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Synthesis and Herbicidal Activity of Isoxazole-Substituted 1-Aminoethylphosphonates and 1-Hydroxyethylphosphonates

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Abstract: Isoxazole-substituted 1-aminoethyl- and 1-hydroxyethylphosphonates were synthesized by a multi-step procedure and were screened for herbicidal activity against *Lepidium sativum* L. and *Cucumis sativus* L. All the synthesized compounds exhibited notable herbicidal activity.

1 INTRODUCTION

Compounds containing the isoxazole ring have been shown to display diverse and useful biological properties. Examples are commercially available herbicides isouron (Fig. 1, **1**) and isoxaben (**2**) and the fungicide hymexazol (**3**).[1]

A wide variety of phosphonic acid derivatives are also known to have extremely potent biological activity.[2,3]

We have prepared a novel series of compounds which incorporate both of these chemical moieties. The resulting isoxazole-substituted 1-aminoethylphosphonates (**4**) and 1-hydroxyethylphosphonates (**5**) were screened for their herbicidal activity against *Lepidium sativum* L. (cress) and *Cucumis sativus* L. (cucumber).

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2 EXPERIMENTAL METHODS

2.1 Chemical syntheses

Compounds **4**, **5** and **6** were synthesized by means of the multi-step procedure outlined in Fig. 2.

The structures of all the synthesized compounds were supported by their infrared and proton magnetic resonance ([^{1}H]NMR) spectra, as well as by elemental analyses. [^{1}H]NMR spectra were determined in deuterochloroform with tetramethylsilane as internal standard.

Oximes of aromatic aldehydes were prepared according to a standard procedure.[4]

2.1.1 *Chlorooximes* (**8**) *of aromatic aldehydes*

These compounds were prepared by the modification of the described procedure.[5]

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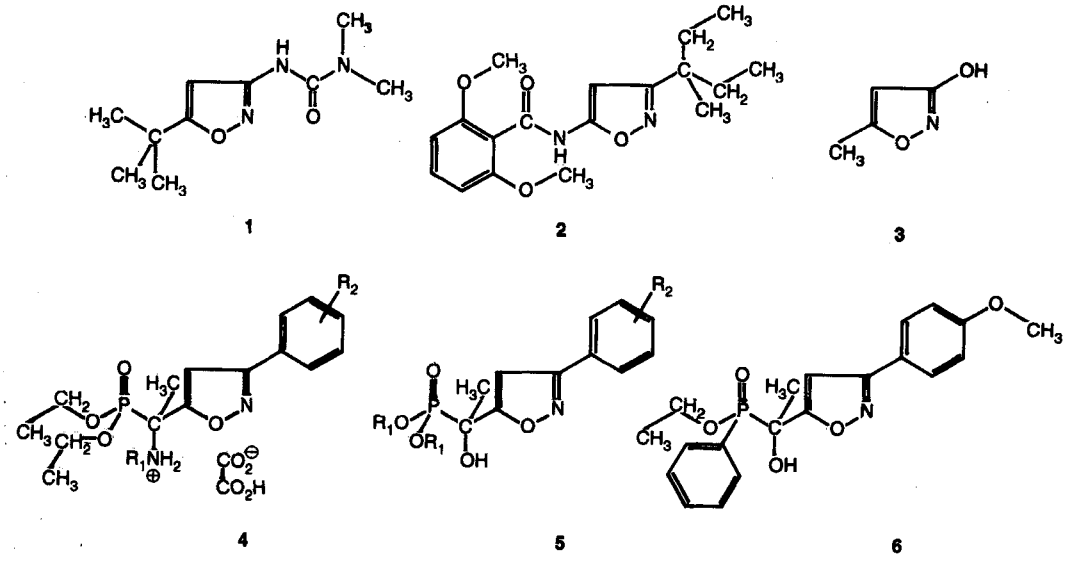

Fig. 1. Isouron (1); isoxaben (2); hymexazol (3) and isoxazole-substituted amino (4) and hydroxyethylphosphonates (5) and ethyl 1-hydroxy-1-[3-(4-methoxyphenyl)isoxazol-5-yl]ethyl (phenyl)phosphinate (6).

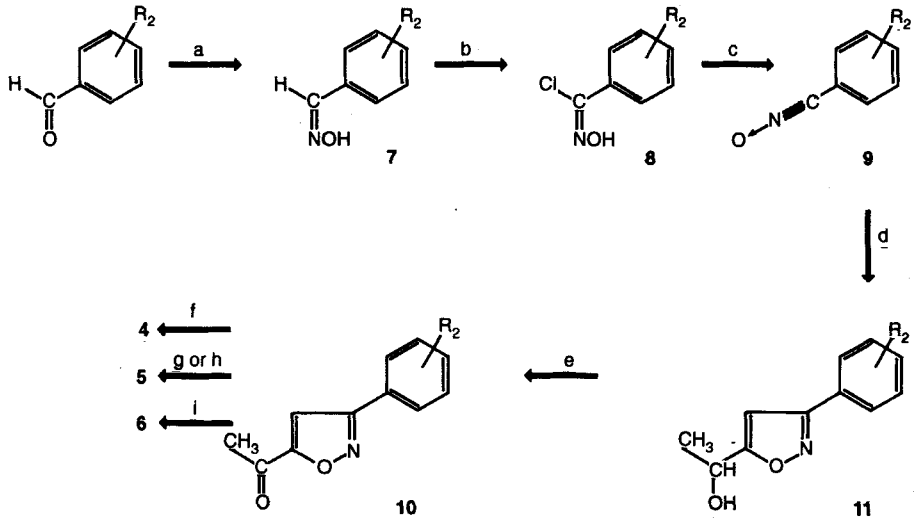

Fig. 2. Synthesis of compounds 4, 5 and 6. *Reagents and conditions:* (a) NH_2OH HCl, C_2H_5OH, H_2O, r.t; (b) *N*-chlorosuccinimide, DMF, 45–50°C; (c) triethylamine, diethyl ether; (d) 3-butyn-2-ol; (e) CrO_3-pyridine adduct, CH_2Cl_2; (f) R_1NH_2, $AlCl_3$, $(C_2H_5O)_2P(H)O$; (g) $(C_2H_2O)_2P(H)O$, triethylamine, toluene; (h) $(R_1O)_2P(H)O$, KF-alumina, toluene; (i) $(C_2H_5O)(C_6H_5)P(H)O$, KF-alumina, toluene.

To the solution of oxime (7) (0·4 mol) in *N*,*N*-dimethylformamide (335 ml) *N*-chlorosuccinimide (0·4 mol) was added in small portions, maintaining the temperature at 40–50°C. The mixture was then cooled to room temperature and poured onto a mixture of water and ice (1000 ml). The product was then extracted into diethyl ether (2 × 200 ml) and the ethereal solution dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave products of satisfactory purity in 72–94 % yields. They were used directly in the cycloaddition step of the synthesis.

2.1.2 *Cycloaddition reaction*

The *N*-oxides of aromatic nitriles (9) were generated *in situ* by the action of triethylamine on the chlorooxime (8) and then immediately reacted with 3-butyn-2-ol. As a rule, nitrile oxides react with monosubstituted alkynes regioselectively via 1,3-cycloaddition to give 5-substituted isoxazoles.[6]

Thus, chlorooxime (8) (0·35 mol) was dissolved in diethyl ether (500 ml) and 3-butyn-2-ol (0·35 mol) was added dropwise. The reaction mixture was cooled in an ice–water bath and triethylamine (0·44 mol) added

dropwise maintaining the temperature below 0°C. The mixture was then left overnight in the bath. After addition of water (350 ml) the ethereal layer was separated. The aqueous layer was additionally extracted with diethyl ether (2 × 50 ml) and the combined ethereal layers dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure yielded a brown solid which was purified by successive washings with toluene. In this manner alcohols (**10**) of satisfactory purity were obtained.

10a. (R_2 = *p*-CH_3O-): 50 % yield; m.p. 71–73°C; [^{1}H]NMR: δ [ppm] = 1·59 (d, J = 6·5 Hz, 3H, CH_3CH); 3·82 (bs, 1H, OH); 3·85 (s, 3H, OCH_3); 5·00 (q, J = 6·5 Hz, 1 Hz, 1H, CHOH); 6·42 (s, 1H, isoxazole proton); 7·38 (AA'BB' system, J = 8·0 Hz, 4H, C_6H_4).

10b. (R_2 = *p*-Br): 45 % yield; m.p. 85–87°C; [^{1}H]NMR: δ [ppm] = 1·57 (d, J = 6·5 Hz, 3H, CH_3); 4·19 (bs, 1H, OH); 5·01 (q, J = 6·5 Hz, 1H, CHOH); 6·46 (s, 1H, isoxazole proton); 7·3–7·7 (m, 4H, C_6H_4).

10c. (R_2 = *o*-Cl): yield 48 %, oil. [^{1}H]NMR: δ [ppm] = 1·56 (d, J = 6·5 Hz, 3H, CH_3); 4·07 (bs, 1H, OH); 5·00 (q, J = 6·6 Hz, 1H, CHOH); 6·62 (s, 1H, isoxazole proton); 7·3–7·7 (m, 4H C_6H_4).

2.1.3 *Oxidation of alcohols* (**10**)

Alcohols (**10**) were oxidized using a modification of a standard procedure.[7]

Thus, to the mixture of dry methylene chloride (150 ml) and dry pyridine (0·06 mol), chromium trioxide (0·3 mol) was added portionwise, cooling the reaction mixture in an ice-bath and stirring until all the oxide dissolved. Then the appropriate alcohol (**10**) (0·05 mol), dissolved in methylene chloride (30 ml), was added dropwise. In order to complete the reaction the mixture was left overnight at room temperature. The solvent was decanted and the dense residue washed with diethyl ether (2 × 50 ml). The combined organic layer was washed successively with: potassium hydroxide solution (50 g litre^{-1}; 4 × 100 ml), water (100 ml), hydrochloric acid (50 g litre^{-1}; 4 × 100 ml), water (100 ml), sodium hydrogen carbonate solution (50 g litre^{-1}; 100 ml) and saturated sodium chloride solution (100 ml). Removal of the solvent yielded chromatographically pure ketones (**11**).

11a (R_2 = *p*-OCH_3): 86 % yield, m.p. 120–122°C;
11b (R_2 = *p*-Br): 83 % yield, m.p. 157–160°C;
11c (R_2 = *o*-Cl): 86 % yield, oil.

2.1.4 *Synthesis of diethyl 1-amino-1-(3-phenylisoxazol-5-yl)ethylphosphonates* (**4**)

Ketone (**11**) (0·005 mol) was dissolved in toluene (10 ml) and amine (0·005 mol) was added, followed by addition of magnesium sulfate (1 g) and catalytic amounts of anhydrous aluminium chloride (20 mg). The mixture was then heated under reflux for 4–6 h, until all the ketone had disappeared (as indicated by TLC on silica-gel coated plates using toluene-ethyl acetate (1 + 1 by volume) as eluent). Then diethyl phosphonate (0·005 mol) was added followed by the next portion of aluminium chloride (50 mg). The mixture was heated under reflux for 2·5 h, following the course of reaction by means of TLC (as indicated above). After cooling to room temperature catalysts were removed by filtration through a thin layer of silica gel, the solvent was removed under reduced pressure and the product isolated as the oxalate salt. Thus, it was dissolved in dry diethyl ether (10 ml) and a solution of anhydrous oxalic acid (0·005 mol) in dry ether (10 ml) added. The precipitate was collected by filtration and washed with ether (2 × 4 ml).

Yields and melting points of the oxalates obtained are given in Table 1.

TABLE 1
Diethyl 1-amino-1-(3-phenylisoxazol-5-yl)ethylphosphonate Oxalates (**4**)

Compound	*Structure*		*Yield* (%)	*m.p.* (°C)
	R_1	R_2		
4a	$(CH_3)_2CHCH_2$-	*p*-Br	30	155–157
4b	$CH_3(CH_2)_3$-	*p*-Br	33	130–133
4c	$(CH_3)_2CHCH_2$-	*p*-CH_3O-	19	148–151
4d	$CH_3(CH_2)_3$-	*p*-CH_3O-	39	semisolid
4e	$(CH_3)_2CHCH_2$-	*o*-Cl	33	144–146
4f	$CH_3(CH_2)_3$-	*o*-Cl	25	116–118

2.1.5 *Synthesis of diethyl 1-hydroxy-1-(3-phenylisoxazol-5-yl)-ethylphosphonates* (**5**, $R_1 = C_2H_5$); *Method A*

Ketone **11** (0·005 mol) was dissolved in toluene (15 ml) and diethyl phosphonate was added (0·005 mol) followed by dropwise addition of triethylamine (0·01 mol). The reaction mixture was left at room temperature for 4 h. Removal of toluene gave chromatographically pure hydroxyphosphonates (**5**) as dense oils. The yields are given in Table 2.

2.1.6 *Synthesis of dialkyl 1-hydroxy-1-(3-phenylisoxazol-5-yl)-ethylphosphonates* (**5**); *Method B*

These compounds were prepared using a modification of a standard procedure.[8]

To a solution of ketone (**11**) (0·005 mol) and dialkyl phosphonate (0·005 mol) in toluene (50 ml), potassium fluoride (5 g) and basic alumina (5 g) were added. The

TABLE 2

Dialkyl 1-hydroxy-1-(3-phenylisoxazol-5-yl)ethylphosphonates (**5**) and Ethyl 1-hydroxy-1-[3-(4-methoxyphenyl)isoxazol-5-yl]ethyl(phenyl)-phosphinate (**6**)

Compound	*Structure*		*Method*	*Yield* (%)	*m.p.* (°C)
	R_1	R_2			
5a	C_2H_5	*p*-Br	A	79	oil
5b	C_2H_5	*p*-CH_3O	A	83	oil
			B	87	
5c	C_2H_5	*o*-Cl	A	84	oil
5d	$(CH_3)_2CH$	*p*-CH_3O	B	82	oil
5e	$CH_3CH_2CH_2$	*p*-CH_3O	B	80	oil
5f	$CH_3(CH_2)_{15}$	*p*-CH_3O	A	16	78–80
			B	76	
5g	$C_6H_5CH_2$	*p*-CH_3O	B	77	60–63
6			B	82	115–117

mixture was then heated under reflux for 3 h, solid material was filtered off and the solvent removed under reduced pressure. This procedure yielded chromatographically pure hydroxyphosphonates (**5**).

In this manner compound **6** was also obtained using ethyl phenylphosphonite as the substrate.

The yields and melting points of compounds **5** and **6** are given in Table 2.

2.2 Biological assays

The herbicidal activity of the synthesized compounds was evaluated in two sets of experiments on *L. sativum* and *C. sativus* var *Wisconsin*. Each experiment was replicated four times.

2.2.1 *Effects of compounds* **4**, **5** *and* **6** *on the growth of* Lepidium sativum

Groups of 40 seeds of *L. sativum* were placed in Petri dishes (9 cm) filled with cotton wool, and kept damp by occasional spraying with distilled water until germination occurred (two days, 4–6 mm total length of the plants). A solution composed of dimethyl sulfoxide (0·5 ml) in distilled water (99·5 ml) (control) or a solution of the test compound in dimethyl sulfoxide (0·5 ml) dispersed in water (99·5 ml) to give final concentrations of 0·05, 0·15, 0·5 or 1·5 mM; 10 ml each) was then applied to the roots. Plants were grown for seven days at 25°C with a 9-h day length under fluorescent tubes (2500–3000 lux at plant level), and the lengths of the roots and shoots then measured.

2.2.2 *Test on* Cucumis sativus

Seeds were germinated at 33°C for 1·5 days in darkness. Groups of 10 uniform seedlings (7–8 mm total length) were transfered to Petri dishes (9 cm) lined with two discs of Whatman No 2 filter paper wetted with a solution of dimethyl sulfoxide (0·5 ml) in distilled water (99·5 ml) (control) or a solution of the test compound in dimethyl sulfoxide (0·5 ml) dispersed in water (99·5 ml) to give final concentrations of 0·05, 0·15, 0·5 or 1·5 mM; 10 ml each). The plants were grown at 25°C with a 12-h day length for nine days under fluorescent tubes (2500–3000 lux at plant level). Separated roots and hypocotyls were weighed independently on a torsion balance.

2.3 Statistical treatment

Dixon's Q-test was used to reject the unreasonable results. The means for samples and controls were compared by testing the null hypothesis at the 5 % significance level.[9]

Results statistically not significant are marked in tables as 'N'.

3 RESULTS AND DISCUSSION

The multi-step procedure used for the preparation of ketones **11**, the key substrates for the synthesis of herbicidal phosphonates **4**, **5** and **6**, is outlined in Fig. 2. These ketones were easily converted into dialkyl 1-hydroxy-1-(3-phenylisoxazol-5-yl)ethylphosphonates (**5**) by dialkyl phosphonate addition catalyzed either by triethylamine or by potassium fluoride/alumina mixture. We recommend the use of the latter catalyst since it gave the desired products in good yield and high purity. The low yields of the conversion of ketones (**11**) into diethyl 1-amino-1-(3-phenyl-isoxazol-5-yl)ethylphosphonates (**4**) by the Kabachnik–Medved approach[10] are not surprising considering the complex character of this reaction.[11]

As seen from Table 3, all the synthesized compounds, including ketone **11a**, displayed significant activity against *L. sativum* if applied at a concentration of 1·5 mM. Applied in lower concentrations they were, however, considerably less active than the herbicide glyphosate.

Reflecting the mode of application, their influence on the growth of plant roots was usually more pronounced than their action on shoots. Many of the compounds studied influenced the growth of *L. sativum* shoots more strongly than did glyphosate, with compounds **5d**, **5e** and **5g** being the most active at lower concentrations and **5a**, **5b**, **5c** and **6** at higher concentrations.

Results presented in Table 4 also show *C. sativus* to be more tolerant to the action of the compounds studied than to glyphosate. Considering their influence on root growth, the compounds **4b**, **4e**, **4f**, **5a**, **5b** and **5e** appeared to be nearly equipotent to glyphosate if applied at a concentration of 1·5 mM. Lowering the concentration of the test compounds resulted in a sharp decrease in their herbicidal activity towards *C. sativus* roots. Most of the

TABLE 3
Effect of Isoxazole-Substituted Phosphonates **4**, **5**, Phosphonite **6** and ketone **11a** on the Growth of *Lepidium sativum*, Measured as Percentage Change in Root and Shoot Length Compared to that of the Control

Compound	*Root or shoot*	*Concentration (mM)*			
		0·05	*0·15*	*0·5*	*1·5*
Glyphosate[a]	R	−86		−90	−93
	S	−13		−20	−44
4a	R	N[b]	N	N	−95
	S	N	N	N	−34
4b	R	N	N	N	−94
	S	N	N	N	−40
4c	R	N	N	N	−94
	S	N	N	N	−30
4d	R	N	N	N	−96
	S	N	N	−38	−67
4e	R	N	N	N	−95
	S	N	N	N	−34
4f	R	N	N	N	−97
	S	N	N	N	−84
5a	R	N	N	N	−95
	S	N	N	−24	−97
5b	R	N	N	N	−97
	S	N	N	−22	−97
5c	R	N	N	N	−100
	S	N	−11	−33	−100
5d	R	N	N	−34	−58
	S	−16	−28	−48	−64
5e	R	N	N	−47	−92
	S	N	−25	−58	−72
5f	R	N	N	N	−59
	S	N	N	−12	−61
5g	R	N	N	−60	−80
	S	N	−15	−63	−72
6	R	N	N	−78	−100
	S	N	−15	−63	−100
11a	R	N	N	−36	−71
	S	N	N	−19	−50

[a] Data taken from Ref. 11.
[b] N = not significantly different from control.

TABLE 4
Effect of Isoxazole-Substituted Phosphonates **4**, **5**, Phosphonite **6** and ketone **11a** on the Growth of *Cucumis sativus*, Measured as Percentage Change in Root and Hypocotyl Weight Compared to that of the Control

Compound	*Root or hypocotyl*	*Concentration (mM)*			
		0·05	*0·15*	*0·5*	*1·5*
Glyphosate[a]	R	−60		−78	−84
	S	N[b]		N	−22
4a	R	N	N	N	−54
	S	N	N	N	−28
4b	R	N	N	−32	−71
	S	−32	−26	−36	−44
4c	R	N	N	N	−54
	S	N	N	N	−17
4d	R	N	N	−26	−41
	S	N	N	−20	−37
4e	R	N	N	−38	−85
	S	N	N	N	N
4f	R	−17	−18	−24	−85
	S	N	N	−24	−29
5a	R	−12	−22	−30	−78
	S	N	N	−30	−51
5b	R	N	N	N	−70
	S	N	N	−25	−41
5d	R	+14	+22	N	−34
	S	N	−13	−22	−29
5e	R	N	N	−45	−87
	S	N	N	−32	−82
5f	R	N	N	−20	−66
	S	N	N	−27	−40
5g	R	+38	+18	+23	−31
	S	N	N	N	N
6	R	N	N	−33	−69
	S	N	−19	−28	−26
11a	R	N	+23	N	−28
	S	N	+12	N	−12

[a] Data taken from Ref. 11.
[b] N = not significantly different from control.

compounds studied, however, influenced the growth of *C. sativus* hypocotyl more strongly than did glyphosate. Plant growth promotion of roots treated with low doses of compounds **5d** and **5g** was also noted.

Based on the data presented in this paper it is not possible to draw any meaningful conclusions on structure–activity relationships for these isoxazole-substituted ethylphosphonates. However, compounds **4**, **5** and **6** may be recognized as promising leads for further studies.

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