# Synthesis and Biological Activity of Aminomethylphosphonic Acids Related to the Herbicide Glyphosate

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Aminomethylphosphonic Acids, Herbicides, Glyphosate Analogues

Several aminomethylphosphonic acids related to the herbicide glyphosate have been synthesised and their post-emergent herbicidal properties studied.

The herbicidal activity of N-phosphonomethylglycine (**1**) (carboxymethylaminomethylphosphonic acid), known as glyphosate, has attracted considerable interest over the past few years [1, 2]. It is a post-emergent herbicide which is readily translocated in plants and, like the bipyridinium herbicides diquat and paraquat [3] is essentially inactivated by most soils.

We have recently initiated a programme of study of the relationship between chemical structure and herbicidal activity in compounds related to glyphosate. This paper is concerned with the synthesis and evaluation as herbicides of a series of substituted aminomethylphosphonic acids.

The N-alkylaminomethylphosphonic acids (**2**; R = alkyl) listed in Table I were prepared by reacting chloromethylphosphonic acid (**3**) with an excess of the appropriate alkylamine. The desired product was obtained by dissolving the crude reaction product in water and passing the solution through an ion-exchange resin in the $H^+$ form. The aminomethylphosphonic acids were recovered by evaporation of the solvent from appropriate fractions (see Experimental Section). The nuclear magnetic resonance spectra of the N-alkylaminomethylphosphonic acids were in accord with the assigned structures (Table II).

A number of N-arylaminomethylphosphonic acids (**2**; R = aryl) were also prepared in a similar way from appropriate aromatic amines (Table III). Their NMR spectra are recorded in Table IV. The investigation was extended to include representatives of N,N-dialkylaminomethylphosphonic acids (**4**; R = alkyl) and related cyclic analogues (**5**) (Tables V and VI).

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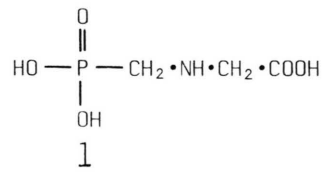
In biological tests the compounds **2a–2p**, **4a–4c** and **5a** and **5b** were tested as post-emergent herbicides at the rate of 8 kg/hectare against pigweed (*Amaranthus retroflexus*), velvet leaf (*Abutilon theophrasti*), wild mustard (*Brassica kaber*), red millet (*Panicum milliaceum*), green foxtail (*Setaria viridis*), barnyard grass (*Echinochloa crusgalli*), cotton, soyabean and maize. The only compounds which showed any significant activity were the alcohols **2h**, **2l** and **4c** but they were much less active than glyphosate. Perhaps the activity can be explained by the oxidation of the alcohols *in vivo* to glyphosate or closely related carboxylic acids. Oxidation of alcohol side chains to carboxylic acids is known to be responsible for the herbicidal activity of alcohol analogues of the phenoxyacetic acid herbicides [19].



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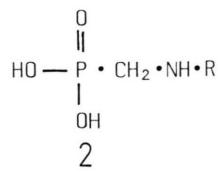

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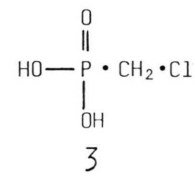

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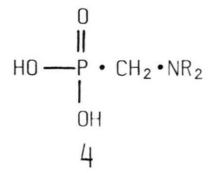

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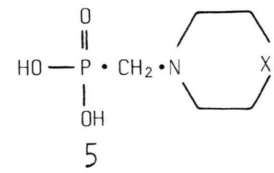

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Table I. N-alkylaminomethylphosphonic acids (**2**; R = alkyl).

| Compound | Alkyl group | M.p. [°C] | Molecular formula | Found [%] | | | Requires [%] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | C | H | N |
| **2 a** | $CH_2 \cdot CH_2 \cdot CH_3$ | 260–262 [a] | $C_4H_{12}NO_3P$ | 31.6 | 7.9 | 9.0 | 31.4 | 7.9 | 9.15 |
| **2 b** | $CH_2(CH_2)_2CH_3$ | 235–237 [a] | $C_5H_{14}NO_3P$ | 36.1 | 8.3 | 8.4 | 35.9 | 8.4 | 8.4 |
| **2 c** | $CH_2(CH_2)_3 \cdot CH_3$ | 247–249 [a] | $C_6H_{16}NO_3P$ | 40.2 | 8.85 | 7.8 | 39.8 | 8.9 | 7.7 |
| **2 d** | $CH_2(CH_2)_4 \cdot CH_3$ | 249–251 [a] | $C_7H_{18}NO_3P$ | 42.8 | 9.1 | 7.2 | 43.1 | 9.3 | 7.2 |
| **2 e** | $CH(CH_3) \cdot CH_3$ | 267–269 [a] | $C_4H_{12}NO_3P$ | 31.7 | 8.0 | 9.45 | 31.4 | 7.9 | 9.15 |
| **2 f** | $CH(CH_3) \cdot CH_2 \cdot CH_3$ | 231–232 [a] | $C_5H_{14}NO_3P$ | 35.9 | 8.4 | 8.1 | 35.9 | 8.4 | 8.4 |
| **2 g** | $CH_2 \cdot Ph$ | 265–266 [b,c] | $C_8H_{12}NO_3P$ | 47.6 | 6.1 | 7.0 | 47.8 | 6.0 | 7.0 |
| **2 h** | $CH_2 \cdot CH_2 \cdot OH$ | 191–192 [d,e] | $C_3H_{10}NO_4P$ | 23.3 | 6.5 | 9.0 | 23.2 | 6.5 | 9.0 |
| **2 i** | $CH_2 \cdot CHOH \cdot CH_3$ | 215–216 [a] | $C_4H_{12}NO_4P$ | 28.4 | 7.1 | 8.0 | 28.4 | 7.15 | 8.3 |
| **2 j** | $CH_2 \cdot CH_2 \cdot NH_2$ | 251–253 [a,f] | $C_3H_{11}N_2O_3P$ | | | | | | |
| **2 k** | cyclohexyl | 272–273 [a,g] | $C_7H_{16}NO_3P$ | 43.5 | 8.5 | 7.1 | 43.5 | 8.35 | 7.25 |
| **2 l** | $CH_2 \cdot (CH_2)_2 \cdot OH$ | 213–214 [a] | $C_4H_{12}NO_4P$ | 28.0 | 7.15 | 8.35 | 28.4 | 7.15 | 8.3 |

[a] Recrystallized from aqueous ethanol.
[b] Recrystallized from water.
[c] Redmore [4] reported 272–274°.
[d] Recrystallized from aqueous methanol.
[e] This compound has been reported in several patents [5–7].
[f] Uhlig and Achilles [8] also give m.p. 251–253°.
[g] Also reported in a patent [9].

Table II. NMR spectra in $D_2O$ of N-alkylaminomethylphosphonic acids (**2**; R = alkyl).

| Compound | δ[ppm] |
|---|---|
| **2 a** | 0.95 (3H, t, $CH_3$), 1.70 (2H, m, $-\underline{CH_2}-CH_3$), 3.0–3.23 (2H, m, $N-CH_2-C$), 3.16 (2H, d, $P-CH_2-N$, $J = 13$ Hz) |
| **2 b** | 0.7–1.1 (3H, t, $CH_3$), 1.1–2.0 (4H, m, $C-CH_2-CH_2-C$), 3.05–3.28 (2H, m, $N-CH_2-C$), 3.21 (2H, d, $P-CH_2-N$, $J = 13$ Hz) |
| **2 c** | 0.88 (3H, t, $CH_3$), 1.1–2.07 (6H, m, $C-(CH_2)_3-C$), 2.78–3.19 (2H, m, $N-CH_2-C$), 3.17 (2H, d, $P-CH_2-N$, $J = 12$ Hz) |
| **2 d** | 0.84 (3H, t, $CH_3$), 1.2–2.0 (8H, m, $C-(CH_2)_4-C$), 2.80–3.12 (2H, m, $N-CH_2-C$), 3.10 (2H, d, $P-CH_2-N$, $J = 13$ Hz) |
| **2 e** | 1.35 (6H, d, $(CH_3)_2-C$, $J = 7$ Hz), 3.18 (2H, d, $P-CH_2-N$, $J = 13$ Hz), 3.55 (1H, m, $N-CH$) |
| **2 f** | 0.96 (3H, t, $\underline{CH_3}-CH_2$, $J = 7.5$ Hz), 1.31 (3H, d, $\underline{CH_3}-CH$, $J = 6.6$ Hz), 1.68 (2H, m, $CH_3-\underline{CH_2}$), 3.16 (2H, d, $P-CH_2-N$, $J = 14$ Hz), 3.25 (1H, m, $CH_3-\underline{CH}$) |
| **2 g** [a] | 3.41 (2H, d, $P-CH_2-N$, $J = 14$ Hz), 4.43 (2H, s, $N-CH_2-Ar$), 7.60 (5H, s, aromatic) |
| **2 h** | 3.35 (2H, m, $N-CH_2-C$), 3.38 (2H, d, $P-CH_2-N$, $J = 13$ Hz), 3.95 (2H, m, $C-CH_2-O$) |
| **2 i** | 1.23 (3H, d, $CH_3$, $J = 6.6$ Hz), 3.20 (2H, m, $N-CH_2-C$), 3.22 (2H, d, $P-CH_2-N$, $J = 13$ Hz), 4.20 (1H, m, $\underline{CH}-OH$) |
| **2 j** | 3.00 (2H, d, $P-CH_2-N$, $J = 11$ Hz), 3.42 (4H, s, $N-CH_2-CH_2-N$) |
| **2 k** | 1.1–2.3 (10H, m, $CH_2$ ring protons), 3.15 (2H, d, $P-CH_2-N$, $J = 14$ Hz), ~ 3.4 (1H, m, $N-CH$) |
| **2 l** | 1.96 (2H, m, $C-CH_2-C$), 3.25 (2H, d, $P-CH_2-N$, $J = 13$ Hz), 3.32 (2H, t, $N-CH_2-C$), 3.77 (2H, t, $C-CH_2-O$) |

[a] Run in $D_2O$/DCl.

Table III. N-arylaminomethylphosphonic acids (**2**; R = aryl).

| Compound | Aryl group | M.p. [°C] | Molecular formula | Found [%] | | | Requires [%] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | C | H | N |
| **2 m** | phenyl | 215–216 [a,b] | $C_7H_{10}NO_3P$ | | | | | | |
| **2 n** | 2-tolyl | 168–169 [a] | $C_8H_{12}NO_3P$ | 47.8 | 6.3 | 7.2 | 47.8 | 6.0 | 7.0 |
| **2 o** | 3-tolyl | 192–193 [a] | $C_8H_{12}NO_3P$ | 47.8 | 6.1 | 6.9 | 47.8 | 6.0 | 7.0 |
| **2 p** | 4-tolyl | 232–234 [c] | $C_8H_{12}NO_3P$ | 47.5 | 6.1 | 6.9 | 47.8 | 6.0 | 7.0 |

[a] Recrystallized from aqueous ethanol.
[b] Kreutzkamp and Mengel reported 221° [10].
[c] Recrystallized from dilute hydrochloric acid.

Table IV. NMR spectra in $D_2O$ of N-arylaminomethylphosphonic acids (**2**; R = aryl).

| Compound | δ[ppm] |
|---|---|
| **2 m** | 3.57 (2H, d, P–$CH_2$–N, $J$ = 13 Hz), 7.52 (5H, s, aromatic) |
| **2 n** | 2.44 (3H, s, $CH_3$), 3.52 (2H, d, P–$CH_2$–N, $J$ = 13 Hz), 7.41 (4H, s, aromatic) |
| **2 o** | 2.38 (3H, s, $CH_3$), 3.52 (2H, d, P–$CH_2$–N, $J$ = 12 Hz), 7.33 (4H, s, aromatic) |
| **2 p** [a] | 2.20 (3H, s, $CH_3$), 3.23 (2H, d, P–$CH_2$–N, $J$ = 13 Hz), 6.57–7.08 (4H, m, aromatic) |

[a] Run in DMSO–$d_6$.

Table V. N,N-dialkylaminomethylphosphonic acids (**4**; R = alkyl) and related compounds (**5**).

| Compound | Alkyl group | M.p. [°C] | Molecular formula | Found [%] | | | Requires [%] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | C | H | N |
| **4 a** | $CH_2 \cdot CH_3$ | 186–187 [a,c] | $C_5H_{14}NO_3P$ | 36.3 | 8.6 | 8.1 | 35.9 | 8.4 | 8.4 |
| **4 b** | $CH_2(CH_2)_2CH_3$ | 167–168 [a] | $C_9H_{22}NO_3P$ | 48.1 | 9.9 | 6.2 | 48.4 | 9.9 | 6.3 |
| **4 c** | $CH_2 \cdot CH_2 \cdot OH$ | syrup [d,e] | $C_5H_{14}NO_5P$ | 29.7 | 7.1 | 7.1 | 30.15 | 7.1 | 7.0 |
| **5 a** (X = $CH_2$) | – | 249–250 [b,f] | $C_6H_{14}NO_3P$ | 40.4 | 8.3 | 7.7 | 40.2 | 7.9 | 7.8 |
| **5 b** (X = O) | – | 261–263 (dec) [b,g] | $C_5H_{12}NO_4P$ | 33.1 | 6.6 | 7.4 | 33.15 | 6.7 | 7.7 |

[a] Recrystallized from methanol/acetone.
[b] Recrystallized from aqueous ethanol.
[c] See also Maier [11–14] and Azerbaev, *et al.* [15].
[d] See also Ramsey and Kezerian [5, 6], Maier [13] and Worms and Wollmann [16].
[e] Moedritzer and Irani [17] give m.p. 246° but carbon microanalysis was unsatisfactory.
[f] See also Maier [13] and Azerbaev, *et al.* [15, 18].
[g] See also Maier [12] and Azerbaev, *et al.* [15].

Table VI. NMR spectra in $D_2O$ of N,N-dialkylaminomethylphosphonic acids (**4**; R = alkyl) and related compounds (**5**).

| Compound | δ[ppm] |
|---|---|
| **4 a** | 1.31 (6H, t, $CH_3$, $J$ = 7.2 Hz), 3.30 (2H, d, P–$CH_2$–N, $J$ = 13 Hz), 3.39 (4H, m, N–$CH_2$–C) |
| **4 b** | 0.92 (6H, t, $CH_3$), 1.52 (8H, m, C–$CH_2$–$CH_2$–C), 3.26 (4H, m, N–$CH_2$–C), 3.27 (2H, d, P–$CH_2$–N, $J$ = 13 Hz) |
| **4 c** | 3.3–3.8 (4H, m, N–$CH_2$–C), 3.52 (2H, d, P–$CH_2$–N, $J$ = 13 Hz), 3.8–4.2 (4H, m, C–$CH_2$–O) |
| **5 a** | 1.4–2.2 (6H, m, 3, 4, 5 protons), 2.8–3.8 (4H, m, 2, 6 protons), 3.25 (2H, d, P–$CH_2$–N, $J$ = 13 Hz) |
| **5 b** | 3.3 (2H, d, P–$CH_2$–N, $J$ = 13 Hz), 3.50 (4H, m, ring N–$CH_2$), 3.98 (4H, m, O–$CH_2$) |

## Experimental

Microanalyses were performed by the Australian Microanalytical Service. The NMR spectra (60 MHz) were determined for 10% w/v solutions with sodium 3-trimethylsilylpropane-1-sulphonate as the internal standard.

Chloromethylphosphonic acid (**3**) was prepared by the hydrolysis of chloromethylphosphonic dichloride [20]. It was dried *in vacuo* at 80° over $P_2O_5$. The amines were obtained from commercial sources and were dried over potassium hydroxide and purified by distillation.

*N-Alkylaminomethylphosphonic acids*
(**2**; R = alkyl) (Table I)

The amine (0.2–0.5 mol) was added with cooling (ice-bath) to chloromethylphosphonic acid (0.04 mol). Cooling was necessary because of the immediate formation of a salt with evolution of heat. The mixture was heated to boiling whereupon the salt slowly dissolved. Heating was continued under reflux for 18 h. In cases where the boiling point of the amine was below 100°, the reaction was carried out in a sealed glass tube at 150° for 24 h. With very high boiling amines (> 230°) the reaction was carried out at 150° in an oil-bath for 65 h. When reaction was complete the mixture was cooled and the crude product was precipitated by the addition of ethanol or acetone. Where the product was solid it was obtained by filtration and where it was an oil or syrup it was obtained by decanting the solvent.

The crude product was dissolved in the minimum amount of water and the solution was added to a column containing the ion-exchange resin Dowex 50 W –X8 ($H^+$ form; 20–50 mesh size). About 20 ml of resin were used for each g of crude product. The column was eluted with water. Initially an acidic fraction (~ pH 2–3) was eluted from the column. This was discarded. A second fraction was then collected (~ pH 6–7). Removal of the water under reduced pressure gave the aminomethylphosphonic acid usually as a white powdery solid. It was recrystallized (Table I). Yields were in the range 50–75%.

*N-Arylaminomethylphosphonic acids*
(**2**; R = aryl) (Table III)

These compounds were prepared similarly using aromatic amines. In the purification procedure hot water (60°) was used to elute the ion-exchange column. Yields were in the range 40–65%.

*N,N-Dialkylaminomethylphosphonic acids*
(**4**; R = alkyl) *and related compounds* (**5**) (Table V)

These phosphonic acids were prepared likewise using secondary aliphatic or heterocyclic amines. Yields were in the range 50–70%.

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