb, 1H, NH), 4.07–4.10 (m, 2H,CH_2), 4.13 (dd, $J =$ 10.8 Hz, $J = 7.6$ Hz, 2H, CH_2N), 7.03–7.58 (m, 5H, Ar-H, Py-H), 7.60

(d, $J = 8.4$ Hz, 1H, Py-H), 8.28 (s, 1H, Py-H); $^{31}P\{^{1}H\}$NMR ($CDCl_3$, 162 MHz) δ:3.40 (s); Anal. calcd. for $C_{15}H_{18}ClN_2O_3P$: C 52.87, H 5.32, N 8.22; found C 52.94, H 5.20, N 8.17.

O-ethyl, *O*-(2,4-dichlorophenyl), *N*-(2-chloropyridin-5-yl-methyl) amidophosphoric acid ester (**IId**), an orange solid, m.p. 52–53°C, yield 66%; IR (KBr) υ: 3208 (N-H), 1579 (C=N), 1392–1578 (C=C), 1240 (P=O), 939 (P-O-C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (t, $J = 7.2$ Hz, 3H,CH_3), 4.10 (dd, $J = 10.4$ Hz, $J = 24.4$ Hz, 1H, NH), 4.18–4.22 (m, 4H,2CH_2), 7.18 (d, $J = 8.4$ Hz, 1H, Py-H), 7.24 (d, $J = 8.0$ Hz, 1H, Ar-H), 7.39–7.42 (m, 2H, Ar-H), 7.61 (d, $J = 8.0$ Hz, 1H, Py-H), 8.31 (s, 1H, Py-H); $^{31}P\{^{1}H\}$NMR ($CDCl_3$, 162 MHz) δ:3.05 (s); MS (70eV) m/z (%): 399 (14), 396 (31.1), 394 (M^+, 42.8), 359 (43.6), 330 (25.5), 284 (25.2), 205 (16.1), 140 (97.2), 125 (100), 89 (24.4), 75 (7.1); Anal. calcd. for $C_{14}H_{14}Cl_3N_2O_3P$: C 42.50, H 3.57, N 7.08; found C 42.09, H 3.25, N 7.19.

O-ethyl, *O*-(2,3,4,5,6-pentachlorophenyl), *N*-(2-chloropyridin-5-yl-methyl) amidophosphoric acid ester (**IIe**), an orange solid, m.p. 43–45°C, yield 73%; IR (KBr) υ: 3219 (N-H), 1580 (C=N), 1390-1566 (C=C), 1239 (P=O), 954 (P-O-C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (t, $J = 5.8$ Hz, 3H, CH_3), 3.90–3.94 (m, 2H,CH_2), 4.05 (d, $J = 11.0$ Hz, 2H, CH_2N), 4.22 (sb, 1H, NH), 7.30 (d, $J = 8.0$ Hz, 1H, Py-H), 7.67 (d, $J = 8.0$ Hz, 1H, Py-H), 8.34 (s, 1H, Py-H); $^{31}P\{^{1}H\}$NMR ($CDCl_3$, 162 MHz) δ: 3.04 (s); Anal. calcd. for $C_{14}H_{11}Cl_6N_2O_3P$: C 33.70, H 2.22, N 5.61; found C 33.61, H 2.17, N 5.78.

O-ethyl, *O*-(2-methylphenyl), *N*-(pyridin-3-yl-methyl) amidophosphoric acid ester (**IIf**): an orange oil, yield 75%; IR (KBr) υ: 3219 (N-H), 1588 (C=N), 1389–1578 (C=C), 1241 (P=O), 948 (P-O-C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (t, $J = 5.8$ Hz, 3H,CH_3), 3.28 (sb, 1H, NH), 4.06–4.08 (m, 2H,CH_2), 4.11 (d, $J = 11.0$ Hz, 2H, CH_2N), 7.08–7.30 (m, 5H, Ar-H, Py-H), 7.35 (d, $J = 7.8$ Hz, 1H, Py-H), 7.70 (d, $J = 7.8$ Hz, 1H, Py-H), 8.55 (s, 1H, Py-H); $^{31}P\{^{1}H\}$NMR ($CDCl_3$, 162 MHz) δ: 3.05 (s); Anal. calcd. for $C_{15}H_{19}N_2O_3P$: C 58.82, H 6.25, N 9.15; found C 58.71, H 6.03, N 9.31.

O-ethyl, *O*-(2,3,4,5,6-pentachlorophenyl), *N*-(pyridin-3-yl-methyl) amidophosphoric acid ester (**IIg**): an orange oil, yield 68%; IR (KBr) υ: 3215 (N-H), 1587 (C=N), 1398–1575 (C=C), 1232 (P=O), 949 (P-O-C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (t, $J = 5.4$ Hz, 3H,CH_3), 1.96 (sb, 1H, NH), 3.94-3.98 (m, 2H,CH_2), 4.10 (dd, $J = 11.4$ Hz, $J = 8.0$ Hz, 2H, CH_2N), 7.28 (d, $J = 8.2$ Hz, 1H, Py-H), 7.34 (d, $J = 8.2$ Hz, 1H, Py-H), 7.59 (d, $J = 7.4$ Hz, 1H, Py-H), 8.36 (s, 1H, Py-H); $^{31}P\{^{1}H\}$NMR ($CDCl_3$, 162 MHz) δ: 3.04 (s); Anal. calcd. for $C_{14}H_{12}Cl_5N_2O_3P$: C 36.20, H 2.60, N 6.03; found C 36.36, H 2.44, N 5.89.

O-ethyl, *O*-(4-chlorophenyl), *N*-(pyridin-3-yl-methyl) amidophosphoric acid ester (**IIh**): a light yellow oil, yield 75%; IR (KBr) υ: 3225 (N-H), 1588 (C=N), 1380–1581 (C=C), 1246 (P=O), 955 (P-O-C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (t, $J = 5.4$ Hz, 3H,CH_3), 2.10 (sb, 1H, NH), 4.05–4.08 (m, 2H,CH_2), 4.13 (dd, $J = 11.6$ Hz, $J = 7.6$ Hz, 2H, CH_2N), 7.08–7.27 (m, 5H, Ar-H, Py-H), 7.58 (d, $J = 7.6$ Hz, 1H, Py-H), 8.47 (d, $J = 4.8$ Hz, 1H, Py-H), 8.50 (s, 1H, Py-H); ^{31}P{^{1}H}NMR ($CDCl_3$, 162 MHz) δ: 3.05 (s); Anal. calcd. for $C_{14}H_{16}ClN_2O_3P$: C 51.47, H 4.94, N 8.57; found C 51.59, H 5.12, N 8.40.

O-ethyl, *O*-(2,4-dichlorophenyl), *N*-(pyridin-3-yl-methyl) amidophosphoric acid ester (**IIi**): a light yellow solid, m.p. 47–48^{o}C, yield 65%; IR (KBr) υ: 3223 (N-H), 1587 (C=N), 1389–1568 (C=C), 1248 (P=O), 953 (P-O-C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (t, $J = 5.4$ Hz, 3H,CH_3), 3.96 (s, 1H, NH), 4.01–4.05 (m, 2H,CH_2), 4.23 (dd, $J = 11.2$ Hz, $J = 8.0$ Hz, 2H, CH_2N), 7.17–7.44 (m, 4H, Ar-H, Py-H), 7.63 (d, $J = 7.6$ Hz, 1H, Py-H), 8.50 (d, $J = 7.6$ Hz, 1H, Py-H), 8.53 (s, 1H, Py-H); ^{31}P{^{1}H}NMR ($CDCl_3$, 162 MHz) δ: 3.00 (s); Anal. calcd. for $C_{14}H_{15}Cl_2N_2O_3P$: C 46.56, H 4.19, N 7.76; found C 46.39, H 4.13, N 7.95.

Insecticidal Bioassay Method Against Aphis by Dipping

Two cucumber leaves *ca*. 8 cm in diameter were dipped into the distilled water solution of the various concentrations of the test compound for a few seconds until the leaf surface was wet. After drying, the leaves were place on soil in a pet cup. Ten 2nd-instar larvae were released into the cup. The cup was covered with a lid and stored at 25°C, 50–55% relative humidity (RH), and 14 h light/10 h dark for 5 days. The mortality was assessed after treatment. The test was run three times, the results were averaged, 0 means no effect, and 100% means excellent insecticidal activity, and given as death rate in Table I.

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