Studies on Optically Active Pesticides, I

Synthesis and Herbicidal Activity of d(+) and l(−) Methyl-2-chloro-3-(4-chlorophenyl)-propionate

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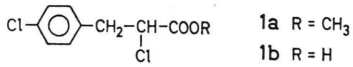
Methyl-2-chloro-3-(4-chlorophenyl)-propionate, Herbicidal Activity

d(+) and l(−) Methyl-2-chloro-3-(4-chlorophenyl)-propionate (common name chlorfenprop-methyl; trade mark Bidisin®) were prepared and their herbicidal activities studied on *Avena fatua* L. and *Avena sativa* L. ("Flämingskrone"). The l(−) enantiomer was found to be twice as active as the racemate; the d(+) form almost inactive.

Introduction

Many cases are known in which only one optical isomer of a racemic, biologically active substance possesses the activity, its enantiomer being much less potent. Pharmaceuticals are usually thoroughly investigated in this respect. For pesticides too there is a growing interest as the results might allow some conclusion regarding the mechanism and site of action.

Chlorfenprop-methyl (**1a**) (methyl-2-chloro-3-(4-chlorophenyl)-propionate; trade mark Bidisin®) controls wild oats (*Avena fatua* L.) very selectively [1, 2]. Its mechanism of action has been investigated



1

by Fedtke [3] and more recently by Amrhein *et al.* [4]. The product of hydrolysis, chlorfenprop (**1b**) (2-chloro-3-(4-chlorophenyl)-propionic acid), is thought to interfere with the action of auxin. We wish to report in this paper the synthesis of the optical isomers of chlorfenprop-methyl (**1a**) and their comparative herbicidal activities.

Chemical Methods

Melting points are uncorrected. The optical rotations were determined on a LEP 0.005° A-1 Zeiss spectrometer. The NMR-spectra were obtained on a Varian T-60 spectrometer in carbon tetrachloride solution using tetramethylsilane as an internal reference. The optically active shift reagent tris-[3-(heptafluoro-*n*-propyl-hydroxymethylene)-d-camphorato]-europium(III) was purchased from Willow Brook Laboratories INC, P.O. Box 526, Waukesha, Wisconsin 53186, USA.

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Racemic 2-chloro-3-(4-chlorophenyl)-propionic acid (**1b**)

To a solution of 219 g (1 mol) methyl-2-chloro-3-(4-chlorophenyl)-propionate [5] in 1 l methanol, a solution of 40 g (1 mol) NaOH in 1 l water was added dropwise. An internal temperature of 10 °C was maintained. The mixture was stirred at room temperature overnight, concentrated to about 1/4 of its volume and acidified with concentrated hydrochlorid acid. The brown precipitate was taken up in methylene chloride, dried over sodium sulfate, filtered and evaporated to dryness. The residue was recrystallised three times from carbon tetrachloride yielding 151 g (69.2%) of the racemic acid **1b**, m.p. 99 °C.

Brucine salt of 2-chloro-3-(4-chlorophenyl)-propionic acid

Water was added dropwise to a stirred solution of 4.38 g (0.02 mol) **1b** and 7.88 g (0.02 mol) brucine in 50 ml of absolute ethanol until the mixture started to become turbid. After being allowed to stand overnight, the precipitate was filtered off and dried at 50 °C in vacuum. Recrystallisation twice from ethanol/water gave 4.7 g (38.4%) salt, m.p. 107 °C.

d(+)2-Chloro-3-(4-chlorophenyl)-propionic acid (d(+) **1b**)

4.7 g (0.0077 mol) brucine salt of d(+) 2-chloro-3-(4-chlorophenyl)-propionic acid, 50 ml of ether, 50 ml of water and 2 ml of concentrated hydrochloric acid were placed in a separatory funnel and shaken until all solid had dissolved. The organic layer was separated, washed with 10 ml 2 N hydrochloric acid and twice with 10 ml of water and dried over sodium sulfate. After evaporation of solvent 1.6 g (95%) crystalline acid were obtained, m.p. 104 °C; $[\alpha]_D^{20} = +0.7°$ (10% in ethanol).

Determination of enantiomeric composition by NMR

50 mg of d(+) 2-chloro-3-(4-chlorophenyl)-propionic acid $[\alpha]_D^{20} = +0.7°$ were esterfied with diazomethane, dissolved in carbon tetrachloride and the enantiomeric composition determind from the NMR-spectrum using the optically active europium shift reagent tris-[3-(heptafluoro-*n*-propylhydroxymethylene)-d-camphorato]-europium (III) complex. The ester was found to consist of 68.6% of d(+) and 31.4% of l(−) isomer. From the $[\alpha]_D^{20}$ value of +0.7° for the original acid, the optical rotation of the pure enantiomeric 2-chloro-3-(4-chlorophenyl)-propionic acid was calculated as $[\alpha]_D^{20} = \pm 1.88°$.

d(+) Methyl-2-chloro-3-(4-chlorophenyl)-propionate (d(+) **1a**)

In a somewhat bigger scale the salt from 0.1 mol brucine and 0.1 mol 2-chloro-3-(4-chlorophenyl)-propionic acid (**1b**) was prepared as described above. After nine recrystallisations 15.2 g (24.8%) brucine salt of the d(+) acid **1b** were obtained, leading to 5.2 g (90.3%) of the d(+) ester **1a**, b.p. 97 – 100 °C/0.1 mmHg, $[\alpha]_D^{20} = +5.9987°$ (10% in ethanol), enantiomeric composition d(+) **1a** = 92.4% and l(−) **1a** = 7.6%.

l(−) Methyl-2-chloro-3-(4-chlorophenyl)-propionate (l(−) **1a**)

The mother liquors from the preparation of the brucine salt of d(+) 2-chloro-3-(4-chlorophenyl)-propionic acid were combined and the solvent evaporated at 50 °C. The residue was dissolved in absolute ethanol and water added dropwise very slowly over a period of several days to precipitate as much of the less soluble brucine salt as possible. After filtration the solution was evaporated, yielding 10.5 g (17.1%) of solid salt which led to 3.1 g (78.4%) of l(−) **1a**, b.p. 97 – 100 °C/0.1 mmHg $[\alpha]_D^{20} = -4.8876°$ (10% in ethanol), enantiomeric composition l(−) **1a** = 86.4% and d(+) **1a** = 15.6%.

From the two enantiomeric compositions and their corresponding optical rotations, the $[\alpha]_D^{20}$ was calculated for optically pure **1a**

$$\frac{5.9987}{92.4 - 7.6} \cdot 100 = 7.06,$$

$$\frac{4.8876}{84.6 - 15.4} \cdot 100 = 7.06,$$

leading to a value of $[\alpha]_D^{20} = \pm 7.06°$.

Biological Method

"Leaching test": Oats (*Avena sativa* L., variety "Flämingskrone") were germinated for 6 days in the dark at 21 °C. Tissue pieces were cut from the plants representing the part 0 to 1 cm above the seed ("plant bases"). This tissue has been found to be most sensitive to chlorfenprop-methyl (**1a**). Five hundred mg of washed tissue were incubated in 10 ml 0.02 M phosphate buffer pH 6.2 on a rotary shaker for 16 h in the light. The test compound was included in the buffer. The amino acid content in 0.2 ml medium after 16 h was analysed by the ninhydrin reaction.

Post emergence application: Wild oat (*Avena fatua* L.) and oat (*Avena sativa* L., variety "Flämingskrone") were sprayed at the 2 – 3 leave stage with 50 ml of the herbicidal preparations. These preparations were made by dissolving the desired amount of either optically active or racemic chlorfenprop-methyl (**1a**) in 1 ml of acetone and adding 49.5 ml distilled water and 0.5 ml Tween 20. Three weeks after spraying, damage to the treated plants was estimated in comparison to that of control plants which had been treated with a 50 ml solution containing distilled water, acetone and Tween 20 in the same quantities as mentioned above.

Results and Discussion

Chemical

Optically pure chlorfenprop (**1b**) has a very small specific rotation $[\alpha]_D^{20} = \pm 1.88°$ and was not suitable for the determination of enantiomeric compositions. Therefore the method of Goering *et al.*[6] was used to follow the separation of enantiomers and to determine the final optical purities. In a typical experiment 100 mg of the brucine salt of **1b** were treated with dilute hydrochloric acid. The propionic acid **1b** (partly optically active) was extracted with ether and esterified with an ethereal

solution of diazomethane. After evaporation of solvent the residual ester **1a** was taken up in carbon tetrachloride and subjected to NMR spectroscopic study. The NMR sample was treated with an optically active chemical shift reagent which formed two soluble diasteriomeric complexes with d(+) **1a** and l(−) **1a**. These gave rise to two sharp, clearly separated singulets for the protons of the ester methyl groups. Integration showed the quantitative enantiomeric composition directly.

The two diastereomeric brucine salts of **1b** could not be separated completely by recrystallisation. Thus the enantiomers of **1a** were obtained in an optically slightly impure form. The d(+) component contained 7.6% of the l(−) isomer and the l(−) component 15.6% of the d(+) form. Using the enantiomeric compositions and their corresponding optical rotations the specific rotation of optically pure **1a** could be calculated, leading independently to the same value of $[\alpha]_D^{20} = \pm 7.06°$ for both enantiomers.

Biological

The biological activities of the optically active samples of chlorfenprop-methyl (**1a**) were tested by post emergence application to oat plants and by incubation of tissue slices in a submersed system ("leaching test"). The results of the experiments with wild oat (*Avena fatua* L.) and a susceptible variety of oats (*Avena sativa* L., "Flämingskrone") are shown in Table I.

Oats of the variety *Avena sativa* L. ("Flämingskrone") were also used for the "leaching test". In this test an analysis is made of the amino acids in the medium which have left the tissue as a consequence of cell damage. Many herbicides, including chlorfenprop-methyl, cause damage to the cell membranes during their herbicidal action enabling the soluble cell contents to be leached. The estimation of the amino acids has been found to be a most useful measure of any damage caused. In Fig. 1 the reaction of oat tissue slices to the optically active enantiomers of chlorfenprop-methyl is shown.

Table I. % Damage three weeks after treatment of wild oat (*Avena fatua* L.) and oat (*Avena sativa* L., "Flämingskrone") with racemic and optically active samples of chlorfenprop-methyl (**1a**).

Sample	Concentration [%]	Wild oat *Avena fatua* L.	Oat *Acena sativa* L.
racemic **1a**	0,1	90	80
	0,05	60	60
d(+) **1a**	0,1	40	40
	0,05	0	0
l(−) **1a**	0,1	100	100
	0,05	85	80

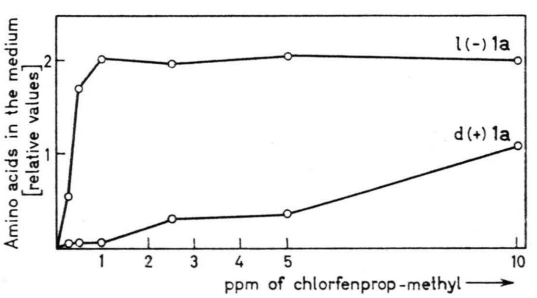

Fig. 1. Leaching of amino acids from tissue of the oat *Avena sativa* L. ("Flämingskrone") shaken 16 h in a chlorfenprop-methyl solution.

As may be seen from the greenhouse test and the "leaching test" only the l(−) enantiomer of chlorfenprop-methyl is active. The activity of the d(+) enantiomer is not greater than would be expected from the amount of l(−) form known to be present (7.6%).

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