Note

2-Bromo-1-ethoxy-(2',4'-dichloro)styrene and 2,2-dibromo-1-ethoxy-(2',4'-dichloro)styrene—the two impurities of bromfenvinphos; their identification, synthesis and full characterization

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Insecticide bromfenvinphos of 94–96% purity is manufactured in the Institute of Industrial Organic Chemistry. Besides the main component (bromfenvinphos), more than ten impurities are observed. Two new impurities: 2-bromo-1-ethoxy-(2',4'-dichloro)styrene (as a mixture of geometric isomers) and 2,2-dibromo-1-ethoxy-(2',4'-dichloro)styrene were identified by means of mass spectrometry (MS) analysis. Both impurities were independently synthesized using 2,4-dichloroacetophenone as the starting material. The synthesized compounds were characterized spectroscopically and were found identical to the impurities which had been previously identified in bromfenvinphos. © Pesticide Science of Japan

Keywords: bromfenvinphos, impurities, mass spectrometry.

Introduction

Bromfenvinphos (Fig. 1) is a known, original insecticide with varroacidal activity.^{1–4)} Methods concerning its synthesis and process of manufacturing,^{5–7)} knowledge about its biological activity,^{8–13)} as well as determination of its residues in the environment^{14–17)} have been developed in the Institute of the Industrial Organic Chemistry since the beginning of 1970s.

Bromfenvinphos of 94–96% purity is manufactured in the Institute of Industrial Organic Chemistry. Besides the main component (bromfenvinphos), more than ten impurities are observed.^{18–20)} Because the impurities of the manufactured brom-

Fig. 1. (*E,Z*)-*O,O*-Diethyl-*O*-[1-(2,4-dichlorophenyl)-2-bromovinyl] phosphate, bromfenvinphos.

fenvinphos should be fully, unambiguously and completely characterized, herein we present the identification and independent synthesis of two, so-far uncharacterized, impurities.

Materials and Methods

1. General

All reagents were commercially available and were used as received without further purification. The reaction progress was monitored by means of TLC: silica gel: Merck Alufolien 5554; visualization: UV 254 nm and/or 1% ethanolic AgNO₃/UV; mobile phases: hexane : benzene 1 : 1 (v/v) (for **1,4**), hexane:benzene 3 : 2 (v/v) (for **2,5**). Column chromatography: silica gel Merck 7734, 70–230 mesh, mobile phase: hexane. Refractive index values were measured with an Abbe refractometer (Carl Zeiss/Jena). GC/MS were recorded using a gas chromatograph (6890N Series Network GC System; Agilent Technologies) equipped with a DB-5MS capillary column 30 m×0.25 mm, film thickness 0.25 μm, column temperature starting at 100°C (3 min.) and increased to 250°C (10°C/min.), and an injector (split/splitless 20 : 1), temperature 240°C. Helium was used as a carrier gas; 500 to 1000 ng of the analyzed substance was introduced into the injector in 0.2 μl of hexane solution. EI MS (70 eV) and CI MS (isobutane) (*m/z*, int. [%]) were recorded using a mass detector (MSD 5975B series; Agilent Technologies) (ion source temperature: 230°C) spectrometer. ¹H NMR data (200 MHz or 500 MHz, δ_H [ppm], *J* [Hz], CDCl₃, TMS as a standard) were recorded using a spectrometer (UNITYplus 200 or UNITYplus 500; Varian, respectively). ¹³C NMR data (50 MHz, δ_C [ppm], *J* [Hz], CDCl₃, TMS as a standard) were recorded using a spectrometer (UNITYplus 200; Varian). IR (ν [cm⁻¹]) data were recorded using a FT/IR spectrophotometer (420; Jasco).

2. Synthesis of the compounds

2.1. 2,4-Dichlorophenacyl bromide (**4**)

2,4-Dichloroacetophenone (**3**) (113.4 g, 0.6 mol) and carbon tetrachloride (360 ml) were placed in a reactor of 750 ml capacity, equipped with a heating mantle, mechanical stirrer, dropping funnel, thermometer, and reflux condenser with a hydrogen bromide

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absorber. Bromine (96 g, 0.6 mol) was added dropwise at 35–40°C for 1 hr, at such a rate to keep the reaction mixture colorless. Stirring was continued at 40°C for 2 hr. The reaction mixture was washed with 5% sodium bisulfite (180 ml), twice with water, and dried over anhydrous magnesium sulfate. After filtration, the filtrate was concentrated under reduced pressure, and the residue was distilled (103–106°C/0.4 mmHg) to give crude 2,4-dichlorophenacyl bromide (**4**) (108 g, 67%, n_D^{30} 1.6018). The crude **4** (108 g) and hexane (300 ml) were placed in a reactor of 750 ml capacity at 25–30°C and kept at this temperature for 1 hr. The solution was slowly cooled to 0°C and stirred at 0°C for 1 hr. After filtration and drying in a dessicator, purified 2,4-dichlorophenacyl bromide (**4**) (89.3 g) was obtained. The crystallization process was repeated to afford 2,4-dichlorophenacyl bromide (**4**) as a certified reference material of min. 99.8% purity (HPLC, GC, TLC): 69.9 g, 44%, m.p. 23–24°C (23–24°C,²⁰ 25–29°C,²¹ 30–32°C²²).

2.2. 2,4-Dichlorophenacyl bromide diethyl ketal (**5**)

2,4-Dichlorophenacyl bromide (**4**) (26.8 g, 0.1 mol), triethyl orthoformate (25 ml, 22.3 g, 0.15 mol), anhydrous ethanol (53.5 ml) and Nafion NR 50 (1.5 g) were placed in a round-bottomed flask. The reaction mixture was stirred and heated at boiling point for 14 hr. The progress of the reaction was monitored by TLC. After the reaction had been finished, the reaction mixture was alkalized with 5% sodium ethoxide to pH 7. The formed precipitate was filtered off, and the filtrate was concentrated to dryness to give 26.6 g of the residue, which was purified by column chromatography to give 2,4-dichlorophenacyl bromide diethyl ketal (**5**) as a colorless oil: 9.6 g, 28%; purity: 98.7% (GC), n_D^{25} 1.5209.

EI GC/MS; retention time: 13.893 min, 99.0% (internal standardization): 299 (13), 297 (30), 295 (19, M-OEt), 271 (19), 269 (43), 267 (27), 249 (64), 247 (100), 221 (15), 219 (24), 193 (48), 191 (77), 175 (49), 173 (79), 161 (17), 159 (29).

¹H NMR δ_H (200 MHz, CDCl₃): 1.27 (t, 6H, $J=7.0$ Hz, CH₃), 3.3–3.6 (m, 4H, 2(OCH₂CH₃)), 3.93 (s, 2H, CH₂Br), 7.32 (dd, 1H, $J=2.1$, 8.5 Hz, H_{ar}), 7.39 (d, 1H, $J=2.1$ Hz, H_{ar}), 7.85 (d, 1H, $J=8.5$ Hz, H_{ar}).

¹³C NMR δ_C (50 MHz, CDCl₃): 15.2, 32.5, 57.4, 100.1, 126.7, 130.8, 132.1 133.5, 134.5, 135.1.

IR (film): 2977, 2920, 2890, 1586, 1557, 1468, 1376, 1268, 1054, 823, 636.

2.3. 2-Bromo-1-ethoxy-(2',4'-dichloro)styrene (**1**) (a sum of isomers)

2,4-Dichlorophenacyl bromide diethyl ketal (**5**) (13.1 g; 0.038 mol) was placed in a flask of 250 ml capacity equipped with a distillation condenser. Xylene (mixture of isomers, 60 ml) and a catalyst, Nafion NR50 (0.15 g) were added. The mixture of xylene and ethanol was slowly distilled off. Simultaneously, additional xylene (100 ml) was added dropwise into the distillation flask from a dropping funnel placed on the top of a distillation adapter. Overall, 153 ml of the mixture of xylene and ethanol were distilled off. The residue contained 36% of the product (GC) was diluted with chloroform (20 ml) and placed in a separa-

tion funnel. The chloroform layer was washed with 5% sodium carbonate solution (15 ml), water (2×15 ml), dried with anhydrous magnesium sulfate, filtered, and concentrated to dryness to afford the crude product (11.3 g), which was subjected to column chromatography to give 2-bromo-1-ethoxy-(2',4'-dichloro)styrene (**1**) as a colorless oil: 9.212 g, 82%, n_D^{26} 1.5734, purity 98.2% (GC, isomer ratio: 42.9%:55.2%), content of the starting ketal **5**: 1.4%.

EI GC/MS; retention time: 12.616 min (43.1%), 12.916 min (55.2%) (internal standardization); the same mass spectrum for both isomers: 298 (28), 296 (62), 294 (43, M), 270 (46), 268 (100), 266 (62), 241 (9), 237 (13), 189 (34), 187 (52), 175 (50), 173 (95), 171 (42), 161 (30), 159 (47), 148 (21), 146 (32), 136 (14), 135 (15), 125 (25), 123 (76), 111 (11), 109 (20), 99 (21), 75 (21), 74 (22).

¹H NMR δ_H (500 MHz, sum of isomers, CDCl₃): 1.26 (t, 3H, $J=7.0$ Hz, OCH₂CH₃), 1.35 (t, 3H, $J=7.0$ Hz, OCH₂CH₃), 3.69 (q, 2H, $J=7.0$ Hz, OCH₂CH₃), 3.90 (q, 2H, $J=7.0$ Hz, OCH₂CH₃), 5.56 (s, 1H, CHBr), 5.59 (s, 1H, CHBr), 7.24–7.31 (m, 4H, H_{ar}), 7.42–7.45 (m, 2H, H_{ar}).

¹³C NMR δ_C (50 MHz, sum of isomers, CDCl₃): 14.6, 15.4, 64.9, 65.6, 82.8, 90.1, 127.2, 127.4, 129.8, 130.1, 131.6, 131.8, 132.1, 132.2, 133.5, 134.4, 135.6, 136.0, 153.3, 155.3.

IR (sum of isomers, film): 2981, 1625, 1584, 1470, 1377, 1305, 1187, 1130, 1102, 1052.

2.4. 2,2-Dibromo-1-ethoxy-(2',4'-dichloro)styrene (**2**)

2-Bromo-1-ethoxy-(2',4'-dichloro)styrene (**1**) (0.760 g, 0.0026 mol) in methylene chloride (2 ml) was placed in a reactor equipped with a magnetic stirring bar, reflux condenser, dropping funnel, thermometer, and hydrogen bromide absorber. The solution of bromine (0.41 g, 0.129 ml) in methylene chloride (3.2 ml) was added dropwise at 0°C at such a rate to maintain a colorless solution. After all the bromine solution had been added, the temperature of the reaction mixture was increased to 10°C and triethylamine (0.44 g, 0.6 ml, 0.004 mol) was added dropwise. The temperature of the reaction mixture rose violently to 45°C, the solution was stirred for 0.5 hr, and then was left for 48 hr at room temperature. Hexane (10 ml) was added to the solution, and the formed precipitate was filtered off. The filtrate was concentrated to dryness to afford a dark residue (0.934 g), which was subjected to column chromatography to give 2,2-dibromo-1-ethoxy-(2',4'-dichloro)styrene (**2**) as a colorless oil: 0.551 g, n_D^{25} 1.5925, purity 89.5% (GC), content of the 2-bromo-1-ethoxy-(2',4'-dichloro)styrene (**1**), only one isomer: 9%. Yield of **2**: 50.6%.

EI GC/MS; retention time: 14.556 min, 89.5% (internal standardization): 378 (14), 376 (41), 374 (45), 372 (18, M), 350 (31), 348 (88), 346 (100), 344 (40), 319 (7), 317 (8), 269 (10), 267 (23), 265 (14), 250 (15), 248 (10), 241 (13), 239 (29), 237 (19), 202 (24), 200 (47), 198 (23), 175 (55), 173 (85), 159 (39), 157 (57), 147 (26), 145 (40), 123 (20), 109 (30), 99 (13), 98 (15), 87 (21), 75 (20), 74 (22), 73 (13).

¹H NMR δ_H (200 MHz, CDCl₃): 1.26 (t, 6H, $J=7.0$ Hz, CH₃), 3.63 (q, 1H, $J=7.0$ Hz, OCH₂), 7.28 (d, 1H, $J=8.5$ Hz, H_{ar}), 7.32 (dd, 1H, $J=2.0$, 8.5 Hz, H_{ar}), 7.48 (d, 1H, $J=2.0$ Hz, H_{ar}).

^{13}C NMR δ_{C} (50 MHz, CDCl_3): 15.3, 66.3, 78.9, 127.4, 129.9, 131.1, 132.1, 134.8, 136.3, 151.4.

IR (film): 2981, 1583, 1469, 1377, 1284, 1241, 1108, 1054.

Results and Discussion

Bromfenvinphos manufactured in the Institute of Industrial Organic Chemistry was analyzed by both electron ionization mass spectrometry (EI GC/MS) and chemical ionization mass spectrometry (CI GC/MS).

GC peaks were attributed to the main component, bromfenvinphos and the known impurities were recognized. Besides the above mentioned peaks, three new signals were identified. The following retention times were found: $\tau_1=12.6$ min (0.04%), $\tau_2=12.9$ min (0.32%) and $\tau_3=14.5$ min (0.15%) (Fig. 2).

The impurity, which is characterized by a peak retention time of $\tau_2=12.9$ min (EI GC/MS) exhibits a molecular peak at $m/z=294$ and an isotope profile corresponding to 2Cl and 1Br. The peak retention time of $\tau_3=14.5$ min (EI GC/MS) exhibits a molecular peak at $m/z=372$ and an isotope profile corresponding to 2Cl and 2Br. Analysis of both peaks (τ_2 , τ_3) by CI GC/MS confirmed that the respective signals $[\text{M}+1]^+$ ions at m/z 295 and m/z 373 correspond to the recognized molecular ions 294 and 372. Analysis of the impurity, which is characterized by the peak retention time of $\tau_1=12.6$ min (CI GC/MS) exhibits a signal at $[\text{M}+1]^+$ ion at m/z 295 and an isotope profile similar to 2Cl and 1Br (analogous to the peak retention time of $\tau_2=12.9$ min), which corresponds to molecular mass 294.

The following fragmentation pathways for the signals characterized by the peak retention times of $\tau_2=12.9$ min and $\tau_3=14.5$ min (EI GC/MS) are proposed (Eqs. 1, 2).

Fig. 2. Part of the GC/MS chromatogram of bromfenvinphos.

Fig. 3. Structures of 2-bromo-1-ethoxy-(2',4'-dichloro)styrene ($1 \Leftrightarrow \tau_1$, τ_2), two geometric isomers and 2,2-dibromo-1-ethoxy-(2',4'-dichloro)styrene ($2 \Leftrightarrow \tau_3$).

and

For both signals (τ_2 and τ_3) the characteristic acyl fragment at m/z 173 ($2,4\text{-Cl}_2\text{C}_6\text{H}_3\text{C}\equiv\text{O}^+$) was recognized. The presented characteristic fragments suggested the following structure for both impurities: 2-bromo-1-ethoxy-(2',4'-dichloro)styrene ($1 \Leftrightarrow \tau_1$, τ_2) and 2,2-dibromo-1-ethoxy-(2',4'-dichloro)styrene ($2 \Leftrightarrow \tau_3$) (Fig. 3).

The expected *O,O*-dialkyl-*O*-[1-(2,4-dichlorophenyl)]-2-bromovinyl phosphates are the products of the Perkow reaction²³⁾ between trialkyl phosphites and 2,4-dichlorophenacylidene bromide. Besides the expected main product, compounds with two bromine atoms, without bromine at all, and compounds with *alpha*-alkoxy substituent and 2,4-dichlorophenacyl bromide are present.²⁰⁾ The authors propose the formation mechanism of the above products (including 1 and 2). The following ion pairs are suspected to play a key role in the formation of 1 and 2 (Fig. 4).

The best way to confirm the structure of any compound being identified is to synthesize it and to compare its properties with an analyzed compound. We therefore independently synthesized the investigated impurities 1 and 2; however, although the syntheses of 2-bromo-1-methoxy-(2',4'-dichloro)styrene and 2,2-dibromo-1-methoxy-(2',4'-dichloro)styrene were successful,²⁰⁾ attempts by the same authors to synthesize 2-bromo-1-ethoxy-(2',4'-

Fig. 4. Ion pairs suspected of playing a key role in the formation of 1 and 2.

Fig. 5. Synthesis of 1 and 2.

dichloro)styrene (1) and 2,2-dibromo-1-ethoxy-(2',4'-dichloro)styrene (2) surprisingly failed.²⁰⁾

In our hands the independent synthesis of 1 and 2 succeeded. Comparative analysis of the synthesized compounds with the identified 1 and 2 matched their structures with the proposed structures of the investigated impurities.

1 and 2 were obtained from 2,4-dichloroacetophenone (3), as shown in Fig. 5.

2,4-Dichloroacetophenone (3) was brominated to 2,4-dichlorophenacyl bromide (4), which was obtained in 44% yield as a certified reference material of 99.8% purity (greater than the purity of 4 commercially available). Compound 4 was acetalized with ethyl orthoformate in the presence of various acidic catalysts in anhydrous ethanol. Using 4-toluenesulfonic acid led to 2,4-dichlorophenacyl bromide diethyl ketal (5) in only 7–9% yield. Other acidic catalysts, such as concentrated sulfuric acid, silica gel, alumina, and montmorillonit K, failed. Compound 5 was obtained in 28% yield when superacidic fluorinated resin (Nafion NR 50)^{24–26)} was used. Ethanol was eliminated from 5 in boiling xylene in the presence of an acidic catalyst. Using 4-toluenesulfonic acid led to 1 in 55% yield (sum of isomers). The yield of 1 was increased to 82% (a sum of isomers) when Nafion NR 50 was used as a catalyst. Bromination of 1 afforded 2 in 51% yield. Both synthesized 1 and 2 were characterized by spectral methods (GC MS, ^1H and ^{13}C NMR, IR). The retention times and EI MS of synthesized 1 and 2 were fully consistent with the respective data of 1 and 2 observed during the bromfenvinphos analysis.

As 1 and 2 are impurities of bromfenvinphos, their insecticidal activity against house fly (*Musca domestica*), oriental cockroach (*Blatta orientalis*), granary weevil (*Sitophilus granarius*), and two-spotted red spider mite (*Tetranychus urticae*) was tested. Bromfenvinphos was used as a reference compound. No insecticidal activity of 1 and 2 was revealed.

Conclusion

2-Bromo-1-ethoxy-(2',4'-dichloro)styrene (1) (as a mixture of geometric isomers) and 2,2-dibromo-1-ethoxy-2',4'-dichloro)styrene (2) were recognized as bromfenvinphos impurities. They were independently synthesized and fully characterized.

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