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N-METHYL AS A BIOISOSTERE FOR THE OXYGEN LINK BETWEEN THE AROMATIC RINGS OF ARYLOXYPHENOXYPROPIONATE HERBICIDES

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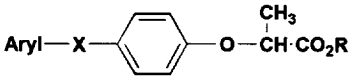
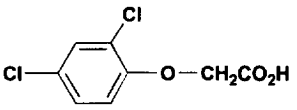
Abstract: The herbicidal activity of a set of N-methyl arylaminophenoxypropionate esters **3** has been compared to the analogous aryloxyphenoxypropionates **1**. The usefulness of N-methyl as a novel bioisostere for ether links is shown by the surprisingly high herbicidal activity of the 6-chloroquinazolin-2-yl- and 7-chloro-1,2,4-benzotriazin-3-yl-N-methylamino-phenoxypropionate esters **3h** and **3i**. © 1997 Elsevier Science Ltd.

Aryloxyphenoxypropionates **1** are a widely used class of post-emergent herbicides, which are highly active on grass (gramineae), but not broad-leaved (dicotyledonous) plants.[1] The structurally related phenoxyalkanoic herbicides, such as 2,4-D **2**, are only active on broadleaf plants and therefore, in general terms, have the opposite spectrum of herbicidal activity to compounds **1**.[2] A few years ago it was established[3] that Acetyl-Coenzyme A Carboxylase (ACCase, E. C. 6.4.1.2), the enzyme responsible for the first committed step in fatty acid biosynthesis, is the likely target site of compounds **1**. Very recently it has been shown that dicotyledonous plants have a second form of ACCase that is not inhibited by the aryloxyphenoxypropionates.[4]



1 X = O, **3** X = NMe, R = alkyl



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Exploration of the structure-activity relationships for the aryloxyphenoxypropionates by many agrochemical companies has led to the discovery and commercialisation of several compounds (eg, **1a-d** below), which vary only in the type of aryl group and the alkyl group of the propionate ester.[5] We have noted also a recent report that certain quinoxylinyloxyphenoxypropionates show potent anticancer activity.[6]

We and others have found that there is a drastic or total loss of herbicidal activity when the ether oxygen atom between the aromatic rings is replaced with any of the atoms or groups: S, SO, CO, CH_2O, OCH_2, CH_2S, CH=N, N=CH, CO_2.[1] We now report the remarkable observation that, with a particular set of aryl rings, the oxygen bridge between the aromatic rings in compounds **1** can be replaced by N-methyl to give compounds **3**, which show substantially higher herbicidal activity on grass species. We believe this is the first reported example in which N-methyl can be used as a bioisostere for an ether bridge to give superior biological activity.[7]

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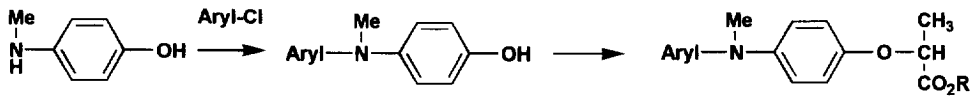
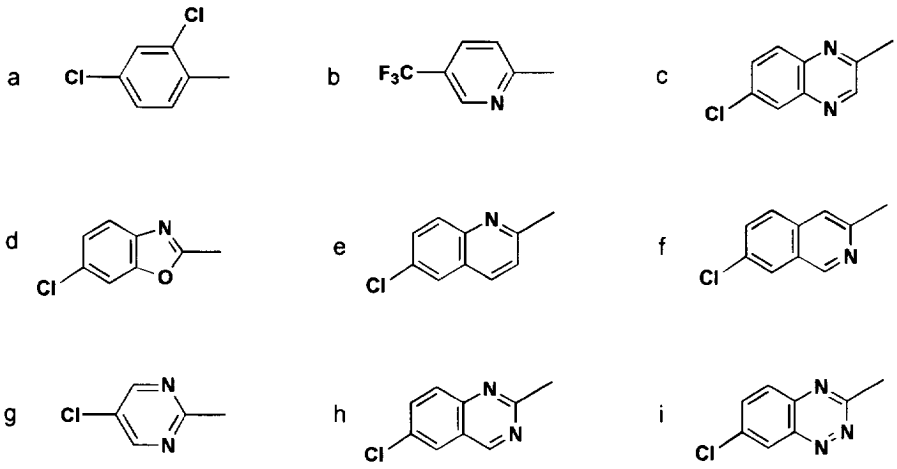
The N-methyl arylaminophenoxypropionates **3** were readily prepared in two stages. Thus, reaction of the various 2- or 3-chloro-heterocycles with the sulfate salt of 4-methylaminophenol **4** in boiling, slightly acidic, aqueous ethanol or acetonitrile gave the corresponding N-methyl arylaminophenols **5** in good yield. Alkylation of the phenols **5** with a suitable 2-halopropionate ester then yielded the final compounds **3**.



4 **5** **3 R = alkyl**

Using the aromatic ring systems **a-i** shown below, a complete set of oxygen and N-methyl linked compounds, **1a-1i** and **3a-3i**, respectively, has been prepared and tested for activity on a range of broad leaf and grass species. With most of the aromatic ring systems **a-i** we also prepared compounds with an NH link between

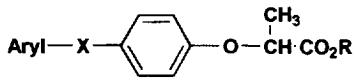


the aromatic rings, but none of these compounds showed any appreciable activity at application rates below 2 Kg/ha. For comparative purposes we used only racemic compounds **1** and **3**, although it is known that essentially all the activity resides in the R(+) enantiomer of aryloxyphenoxypropionates.[8]

Consistent with having the same mode of action as the oxygen linked compounds **1**, the N-methyl compounds **3a-3i** show significant herbicidal activity only against grass species. Representative herbicidal data for all compounds **1a-1i** and **3a-3i** are presented in Table I. The data reveal the wheat selectivity of diclofop **1a** and fenoxaprop **1d**, and shows that the related N-methyl compounds **3a** and **3d**, whilst of similar activity, have lost wheat selectivity. The potent activity of the most widely used general grass killers, fluazifop **1b** and quizalofop **1c**, as well as the quinoline **1e**, is clearly evident, but is almost totally lost in the N-methyl linked

Table I

Post-Emergent Herbicidal Activity of Compounds of Type **1** and **3** on Various Crop and Weed Grass Species[a]



Compound			Phytotoxicity (%) 13 Days after Post-emergent Treatment							
No.	Linking group X	Ester alkyl R	Applic. rate gram/ha	Maize	Rice	Wheat	Wild oats	Johnson grass	Green foxtail	Barnyard grass
1a	O	Me	500	85	0	0	70	70	100	100
3a	N-Me	Me	500	30	0	70	0	85	85	85
1b	O	n-Butyl	50	85	50	70	85	85	85	85
3b	N-Me	Me	500	30	0	30	0	0	0	50
1c	O	Et	50	100	70	85	85	100	100	100
1c	O	Et	5	85	50	85	30	85	70	70
3c	N-Me	Et	500	50	0	85	0	85	85	85
1d	O	Et	50	85	70	0	85	100	100	100
3d	N-Me	Et	100	100	30	85	70	100	85	100
1e	O	Me	500	100	85	85	85	100	100	100
3e	N-Me	Me	500	0	0	0	0	0	30	0
1f	O	Et	500	70	70	85	85	100	85	100
3f	N-Me	Et	500	100	0	85	70	85	85	100
1g	O	Et	250	85	70	70	85	85	85	85
3g	N-Me	Me	250	85	70	85	85	85	85	100
1h	O	Me	500	15	0	0	0	85	65	85
3h	N-Me	Et	50	65	35	65	15	98	98	85
3h	N-Me	Et	12.5	15	0	35	0	65	65	98
1i	O	Me	500	0	0	0	0	30	50	50
3i	N-Me	Me	50	85	85	85	85	100	100	100
3i	N-Me	Me	5	70	0	70	50	50	100	0

[a] All compounds were tested under standardised glasshouse conditions using plants at the two to four leaf growth stage.[9] Damage to test plants was assessed 13 days after spraying as a percentage phytotoxicity relative to untreated control plants and all numbers are based on at least two replicates. Full names of the weed species are: Wild Oats - *Avena fatua*; Johnson Grass - *Sorghum halepense*; Green Foxtail - *Setaria viridis*; Barnyard Grass - *Echinochloa crus-galli*.

analogs **3b**, **3c**, and **3e**. The N-methyl linked 3-isoquinolinyl and 2-pyrimidyl systems **3f** and **3g** show similar moderate activity to the corresponding oxygen linked compounds **1f** and **1g**.

Most remarkable of all the N-methyl compounds are the quinazoline and 1,2,4-benzotriazine systems **3h** and **3i**, which show approximately 100-fold greater activity than the corresponding **1h** and **1i**. Compound **3i** in particular is interesting, being almost equivalent in activity to quizalofop ethyl **1c**, the free acid of which is the most active of all known aryloxyphenoxypropionic acids, both in the field and the ACCase enzyme assay.[10] The free acid of compound **3h** was found to inhibit ACCase from barley leaves with an IC_{50} of 1.5μM, a similar level of activity to that shown by fluazifop **1b**.[10] Both compounds **3h** and **3i** have been extensively field tested, with the quinazoline **3h** showing promise for selective control of barnyard grass in rice and the benzotriazine **3i** for general grass control in broadleaf crops.

We have no convincing explanation for the dramatic reversal in activity that is seen between the quinoxaline and quinoline compounds on the one hand, where the oxygen link is far superior, and the quinazoline and benzotriazine systems where the N-methyl compounds are clearly the best. It seems unlikely that selective metabolism alone could account for the observed activity differences. Possibly in the case of the quinazoline and benzotriazine systems the N-methyl link forces the molecules into a conformation that better fits the ACCase target site.

References and Notes

1. Nestler, H. J. *Chem. Pflanzenschutz-Schaedlingsbekaempfungmittel*, **1982**, 8, 1 (*Chem. Abstr.* **1982**, 97, 51095v).
2. Pillmoor, J. B.; Gaunt, J. K. In *Progress in Pesticide Biochemistry*; Hutson, D. H.; Roberts, T. R., Eds.; John Wiley & Sons, 1981; Vol 1, pp 147-218.
3. Rendina, A. R.; Craig-Kennard, A. C.; Beaudoin, J. D.; Breen, M. K. *J. Agric. Food Chem.* **1990**, *38*, 1282.
4. Konishi, T.; Shinohara, K.; Yamada, K.; Sasaki, Y. *Plant Cell Physiol.* **1996**, *37*, 117.
5. Duke, S. O.; Kenyon, W. H. In *Herbicides: Chemistry, Degradation and Mode of Action*; Kearney, P. C.; Kaufman, D. D., Eds.; Marcel Dekker: New York, 1988; Vol 3, pp 71-116.
6. Behrens, C. H.; Dusak, B. A.; Harrison, B. A.; Orwat, M. J. PCT Patent Application, **1994**, WO 94/13647; *Chem. Abstr.* **1994**, *121*, 157671j.
7. For a review of bioisosterism see: Burger, A. *Progress in Drug Research* **1991**, *37*, 287.
8. Nakahira, K.; Hayashi, O.; Uchiyama, M.; Suzuki, K. *J. Pesticide Sci.* **1990**, *15*, 245.
9. For a detailed description of the herbicidal testing method see: Barton, J. E. D.; Collins, D. J.; Slater, J. W. European Patent Appl. No. 248,554; *Chem. Abstr.* **1988**, *108*, 112489w.
10. Taylor, W. S.; Hixon, M.; Chi, H.; Marsilii, E.; Rendina, A. R. *Pesticide Sci.* **1995**, *43*, 177.

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