# organic compounds

# Two isomeric 2-[4-chloro-2-fluoro-5-(prop-2-ynyloxy)phenyl]hexahydroisoindole-1,3-dione compounds

**Bin Li,[a,b] Hai-Bin Song,[a] Chi-Tung Hsu,[c] Ke-Liang Zhang,[b] Chao Wu[a] and Hua-Zheng Yang[a]***

[a]State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China, [b]Agrochemicals Division, Shenyang Research Institute of Chemical Industry, Shenyang 110021, People's Republic of China, and [c]Applied Chemistry Department, Chaoyang University of Technology, Taichung 41349, Taiwan

Correspondence e-mail: nk_yanghz@126.com

The molecular structures of 2-[4-chloro-2-fluoro-5-(prop-2-ynyloxy)phenyl]-1,3,4,5,6,7-hexahydroisoindole-1,3-dione, $C_{17}H_{13}ClFNO_3$, (I), and the isomeric compound 2-[4-chloro-2-fluoro-5-(prop-2-ynyloxy)phenyl]-cis-1,3,3a,4,7,-7a-hexahydroisoindole-1,3-dione, (II), are, as anticipated, significantly different in their conformations and in the distances between the farthest two atoms. The six-membered ring of the 1,3,4,5,6,7-hexahydroisoindole-1,3-dione moiety in (I) adopts a half-chair conformation. The dihedral angle between the five-membered dione ring of (I) and the benzene ring is 50.96 (7)°. The six-membered ring of the cis-1,3,3a,4,7,7a-hexahydroisoindole-1,3-dione moiety in (II) adopts a boat conformation. The dihedral angle in (II) between the five-membered dione ring and the benzene ring is 61.03 (13)°. In the crystal structures, the molecules are linked by C—H···O hydrogen bonds and weak π–π interactions. Compound (I) is a much more potent herbicide than (II). The Cl···H distances between the farthest two atoms in (I) and (II) are 11.37 and 9.97 Å, respectively.

## Comment

Many 2-(substituted phenyl)tetrahydroisoindole-1,3-diones show good herbicidal activity (Ohta et al., 1976). One of these compounds, chlorophthalim [2-(4-chlorophenyl)-4,5,6,7-hexahydroisoindole-1,3-dione], was commercially available in 1973 (Tomlin, 2003). It acts as a competitive inhibitor of the enzyme protoporphyrinogen IX oxidase (PPO) by binding to the same active site as the substrate protoporphyrinogen IX (Matringe & Scalla, 1988; Duke et al., 1989). Since 1990, one of the title molecules, viz. 2-[4-chloro-2-fluoro-5-(prop-2-ynyloxy)phenyl]-1,3,4,5,6,7-hexahydroisoindole-1,3-dione, (I), has been used as a reference compound during structure–activity relationship (SAR) studies because it has greater herbicidal

activity than chlorophthalim (Boger & Wakabayashi, 1999). The X-ray structures and details of the herbicidal activities of three PPO inhibitors, including chlorophthalim, viz. 2-(4-chlorophenyl)-4,5,6,7-tetrahydroisoindole-1,3-dione (chlorophthalim), 3-(4-chloro-5-cyclopentyloxy-2-fluorophenyl)-5-iso-propylideneoxazolidine-2,4-dione and 2-chloro-1-(3-ethoxy-4-nitrophenoxy)-4-(trifluoromethyl)benzene, have been reported (Kohno et al., 1993). The X-ray structure of chlorophthalim indicated that the angle between the tetrahydro-isoindole-1,3-dione and benzene ring planes is 43.6°, and the distance between the farthest two atoms is 11.37 Å. It was assumed that both the angle and the distance have some bearing on the herbicidal activity of the molecule.
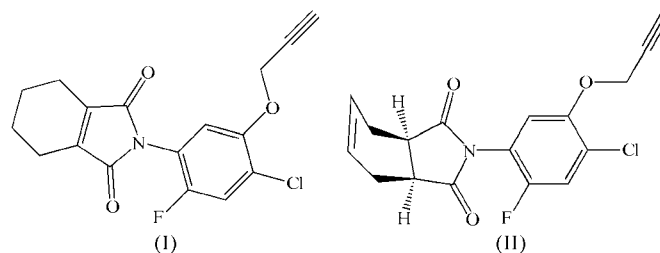


The molecular similarity between (I) and proto-porphyrinogen IX has been investigated on the basis of their computational conformation using MOPAC with MNDO-PM3 parameterizations during a molecular modeling program (Uraguchi et al., 1997).

In an attempt to discover compounds that are more herbi-cidally active, the novel compound 2-[4-chloro-2-fluoro-5-(prop-2-ynyloxy)phenyl]-cis-1,3,3a,4,7,7a-hexahydroisoindole-1,3-dione, (II), an isomer of (I), was prepared. Unfortunately, it was found that (II) is much less active than (I) (Li, 2005). In order to carry out a three-dimensional quantitative structure–activity relationship study on this series of compounds and to interpret the differences in their herbicidal activity, we report here the crystal structures of (I) and (II).

The molecular dimensions in (I) (Fig. 1) are unexceptional; the six-membered ring (C3a/C4–C7/C7a) of the 1,3,4,5,6,7-hexahydroisoindole-1,3-dione moiety adopts a half-chair conformation, with atoms C5 and C6 on opposite sides
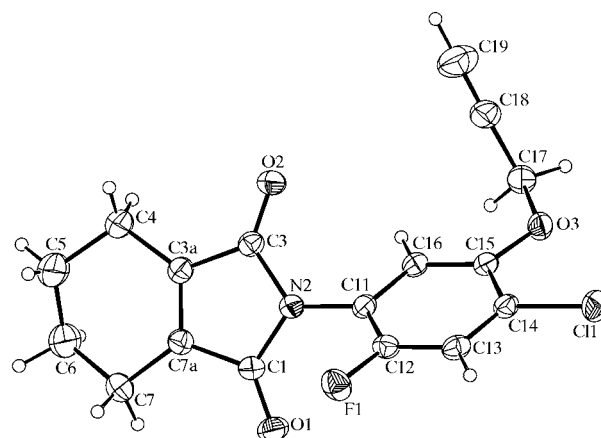


**Figure 1**
The structure of (I), showing 30% probability displacement ellipsoids and the atom-numbering scheme.

[deviating by 0.250 (6) and −0.290 (6) Å, respectively] of the C1/N2/C3/C3A/C4/C7/C7a plane. The dihedral angle between the planes of these seven atoms and the benzene ring (C11–C16) is 50.96 (7)°. Any reduction in this value would lead to an
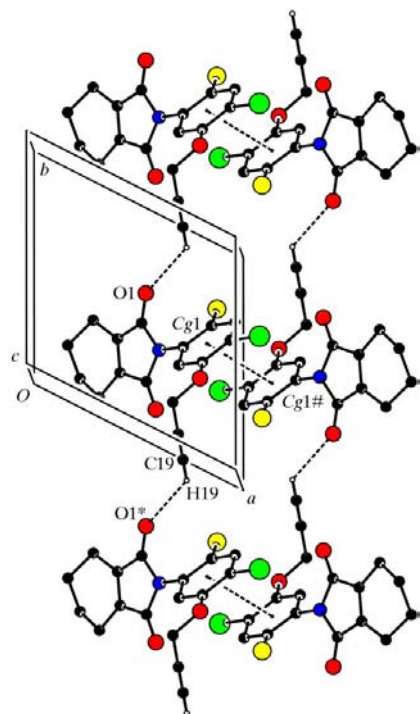
impossibly short intramolecular F1···O1 separation [the present value is only 2.838 (3) Å]. The orientation of the propargyl group relative to the aromatic ring is defined by the C15—O3—C17—C18 torsion angle [73.8 (3)°]. The distance between the farthest two atoms (atom Cl1 and the equatorial H atom at C6) is 11.37 Å.

In (I), there is a well defined acetylenic C—H···O hydrogen bond between the C19—H19 group and carbonyl atom O1 of an adjacent molecule (Table 1 and Fig. 2); this interaction leads to the development of chains of molecules along [010]. A search of the Cambridge Structural Database (July 2004 release; Allen, 2002) revealed 106 compounds with acetylenic C—H···O hydrogen bonds. The hydrogen-bond dimensions in (I) indicate that this C—H···O hydrogen bond is weaker than



**Figure 2**
A view showing the C—H···O hydrogen-bonded chains in (I) and the centroid–centroid separations. Cg1 is the centroid of the phenyl ring. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions (x, y − 1, z) and (2 − x, 1 − y, 1 − z), respectively.
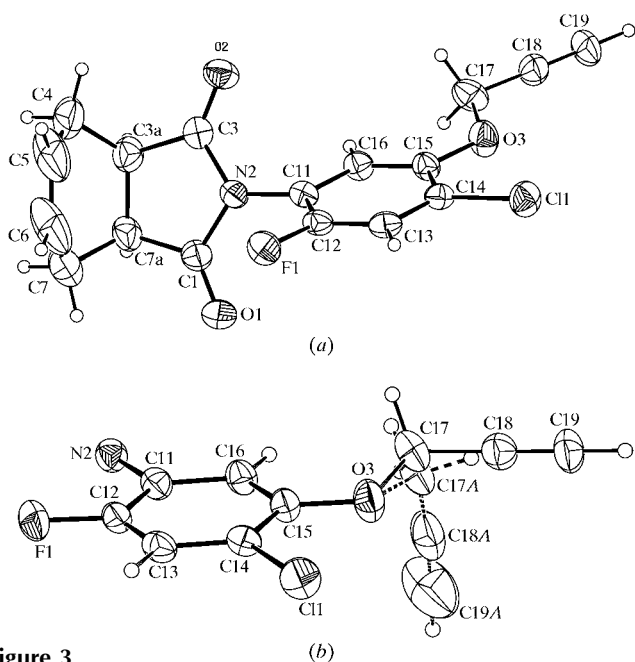


**Figure 3**
(a) The structure of (II), showing 30% probability displacement ellipsoids, the atom-numbering scheme and the major orientation of the disordered propargyl group. (b) A view of part of the molecule of (II), showing the disorder of the propargyl group.
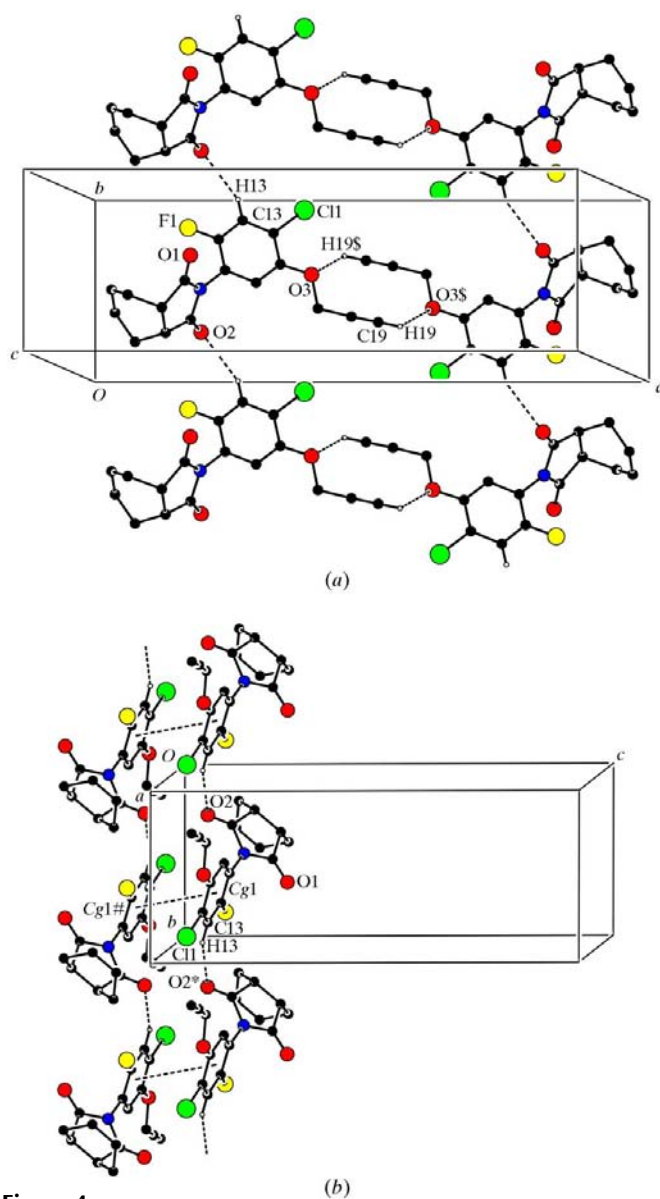


**Figure 4**
Views showing (a) a chain of rings extending along [010] and (b) the weak centroid–centroid interactions between chains. Cg1 is the centroid of the phenyl ring. Atoms marked with an asterisk (*), a dollar sign ($) or a hash (#) are at the symmetry positions (x, 1 + y, z), (1 − x, 1 − y, −z) and (½ − x, 3⁄2 − y, −z), respectively.

# organic compounds

those in *o*-chloro- and *o*-bromobenzoylacetylene (Ferguson & Tyrrell, 1965; Ferguson & Islam, 1966). In the crystal structure of (I), parallel chains are linked by weak $\pi$–$\pi$ interactions; the centroid–centroid distance between the planes of the benzene rings at $(x, y, z)$ and $(2 - x, 1 - y, 1 - z)$ (# in Fig. 2) is 3.736 (3) Å, the shortest C···C contacts being C11···C13# [3.452 (5) Å] and C12···C13# [3.477 (4) Å].

Compound (II) has the solid-state conformation shown in Fig. 3(*a*), with normal dimensions. The six-membered C3a/C4–C7/C7a ring adopts a simple boat conformation. The five-membered C1/N2/C3/C3a/C7a ring is planar; the mean deviation from the plane is 0.005 Å. The dihedral angle between this plane and that of the benzene ring (C11–C16) is 61.03 (13)°, slightly larger than that found in (I) and with a concomitant small increase in the intramolecular F1···O1 separation to 3.004 (4) Å. The propargyl group is disordered unequally [0.549 (5):0.451 (5)] over two orientations (see Fig. 3*b*), with the orientations relative to the aromatic ring defined by the C15—O3—C17—C18 [−179.1 (5)°] and C15—O3—C17A—C18A [−76.5 (9)°] torsion angles. The longest atom–atom separation in (II) is 9.97 Å, between atom Cl1 and the axial H atoms at atoms C4 and C7.

The packing of (II) is controlled by weak acetylenic C—H···O hydrogen bonds, which generate centrosymmetric dimers with $R_2^2(10)$ rings (Bernstein *et al.*, 1995) (Table 2 and Fig. 4*a*). These dimers are linked by C—H···O hydrogen bonds involving the phenyl C13—H13 group and an adjacent carbonyl O atom (O2), generating $R_2^2(32)$ rings. In this way, chains of rings are developed along [010]. These chains are linked by weak $\pi$–$\pi$ interactions, as shown in Fig. 4(*b*) [*e.g.* between the benzene rings at $(x, y, z)$ and $(\frac{1}{2} - x, \frac{3}{2} - y, -z)$ (# in Fig. 4*b*)]; the centroid–centroid separation is 3.830 (3) Å and the shortest C···C separations are C12···C14# [3.376 (5) Å] and C13···C13# [3.461 (5) Å]. The acetylenic moiety of the minor-occupancy propargyl group takes no part in any hydrogen bonding.

From the conformational data made available by this study, it might be implied that the almost flat conformation of the hexahydroisoindole-1,3-dione ring in (I) compared with the folded conformation in (II) plays an important role in maintaining the herbicidal activity of (I) compared with that of (II).

## Experimental

The title compounds were synthesized according to the procedure reported by Nagano *et al.* (1982), by refluxing 4-chloro-2-fluoro-5-(prop-2-ynyloxy)phenylamine with the corresponding anhydrides in acetic acid for 1 h. The crude products were purified by silica-gel column chromatography and then grown from acetone to afford colorless single crystals suitable for X-ray diffraction. For (I), m.p. 409–410 K (409.4 K; Nagano *et al.*, 1982); $^1$H NMR (p.p.m.): 1.82–1.84 (*m*, 2H), 2.58 (*t*, 1H, $J$ = 2.4 Hz, C*CH), 2.44–2.75 (*m*, 4H), 4.75 (*d*, 2H, $J$ = 2.4 Hz, CH$_2$C*C), 6.98 (*d*, 1H, $J$ = 6.6 Hz, Ph), 7.29 (*d*, 1H, $J$ = 9 Hz, Ph). For (II), m.p. 368–369 K; elemental analysis requires: C 61.18, H 3.93, N 4.20%; found: C 61.22, H 4.01, N 4.24%; $^1$H NMR (p.p.m.): 2.35–2.39 (*m*, 2H), 2.58 (*t*, 1H, $J$ = 2.4 Hz, C*CH), 2.68–2.73 (*m*, 2H), 3.30–3.32 (*m*, 2H), 4.75 (*d*, 2H, $J$ = 2.4 Hz, CH$_2$C*C), 5.99–6.01 (*m*, 2H), 6.96 (*d*, 1H, $J$ = 6.6 Hz, Ph), 7.29 (*d*, 1H, $J$ = 9 Hz, Ph).

## Compound (I)

### Crystal data

| | |
|---|---|
| $C_{17}H_{13}ClFNO_3$ | $Z = 2$ |
| $M_r = 333.73$ | $D_x = 1.417$ Mg m$^{-3}$ |
| Triclinic, $P\bar{1}$ | Mo $K\alpha$ radiation |
| $a = 9.313$ (5) Å | Cell parameters from 860 |
| $b = 9.380$ (5) Å | reflections |
| $c = 10.485$ (6) Å | $\theta = 3.3$–26.0° |
| $\alpha = 99.663$ (9)° | $\mu = 0.27$ mm$^{-1}$ |
| $\beta = 104.263$ (9)° | $T = 293$ (2) K |
| $\gamma = 112.778$ (8)° | Prism, colorless |
| $V = 782.1$ (7) Å$^3$ | $0.36 \times 0.24 \times 0.22$ mm |

### Data collection

| | |
|---|---|
| Bruker SMART CCD area-detector diffractometer | 2747 independent reflections |
| | 2059 reflections with $I > 2\sigma(I)$ |
| $\varphi$ and $\omega$ scans | $R_{int} = 0.017$ |
| Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996) | $\theta_{max} = 25.0°$ |
| | $h = -11 \rightarrow 9$ |
| $T_{min} = 0.906$, $T_{max} = 0.943$ | $k = -9 \rightarrow 11$ |
| 4071 measured reflections | $l = -10 \rightarrow 12$ |

### Refinement

| | |
|---|---|
| Refinement on $F^2$ | $w = 1/[\sigma^2(F_o^2) + (0.045P)^2 + 0.3951P]$ |
| $R[F^2 > 2\sigma(F^2)] = 0.043$ | |
| $wR(F^2) = 0.111$ | where $P = (F_o^2 + 2F_c^2)/3$ |
| $S = 1.03$ | $(\Delta/\sigma)_{max} = 0.002$ |
| 2747 reflections | $\Delta\rho_{max} = 0.39$ e Å$^{-3}$ |
| 208 parameters | $\Delta\rho_{min} = -0.28$ e Å$^{-3}$ |
| H-atom parameters constrained | |

**Table 1**
Hydrogen-bond geometry (Å, °) for (I).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| C19—H19···O1$^i$ | 0.93 | 2.59 | 3.295 (4) | 133 |

Symmetry code: (i) $x, y - 1, z$.

## Compound (II)

### Crystal data

| | |
|---|---|
| $C_{17}H_{13}ClFNO_3$ | $D_x = 1.418$ Mg m$^{-3}$ |
| $M_r = 333.73$ | Mo $K\alpha$ radiation |
| Monoclinic, $C2/c$ | Cell parameters from 885 |
| $a = 22.712$ (15) Å | reflections |
| $b = 7.474$ (5) Å | $\theta = 3.0$–24.4° |
| $c = 18.655$ (12) Å | $\mu = 0.27$ mm$^{-1}$ |
| $\beta = 99.061$ (11)° | $T = 293$ (2) K |
| $V = 3127$ (4) Å$^3$ | Prism, colorless |
| $Z = 8$ | $0.34 \times 0.28 \times 0.20$ mm |

### Data collection

| | |
|---|---|
| Bruker SMART CCD area-detector diffractometer | 3206 independent reflections |
| | 2058 reflections with $I > 2\sigma(I)$ |
| $\varphi$ and $\omega$ scans | $R_{int} = 0.027$ |
| Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996) | $\theta_{max} = 26.4°$ |
| | $h = -28 \rightarrow 27$ |
| $T_{min} = 0.902$, $T_{max} = 0.948$ | $k = -5 \rightarrow 9$ |
| 8627 measured reflections | $l = -22 \rightarrow 23$ |

### Refinement

| | |
|---|---|
| Refinement on $F^2$ | $w = 1/[\sigma^2(F_o^2) + (0.0569P)^2 + 5.1958P]$ |
| $R[F^2 > 2\sigma(F^2)] = 0.060$ | |
| $wR(F^2) = 0.155$ | where $P = (F_o^2 + 2F_c^2)/3$ |
| $S = 1.02$ | $(\Delta/\sigma)_{max} < 0.001$ |
| 3206 reflections | $\Delta\rho_{max} = 0.31$ e Å$^{-3}$ |
| 230 parameters | $\Delta\rho_{min} = -0.25$ e Å$^{-3}$ |
| H-atom parameters constrained | |

**Table 2**
Hydrogen-bond geometry (Å, °) for (II).

| $D$—H$\cdots A$ | $D$—H | H$\cdots A$ | $D\cdots A$ | $D$—H$\cdots A$ |
|---|---|---|---|---|
| C13—H13$\cdots$O2$^{i}$ | 0.93 | 2.51 | 3.345 (4) | 149 |
| C19—H19$\cdots$O3$^{ii}$ | 0.93 | 2.78 | 3.400 (6) | 125 |

Symmetry codes: (i) $x, y + 1, z$; (ii) $-x + 1, -y + 1, -z$.

For both (I) and (II), H atoms were found in difference maps and were subsequently allowed for in the refinements as riding atoms, with C—H distances of 0.93, 0.97 and 0.98 Å, and with $U_{iso}$(H) = $1.2U_{eq}$(C). In (II), it soon became apparent that the propargyl group was disordered unequally over two orientations (see supplementary material for a plot of the electron density in the relevant plane). DFIX restraints [1.428 (3), 1.158 (3) and 2.396 (3) Å] were used to control the refinement of the propargyl C—C distances in the two components (C17/C18/C19 and C17A/C18A/C19A), whose occupancies refined to 0.549 (5) and 0.451 (5).

For both compounds, data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1999); structure solution: *SHELXS97* (Sheldrick, 1997); structure refinement: *SHELXL97* (Sheldrick, 1997) in *WinGX* (Farrugia, 1999); molecular graphics: *PLATON* (Spek, 2003); publication software: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1803). Services for accessing these data are described at the back of the journal.

## References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.
Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
Boger, P. & Wakabayashi, K. (1999). In *Peroxidizing Herbicides*. Berlin: Springer.
Bruker (1998). *SMART*. Bruker AXS Inc., Madison, Wisconsin, USA.
Bruker (1999). *SAINT* and *SHELXTL*. Bruker AXS Inc., Madison, Wisconsin, USA.
Duke, S. O., Lydon, J. & Paul, R. N. (1989). *Weed Sci.* **37**, 152–160.
Farrugia, L. (1999). *J. Appl. Cryst.* **32**, 837–838.
Ferguson, G. & Islam, K. M. S. (1966). *J. Chem. Soc. B*, pp. 593–600.
Ferguson, G. & Tyrrell, J. (1965). *Chem. Commun.* pp. 195–196.
Kohno, H., Hirai, K., Hori, M., Sato, Y., Boger, P. & Wakabayashi, K. (1993). *Z. Naturforsch. Teil C*, **48**, 334–338.
Li, B. (2005). PhD thesis, University of Nankai, People's Republic of China.
Matringe, M. & Scalla, R. (1988). *Plant Physiol.* **86**, 619–662.
Nagano, E., Hashimoto, S., Yoshida, R., Matsumoto, H., Oshio, H. & Kamoshita, K. (1982). Eur. Patent Appl. No. 61741.
Ohta, H., Suzuki, S., Watanabe, H., Jikihara, T., Matsuya, K. & Wakabayashi, K. (1976). *Agric. Biol. Chem.* **40**, 745–751.
Sheldrick, G. M. (1996). *SADABS*. University of Göttingen, Germany.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
Tomlin, C. (2003). In *The Pesticide Manual*, 13th ed. Hampshire: BCPC Publications.
Uraguchi, R., Sato, Y., Nakayama, A., Sukekawa, M., Iwataki, I., Boger, P. & Wakabayashi, K. (1997). *J. Pestic. Sci.* **22**, 314–320.