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Plant-Growth-Regulating *N*-(Phosphonoacetyl)amines

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Abstract: A series of *N*-(phosphonacetyl)amine derivatives were synthesized and screened for plant-growth regulating activity on *Lepidium sativum* L. and *Cucumis sativus* L. Aromatic *N*-(phosphonoacetyl)amines, which may be considered as possible analogues of *N*-acylaniline herbicides obtained by replacement of their acyl group by the phosphonacetyl moiety, exhibited significant or moderate herbicidal activity. In contrast, *N*-(phosphonoacetyl)amino acids and *N*-(phosphonoacetyl)aminophosphonic acids promoted the growth of *L. sativum* and *C. sativus* roots.

1 INTRODUCTION

N-Acylanilines, e.g. alachlor (Fig. 1; **1**) and metolachlor (**2**), form a unique class of selective pre-emergent herbicides widely used in many agronomic crops.[1,2] They act as cell-division inhibitors, but the molecular mode of action of these compounds is not yet known.[3]

The replacement of a toxophoric group by another one is a well-established method for designing new active compounds. Thus, we report herein how the replacement of the chloroacetyl moiety in *N*-acylanilines by a phosphonoacetyl or a phosphonoformyl group influences the herbicidal properties of the resulting compounds **3** and **4**.

In order to gain more information for structure–activity relationship studies, we have also evaluated the plant-growth regulating activity of *N*-(phosphonoacetyl)-amino acids (**5**) and *N*-(phosphonoacetyl)aminophosphonates (**6**).

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2 EXPERIMENTAL METHODS

2.1 Syntheses

The structures of all the synthesized compounds were supported by their infrared and proton magnetic resonance spectra, as well as by elemental analyses.

2.1.1 Synthesis of N-(*phosphonoacetyl*)*amines* (**3**)

A solution of amine (0·05 mole) and triethylamine (0·05 mole) in dry chloroform (50 ml) was cooled in an ice bath and chloroacetyl chloride (0·055 mole) was added dropwise for 1 h. The reaction was completed by stirring the mixture for 2 h at room temperature, and the solution was then washed successively with: water (30 ml), hydrochloric acid solution (50 g litre^{-1}; 30 ml), water (30 ml), saturated sodium hydrogen carbonate solution (30 ml), water (30 ml) and saturated sodium chloride (30 ml). The resulting solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was recrystallized

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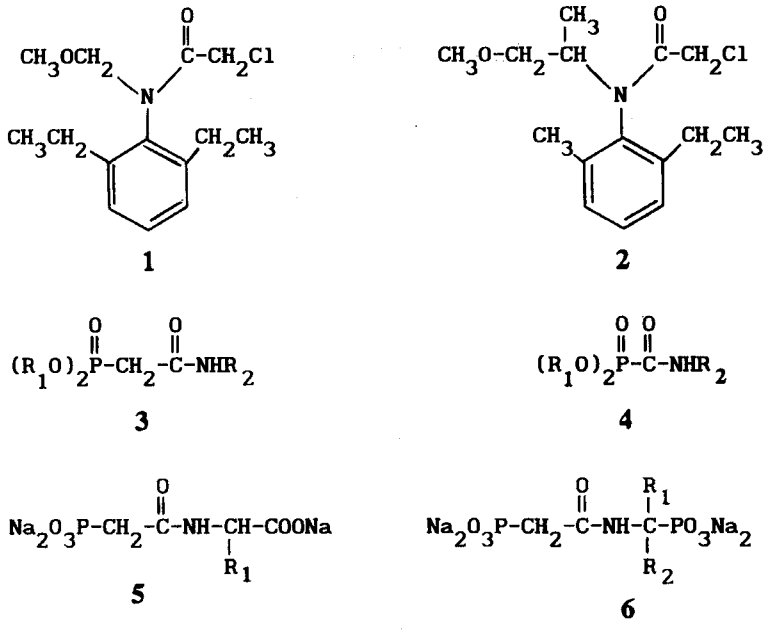


Fig. 1. Alachlor (**1**), metolachlor (**2**), *N*-(phosphonoacetyl)amines (**3**), *N*-(phosphonoformyl)amines (**4**), *N*-(phosphonoacetyl)amino acids (**5**), and *N*-(phosphonoacetyl)aminoalkylphosphonates (**6**).

from a mixture of ethyl acetate and hexane. *N*-(Chloroacetyl)amine was dissolved in triethyl phosphite (30 ml) and heated at 160–180°C for 2 h. The volatile components of the reaction mixture were then removed under reduced pressure and the product (**3**, $R_1 = C_2H_5$) was crystallized from a mixture of ethyl acetate (or diethyl ether) and hexane. The yields and melting points of diethyl *N*-(phosphonoacetyl)amines are given in Table 1.

In order to de-esterify **3**, the above product was dissolved in hydrogen bromide in glacial acetic acid (400 g litre^{-1}; 20 ml) and left overnight. Removal of the volatile components of the reaction mixture on a rotary evaporator yielded crude *N*-(phosphonoacetyl)amine (**3**, $R_1 = H$) which was purified by recrystallization either from glacial acetic acid or from a mixture of diethyl ether (or dioxane) and hexane. Yields and melting points of the resulting compounds are shown in Table 1.

2.1.2 *Synthesis of* N-(*phosphonoformyl*)*amines* (**4**)

A mixture of triethyl phosphonoformate (0·03 mole) and amine (0·05 mole) was left for 2 h at room temperature and then the mixture was dissolved in dry chloroform (30 ml) and washed successively with: water (30 ml), hydrochloric acid solution (50 g litre^{-1}; 30 ml), water (30 ml), saturated sodium hydrogen carbonate solution (30 ml), water (30 ml) and saturated sodium chloride (30 ml). Drying over anhydrous magnesium sulfate followed by removal of solvent under reduced pressure yielded a crude product (**4**, $R_1 = C_2H_5$) which was recrystallized from the mixture of ethyl acetate and hexane. This product was dissolved in hydrogen bromide in glacial acetic acid (400 g litre^{-1}; 20 ml) and left overnight at room temperature. Volatile components of the reaction mixture were then removed under reduced pressure and crude *N*-(phosphonoformyl)amine (**4**, $R_1 = H$) recrystallized from glacial acetic acid.

Melting points and yields of compounds **4** are given in Table 1.

2.1.3 *Synthesis of phosphonoacetic acid* (**7**)

Commercial triethyl phosphonoacetate (0·05 mole; Aldrich) was dissolved in concentrated hydrochloric acid (75 ml) and refluxed for 8 h. The solvent was removed under reduced pressure and crude product purified by crystallization from glacial acetic acid.

Compounds **5** and **6** were synthesized according to standard procedures and used in form of sodium salts which did not melt below 350°C.[4,5] Their yields are given in Tables 2 and 3.

2.2 Biological assays

The plant-growth regulating activity of the synthesized compounds was evaluated in two independent sets of experiments on *Lepidium sativum* L. and *Cucumis sativus* L. var. *Wisconsin*. Each experiment was replicated four times.

2.2.1 *Effects of* N-(*phosphonoacetyl*)*amines and* N-(*phosphonoformyl*)*amines 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 damped

TABLE 1
N-(Phosphonoacetyl)amines (**3**) and *N*-(Phosphonoformyl)amines (**4**)

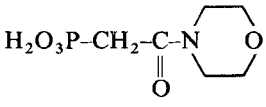
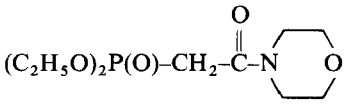
Compound	*Structure*		*Yield* (%)	*m.p.* (°C)
	R_1	R_2		
3a	H	H	70	160–163
3b	H	Cyclohexyl	63	176–177
3c	C_2H_5	Cyclohexyl	81	75–77
3d	H	C_6H_5	48	99–102
3e	C_2H_5	C_6H_5	84	55–56
3f	H	4-ClC_6H_4	52	183–185
3g	C_2H_5	4-ClC_6H_4	80	96–98
3h	H	2,4-$Cl_2C_6H_3$	58	193–196
3i	C_2H_5	2,4-$Cl_2C_6H_3$	76	71–72
3j	H	2-Naphthyl	49	188–190
3k	C_2H_5	2-Naphthyl	68	98–99
3l	C_2H_5	1-Naphthyl	71	89–90
3m			83	198–202
3n			68	oil
4a	H	$CH(CH_3)_2$	66	151–152
4b	C_2H_5	$CH_2C_6H_5$	36	63–65
4c	H	$CH_2C_6H_5$	78	181–183
7	$HOOC-CH_2-PO_3H_2$		93	138–140

TABLE 2
Disodium *N*-(Phosphonoacetyl)amino Acids (**5**)

Compound	*Structure* (R_1).	*Yield* (%)	*Ref. no.*
5a	CH_3[a]	85	4
5b	$CH_2C_6H_5$[a]	86	4
5c	$CH_2PO_3Na_2$[b]	7·5	5

[a] Amino acid of L configuration.
[b] Amino acid of DL configuration.

by occasional spraying with distilled water until germination occurred (two days). Distilled water (control) or aqueous solution of the test compound (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 using fluorescent tubes (2500–3000 lux at plant level). The lengths of the roots and shoots were 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 were transferred to Petri dishes (9 cm) lined with two discs of Whatman No 2 filter paper wetted with distilled water (control) or solutions of test compounds (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 9 days, using 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 unreasonable results. The means for samples and controls were compared by testing the null hypothesis at the 5 % significance level.[6]

Results statistically not significantly different from control are marked in tables as 'N'.

TABLE 3
N-(Phosphoneacetyl)aminoalkylphosphonic Acid Sodium Salts (**6**)

Compound	*Structure*[a]		*Yield* (%)	*Method*[b]	*Ref. no.*
	R_1	R_2			
6a	CH_3	CH_3	29	A	5
6b	H	Cyclopropyl	25·5	A	5
6c	H	Cyclobutyl	11	A	5
6d	H	Cyclopentyl	21	A	5
6e	H	Cyclohexyl	21	A	5
6f	H	$CH(CH_3)_2$	63	B	5
6g	H	$CH_2CH(CH_3)_2$	71	B	5
6h	H	$C(CH_3)_3$	14·5	A	5
6i	H	CH_2COONa	42	A	5
6j	H	CH_2CH_2COONa	25	A	5
6k	$-(CH_2)_4-$		22	A	5
6l	$-(CH_2)_5-$		57	C	
6m	$Na_2O_3P-CH_2-C(O)NHCH_2CH_2PO_3Na_2$		20	A	5
6n	$Na_2O_3P-CH_2-C(O)NH-CH_2-\underset{\underset{ONa}{\vert}}{\overset{\overset{O}{\Vert}}{P}}-C_2H_5$		61·5	A	5
6o	$Na_2O_3P-CH_2-C(O)NH-\underset{\underset{C_6H_5}{\vert}}{CH}-PO_2Na_2$		55	A	5
6p	$(C_2H_5O)_2P(O)CH_2C(O)NH$  $P(O)(OC_2H_5)_2$		63	C	

[a] Racemic mixtures of aminoalkylphosphonates.
[b] Method: A—by reaction of diethyl *N*-(chloroacetyl)aminoalkylphosphonate with triethyl phosphite followed by hydrolysis;
B—by reaction of diphenyl *N*-(chloroacetyl)aminoalkylphosphonate with triethyl phosphite followed by hydrolysis;
C—by reaction of diethyl phosphonoacetyl chloride with diethyl aminoalkylphosphonate followed by hydrolysis.

3 RESULTS AND DISCUSSION

For several years we have been engaged in the synthesis of organophosphonates and evaluation of their plant growth regulatory properties.[7-15] In this paper we report such an activity found for the various *N*-(phosphonoacetyl)amines.

In order to discover the most active compounds, their influence on growth characteristics of *Lepidium sativum* was studied. Data shown in Table 4 concern those compounds which exhibited either significant herbicidal or stimulatory action towards *L. sativum*. Compounds not included in Table 4 were either weakly active (less than 20% of inhibition or promotion of growth) or completely inactive. As seen from Table 4 strong herbicidal properties were found for compounds **3d**, **3f**, **3k**, **4a**. Diethyl *N*-(phosphonoacetyl)-2-naphthylamine (**3k**) was the most active, with similar potency to alachlor. Three of these compounds represent aromatic *N*-(phosphonoacetyl)amines (**3d**, **3f** and **3k**). Other aromatic *N*-(phosphonoacetyl)amines were either moderately or weakly herbicidal (**3g–3j** and **3l**). Compound **39** additionally showed a growth promotion effect on shoots at lower doses, whilst **3e** caused promotion of the test plant growth roots.

Herbicidal activity of phosphonoacetamide (compound **3a**) is not surprising since its herbicidal properties have been already reported.[16]

Our attempts to synthesize aromatic *N*-(phosphonoformyl)amines failed and thus our study is limited to the derivatives of aliphatic amines (**4a–4c**). Significant growth inhibition found for compound **4a** indicates that the search for herbicides within this class of compound may also be fruitful.

Compounds **5** and **6** showed responses at a range of doses from no activity to strong root-growth promotion. The only exceptions were compounds **6f** and **6h** which were moderately herbicidal.

TABLE 4
Effect of *N*-(Phosphonoacetyl)amines and *N*-(Phosphonoformyl)amines on the Growth of *Lepidium sativum*

Compound	*Root or Shoot*	*Change in root or shoot length (%)*			
		Concentration (mM)			
		0·05	*0·15*	*0·5*	*1·5*
Alachlor	R	−52	−55	−57	−62
	S	−16	−28	−33	−30
3a	R	N[a]	−18	−30	−65
	S	N	N	N	N
3d	R	N	−17	−67	−92
	S	N	N	−27	−58
3e	R	+40	+26	+18	N
	S	N	N	N	N
3f	R	+28	N	−12	−90
	S	+16	N	N	−24
3g	R	−17	−10	−10	−32
	S	+27	+17	+12	−10
3h	R	−15	−25	−27	−37
	S	N	N	N	N
3i	R	N	N	−13	−20
	S	N	N	−10	−17
3j	R	N	−13	−24	−38
	S	N	N	−10	−15
3k	R	−63	−65	−67	−78
	S	N	N	N	−26
3l	R	N	N	−17	−20
	S	N	N	N	−13
4a	R	N	N	−31	−71
	S	N	N	N	−14
4b	R	−20	−20	−25	−27
	S	N	N	N	N
4c	R	N	N	−17	−20
	S	N	N	N	−14
5a	R	+48	+48	+64	+62
	S	+28	+13	N	N
5b	R	+33	+31	N	N
	S	+13	+8	N	N
5c	R	+17	+37	+50	+25
	S	N	N	N	+35
6a	R	+29	+27	+50	N
	S	+20	+10	+10	+10
6d	R	+17	+43	+20	+21
	S	+23	+18	+14	N
6f	R	N	N	−43	−53
	S	N	N	−15	−12
6h	R	+20	−23	−23	−36
	S	+18	N	−15	−15
6m	R	+93	+157	+150	+25
	S	N	N	N	N
6o	R	+39	+17	+15	+15
	S	+20	+14	N	N
7	R	N	N	−26	−25
	S	N	N	N	−19

[a] N = not significantly different from control.

TABLE 5
Effect of *N*-(Phosphonoacetyl)amines and *N*-(Phosphonoformyl)amines on the Growth of *Cucumis sativus*

Compound	*Root or Hypocotyl*	*Change in weight (%)*			
		Concentration (mM)			
		0·05	*0·15*	*0·5*	*1·5*
Alachlor	R	−62	−67	−72	−87
	H	−11	−12	−11	−21
3a	R	N[a]	N	−38	−68
	H	N	N	N	N
3b	R	N	N	N	−42
	H	N	N	N	N
3d	R	N	−53	−75	−83
	H	N	N	N	−23
3f	R	N	−42	−62	−74
	H	N	N	N	−26
3j	R	N	N	−38	−64
	H	N	N	N	N
3k	R	N	N	−38	−64
	H	N	N	−35	−51
3l	R	N	−37	−40	−50
	H	N	N	−26	−43
4c	R	N	N	N	−50
	H	N	N	N	N
6c	R	+50	+42	+30	+28
	H	+30	+25	+13	+10
6f	R	+48	+31	+31	+18
	H	+16	+13	+25	+18
6k	R	N	−13	−21	−33
	H	N	N	N	N
7	R	−38	−74	−79	−81
	H	N	N	−21	−35

[a] N = not significantly different from control.

The compounds most active against *L. sativum*, along with some inactive compounds, were also tested on *C. sativus*. Also in this case (Table 5) moderate herbicidal activity was found on this species for compounds **3d**, **3f** and **3k**. Quite surprisingly, however, phosphonoacetic acid (**7**), which exhibited weak herbicidal action on *L. sativum*, was the most effective, and nearly equipotent with alachlor, on *C. sativus*.

Since chloroacetanilides are a class of pre-emergence herbicides, we have also evaluated herbicidal activity of compounds **3d** and **3f** in pre-emergence tests on *C. sativus*. The results obtained were similar to those reported in Table 5 (data not shown).

The findings described above clearly indicate that aromatic *N*-(phosphonoacetyl)amines (**3**) form a promising group of herbicidally active compounds.

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