Synthesis and Selective Herbicidal Activity of Methyl (*E,Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetate and Analogous Compounds

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In an extensive investigation on the effects of a broad range of 3′-substituent groups in the series of compounds represented by 2-chloro-4-(trifluoromethyl)-3′-(substituted)-4′-nitrodiphenyl ethers, which is known to be generally characterized by potent herbicidal activities, those having 1-[(carbalkoxymethoxy)imino]-2-methoxyethyl substituents at the 3′-position, i.e., the ortho position to the nitro group of the benzene ring, were found to exhibit increased herbicidal activity against broadleaf weeds together with an apparent tendency for reduced crop injury. In the present study, 22 derivatives of (*E,Z*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic acid were synthesized and evaluated for herbicidal activity against grass and broadleaf weeds. Among them, the title compound (Code No. AKH-7088) was found to exhibit particularly excellent potential for the selective control of a wide spectrum of broadleaf weeds in soybeans, with control of current problem weeds such as velvetleaf, cocklebur, and jimsonweed at postemergence application rates of 0.1–0.2 kg/ha and excellent soybean tolerance.

The widespread use of preplant and preemergence herbicides in soybeans has resulted in effective annual grass control, but many broadleaf weeds are resistant and because of reduced competition now present a major problem (Baldwin and Frans, 1972; Mahoney and Penner, 1975). Several 2-chloro-4-(trifluoromethyl)-3′-(substituted)-4′-nitrodiphenyl ether herbicides, while demonstrating good preemergent and postemergent activity against a wide spectrum of grasses and broadleaf weeds, are highly phytotoxic to crops and therefore must be used circumspectly in crop application.

One exception to this has been sodium 5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrobenzoate (acifluorfen-sodium; RH-6201; Blazer), developed as a selective postemergence herbicide against broadleaf weeds in soybeans (Johnson et al., 1978).

In our own intensive studies to develop a novel diphenyl ether herbicide with crop selectivity and high herbicidal activity, with systematic synthesis and investigation of the compounds with various substituent groups at the 3′-position, diphenyl ether derivatives having oxime substituent groups (I in Figure 1) were found to exhibit increased herbicidal activity and soybean selectivity (Hayashi and Misumi, 1987). Among those, AKH-7088 (3 in Table I) was selected by structural optimization based on the structure–activity relationships of many synthesized derivatives.

In this paper, I report the syntheses and structure–activity relationships of compounds I and the postemergent herbicidal activity of AKH-7088 against major broadleaf weeds infesting soybean fields.

EXPERIMENTAL SECTION

Synthetic Routes. (*E,Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]-oxy]acetic acid ester derivatives XI, thioester derivatives XII, and amide derivatives XIII were synthesized from compound 1 or its acid chloride VIII, all as shown in Scheme I.

Compounds XI–XIII were synthesized by methods A–D as shown in Scheme I.

Method A. Compounds XI were synthesized from (*E,Z*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic acid (1) and the corresponding alcohol VII in the presence of an acid catalyst such as concentrated sulfuric acid or *p*-toluenesulfonic acid in alcohol or an inert solvent such as benzene or toluene involving the azeotropic removal of water.

Method B. Compounds XI were synthesized from (*E,Z*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetyl chloride (VIII) and the corresponding alcohol VII in the presence of an organic base such as pyridine or dimethylaniline in an inert solvent such as ether or benzene. When the phenyl ester was synthesized, it was preferable to employ another base such as sodium alcoholate, sodium hydride, or thallium alcoholate in an inert solvent such as ether or benzene.

Method C. Compounds XII were synthesized from compound VIII and the corresponding thiol IX in the presence of

Table I. (*E,Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic Acid Ester Derivatives

compd no.	R^1	synthetic method	% yield	mp, °C [n^{30}_D]
1	H		82	100–102
2	Na		100	95–105 dec
3	CH_3	A	99	57–58
4	C_2H_5	A	99	[1.5276]
5	n-C_3H_7	A	98	[1.5210]
6	$CH_2CH{=}CH_2$	A	98	58–59
7	$CH_2C(CH_3){=}CH_2$	B	80	48.5–49.5
8	$CH_2C{\equiv}CH$	A	92	79–80
9	C_6H_5	B	61	[1.5539]
10	CH_2CH_2Cl	A	95	52.5–53.5
11	$CH_2CH_2OCH_3$	A	92	[1.5218]
12	$CH(CH_3)CH_2OCH_3$	B	70	[1.5178]
13	CH_2COOCH_3	B	65	66–68
14	$CH_2COOC_2H_5$	B	70	[1.5177]

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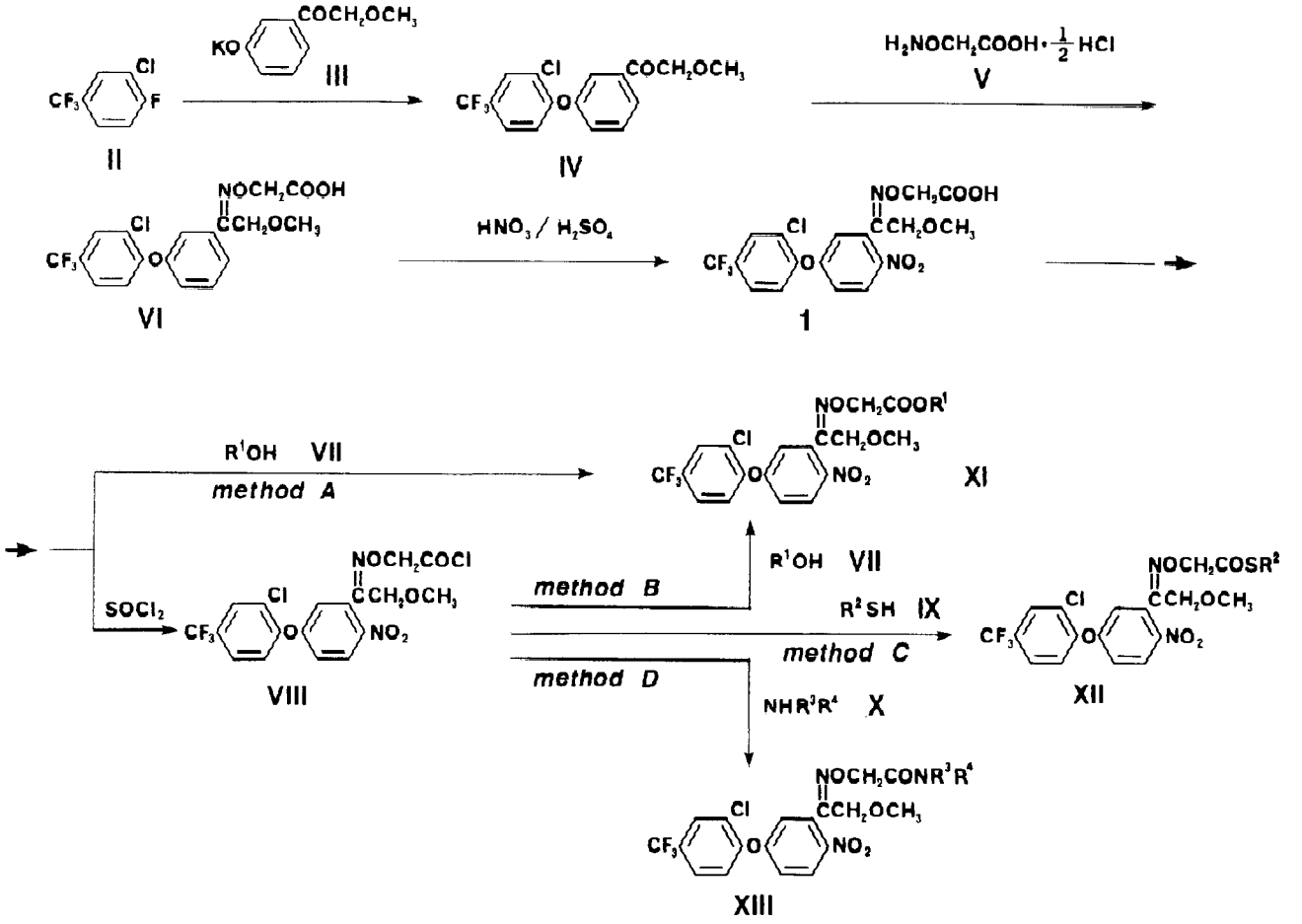
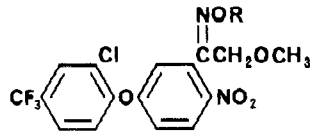
Scheme I. Synthetic Routes of (*E*,*Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]-amino]oxy]acetic Acid Derivatives





(I)

R : CH_2COOR^1, CH_2COSR^2, $CH_2CONR^3R^4$

R^1 : H, Na, alkyl, allyl, propargyl, phenyl

R^2: alkyl, allyl

R^3,R^4: H, CH_3, OCH_3

AKH-7088: $R^1 = CH_3$

Figure 1. General formula of (*E*,*Z*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]-amino]oxy]acetic acid derivatives.

acid acceptor such as pyridine or triethylamine in an inert solvent such as ether, benzene, or *N*,*N*-dimethylacetamide. The alkaline salt of thiol was employed as a suitable reactant.

Method D. Compounds XIII were synthesized from compound VIII and the corresponding amine X in the presence of an acid binder such as triethylamine or excessive reactant amine in an inert solvent such as ether, benzene, or *N*,*N*-dimethylacetamide.

The (*E*,*Z*)-[[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic acid derivatives of this study are listed in Tables I–III.

Melting points were determined with a Mettler FP61 melting point apparatus and are uncorrected (degrees Celsius).

Table II. (*E*,*Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]thioacetic Acid Ester Derivatives

compd no.	R^2	synthetic method	% yield	mp, °C [n^{30}_D]
15	CH_3	C	80	70–72
16	C_2H_5	C	88	61.5–62.5
17	$CH_2CH{=}CH_2$	C	68	52–55
18	CH_2COOCH_3	C	58	[1.5478]

Table III. (*E*,*Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetamide Derivatives

compd no.	R^3	R^4	synthetic method	% yield	mp, °C
19	H	H	D	67	gummy
20	H	CH_3	D	75	gummy
21	CH_3	CH_3	D	88	gummy
22	CH_3	OCH_3	D	92	85–88

Refractive indexes were determined with an Abbe refractometer. Infrared spectra were recorded on a Shimadzu IR-400 infrared spectrometer. Mass spectra were recorded on JEOL DX-303 and Q10A instruments. NMR spectra were recorded on JEOL GX-270 and PMX-60_{SI} instruments. Satisfactory elemental analyses were obtained for all compounds, including those for which the results are not described here.

E and *Z* isomers, known as geometrical isomers of oxime derivatives, were not mutually isolated, and physical properties were therefore determined for the mixture of the two. (In a subsequent, as yet unpublished study, the *E* and *Z* isomers of AKH-7088 were respectively synthesized and isolated, the chemical structures of each were elucidated, and herbicidal activity was evaluated.)

Table IV. Greenhouse Preemergent and Postemergent Herbicidal Activities and Selectivities of (*E,Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic Acid Derivatives, As Determined for Weeds on Day 14 and Crops on Day 21 after Application

	herbicidal activities and crop injury											
	preemergence treatment						postemergence treatment					
compd no.	CG	VL	LQ	SW	SOY	CN	CG	VL	LQ	SW	SOY	CN
1	1	2	4	2	0	0	0	3	2	3	0	0
2	1	2	4	1	0	0	0	3	2	3	0	0
3	4	4	5	5	0	0	3	5	5	5	2	1
4	4	4	5	5	0	0	3	5	5	5	2	1
5	1	3	4	2	0	0	0	5	3	4	0	0
6	2	3	5	4	0	0	0	5	4	5	1	0
7	1	2	5	3	0	0	0	5	3	5	1	0
8	2	3	4	3	0	0	1	5	3	5	1	0
9	3	3	5	4	0	0	1	5	5	5	1	0
10	1	2	4	2	0	0	0	5	5	5	1	0
11	1	2	4	3	0	0	2	4	4	5	1	0
12	1	2	5	3	0	0	1	4	5	5	1	0
13	1	2	2	1	0	0	0	5	3	5	1	0
14	1	2	2	1	0	0	0	5	4	5	1	0
15	2	3	5	4	0	0	1	5	3	5	0	0
16	2	3	5	3	0	0	1	5	5	5	1	0
17	2	3	5	3	1	0	1	5	3	5	1	0
18	2	3	4	3	0	0	0	5	4	5	1	0
19	0	2	4	1	0	0	0	3	2	2	0	0
20	0	2	3	2	0	0	1	4	3	3	0	0
21	0	2	4	1	0	0	1	2	3	3	0	0
22	2	3	5	3	0	0	0	5	5	5	1	0

Table V. Field Herbicidal Activity of Postemergent (*E,Z*)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic Acid Derivatives, as Percent of Untreated Control Growth Determined for Weeds on Day 14 and for Soybean on Day 21 after Application

compd no.	kg/ha	CG	LQ	SW	VL	MG	HS	JW	PW	PS	SP	CB	SOY
3	0.4	55	93	100	100	78	100	100	100	100	78	96	18
	0.2	40	81	100	100	65	100	100	100	99	68	92	8
	0.1	27	73	98	100	40	90	97	100	96	51	88	2
	0.05	14	72	97	100	24	88	95	99	93	40	65	0
4	0.45	35	90	100	100	75	100	100	100	100	72	90	28
	0.15	17	75	100	100	48	100	100	100	94	67	82	18
	0.05	12	68	84	100	20	78	90	91	88	55	65	8
6	0.45	40	90	100	100	72	100	100	100	100	65	91	25
	0.15	20	78	95	100	55	100	100	89	90	50	68	9
	0.05	10	62	78	100	18	80	88	80	78	30	52	0
9	0.45	30	90	100	100	70	100	100	100	100	45	93	22
	0.15	20	82	97	100	47	100	100	91	96	30	61	12
	0.05	10	74	70	100	18	85	86	84	88	20	48	0
10	0.45	37	92	100	100	68	100	100	100	98	48	83	15
	0.15	28	77	94	100	42	100	100	90	80	15	70	8
	0.05	7	65	80	100	20	85	100	81	69	10	45	0
leaf stage		2.5–4.5	6–10	5–8	3–5	2–4	3	3	4–9	2–3.5	2	4.5–5.5	1.2–2 trifoliates
height, cm		6–12	10–15	10–18	6–17	5–9	3–7	8–15	7–15	4–5.5	5–6	15–20	13–16

Syntheses of Compounds. *3′-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-methoxyacetophenone (IV).* A solution of 63.0 g (0.32 mol) of 3-chloro-4-fluorobenzotrifluoride (II) and 61.2 g (0.30 mol) of potassium salt of 3′-hydroxy-2-methoxyacetophenone (III) in 200 mL of dimethyl sulfoxide was stirred at 95–100 °C for 2 h. The cooled reaction mixture was poured into 300 mL of cold water, and the reaction product was extracted twice with 200 mL of ether. The combined ethereal layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to give a crude product. This was subjected to vacuum distillation to obtain a fraction at 160–170 °C (2.5 mmHg). The fraction was allowed to stand to obtain 85.8 g (83% yield) of product, mp 104.5–106 °C, as white crystals. Anal. Calcd for $C_{16}H_{12}ClF_3O_3$: C, 55.74; H, 3.50; Cl, 10.28. Found: C, 55.82; H, 3.52; Cl, 9.98.

(E,Z)-[[[1-[3-[2-Chloro-4-(trifluoromethyl)phenoxy]phenyl]-2-methoxyethylidene]amino]oxy]acetic Acid (VI). A solution of 68.9 g (0.20 mol) of compound IV, 9.0 g (0.11 mol) of anhydrous sodium acetate, and 22.9 g (0.21 mol of carboxymethoxylamine hemihydrochloride (V) in 600 mL of ethanol was heated under reflux for 1 h. After completion of the reaction, sodium chloride was removed by filtration and the filtrate was subjected to evaporation–removal of most of methanol under reduced pressure. Subsequently, 300 mL of water and 300 mL of dichloromethane were added to effect extraction. The dichloromethane layer was separated, washed with water, and dried over anhydrous sodium sulfate, followed by evaporation–removal of the solvent under reduced pressure. As a result, there was obtained 81.8 g (98% yield) of light yellow crystals, mp 89–90 °C. Anal. Calcd for $C_{18}H_{15}ClF_3NO_5$: C, 51.75; H, 3.61; Cl, 8.48. Found: C, 51.83; H, 3.58; Cl, 8.10.

(E,Z)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetic Acid (I). A solution of 41.8 g (0.10 mol) of compound VI in 300 mL of dichloromethane was cooled to about −20 °C. To the resulting solution was added a mixed acid at about 0 °C composed of 50.0 g (0.50 mol) of concentrated sulfuric acid (98%) and 6.75 g (0.105 mol) of concentrated nitric acid (98%) dropwise over a period of 30 min. After completion of the dropwise addition, the reaction mixture was warmed to 25–30 °C in 20 min and held at 25–30 °C for an additional 30 min. The reaction mixture was then poured cautiously into 300 mL of ice–water, followed by extraction with dichloromethane. The decanted dichloromethane layer containing the reaction product was washed

with water until a neutral aqueous layer was obtained and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure afforded 46.4 g of a reddish viscous residue and was followed by addition of 62.5 mL of methanol to precipitate the reaction product. The white precipitate was removed by filtration and dried in vacuo to give 34.7 g (75% yield) of light yellowish crystals, mp 100–102 °C. Anal. Calcd for $C_{18}H_{14}ClF_3N_2O_7$: C, 46.71; H, 3.04; N, 6.05; Cl, 7.66. Found: C, 46.80; H, 3.31; N, 5.88; Cl, 7.49.

(E,Z)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetyl Chloride (VIII). A solution of 46.3 g (0.10 mol) of compound 1 and 23.8 g (0.20 mol) of thionyl chloride in 210 mL of benzene was heated under reflux for 8 h. At the end of this period, the solvent and excessive thionyl chloride were removed under reduced pressure to give 47.6 g (99% yield) of an orange viscous substance of compound VIII. The viscosity prevented determination of its refractive index. Anal. Calcd for $C_{18}H_{13}Cl_2F_3N_2O_6$: C, 44.92; H, 2.72; N, 5.82; Cl, 14.73. Found: C, 44.99; H, 2.60; N, 5.68; Cl, 14.95.

Phenyl (E,Z)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetate (9). To a solution of 0.94 g (10 mmol) of phenol in 20 mL of dried *N,N*-dimethylacetamide (DMAc) maintained at about 10 °C was added 0.26 g (11 mmol) of sodium hydride (in the form of an oil suspension at a concentration of about 60% by weight). The resulting mixture was stirred at room temperature for about 30 min until hydrogen gas was no longer generated, followed by cooling to 5–10 °C. To the resulting solution was added 4.81 g (10 mmol) of compound VIII in 10 mL of dried DMAc at 5–10 °C. Then, the reaction was allowed to proceed at room temperature for 2 h. Cold water and ether were then added to extract the reaction product. The separated ethereal layer was washed with water and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo, thereby to obtain crude product, which was purified by chromatography on a silica gel column. The purified product was eluted from the column with a toluene–acetone gradient system. As a result, there was obtained 3.3 g (61% yield) of compound 9 as a light yellow oily substance having a refractive index n^{30}_D of 1.5539. Anal. Calcd for $C_{24}H_{18}ClF_3N_2O_7$: C, 53.49; H, 3.36; N, 5.19; Cl, 6.57. Found: C, 53.56; H, 3.20; N, 5.01; Cl, 6.25.

S-Ethyl (E,Z)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]thioacetate (16). To a solution of 0.62 g (10 mmol) of ethanethiol in 20 mL of dried *N,N*-dimethylacetamide (DMAc) maintained at about 0 °C was added 0.26 g (11 mmol) of sodium hydride (in the form of an oil suspension at a concentration of about 60% by weight). The resulting mixture was stirred at 10–15 °C for about 30 min until hydrogen gas was no longer generated, followed by cooling to about 5 °C. To the solution was added 4.81 g (10 mmol) of compound VIII in 10 mL of dried DMAc at about 5 °C. The reaction was allowed to proceed at room temperature for 1 h. Cold water and ether were then added to extract the reaction product. The separated ethereal layer was washed successively with dilute alkaline aqueous solution and water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure afforded a crude product that was purified by chromatography on a silica gel column. The purified product was eluted from the column with a toluene–acetone gradient system, to give 4.46 g (88% yield) of light yellow crystals, mp 61.5–62.5 °C. Anal. Calcd for $C_{20}H_{18}ClF_3N_2O_6S$: C, 47.39; H, 3.57; N, 5.52; S, 6.32. Found: C, 47.50; H, 3.66; N, 5.41; S, 5.99.

N-Methyl-N-methoxy-(E,Z)-[[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetamide (22). To a solution of 0.98 g (10 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in 20 mL of dried *N,N*-dimethylacetamide maintained at 5–10 °C was added 2.22 g (22 mmol) of triethylamine. To the resulting solution was added 4.81 g (10 mmol) of compound VIII in 10 mL of dried DMAc at about 5 °C. The reaction was allowed to proceed at room temperature for 30 min. Cold water and ether were then added to extract the reaction product. The separated ethereal layer was washed successively with dilute acidic aqueous solution, dilute alkaline aqueous solution, and water and dried over anhydrous sodium sulfate. The ether was then distilled off in vacuo to obtain crude product, which was purified by recrystallization from a hexane–ethyl acetate mixture, to obtain 4.65 g (92% yield) of light yellow crystals, mp 87–88 °C. Anal. Calcd for $C_{20}H_{19}ClF_3N_3O_7$: C, 47.48; H, 3.78 N, 8.30; Cl, 7.00. Found: C, 47.65; H, 3.61 N, 8.19; Cl, 6.78.

Methyl (E,Z)-[[[1-[5-[2-Chloro-4-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetate (3, AKH-7088). A solution of 46.3 g (0.1 mol) of compound 1 and 1.52 g (8 mmol) *p*-toluenesulfonic acid monohydrate in 400 mL of methanol was heated under reflux for 2 h. The catalyst was then titrated with 1 equiv of sodium hydroxide to prevent hydrolysis of an ester product during solvent removal. The methanol was distilled off under reduced pressure. The residue was dissolved in ethyl acetate, and the ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate, followed by evaporation–removal of the solvent in vacuo. As a result, there was obtained 47.1 g (99% yield) of a gummy substance that was allowed to stand at room temperature to obtain white crystals, mp 57–58 °C. Anal. Calcd for $C_{19}H_{16}ClF_3N_2O_7$: C, 47.86; H, 3.38; N, 5.87; Cl, 7.43. Found: C, 47.75; H, 3.29; N, 5.61; Cl, 7.08. ^1H NMR ($CDCl_3$): δ 3.20 and 3.36 (s, 3 H, CH_3), 3.70, 3.77 (s, 3 H, CH_3), 4.31, 4.55, 4.57, and 4.72 (s, 2 H, CH_2), 6.98–8.22 (m, 6 H, aromatic).

Biological Testing. All new compounds, 1–22, were evaluated for preemergent and postemergent herbicidal activity in the greenhouse. Each test formulation, as an emulsifiable concentrate, was prepared by the thoroughly mixing 10 parts by weight of the test compound, 10 parts by weight of Sorpol 3005X (surfactant), 40 parts by weight of xylene, and 40 parts by weight of cyclohexanone. All application composition, for both the greenhouse test and the subsequent field test, were prepared by dilution of the concentrate in water at 1000 L/ha.

Seeds of three broadlead species, one grassy weed species, and two crops were planted in pots each having a surface area 0.24 m^2 filled with a sterilized upland soil. The test broadleaf species were velvetleaf (*Abutilon theophrasti*; VL), lambsquarter (*Chenopodium album*; LQ), and smartweed (*Polygonum lapathifolium*; SW); the grass was large crabgrass (*Digitaria ciliaris*; CG); the crops were soybean (*Glycine max* var. Williams; SOY) and corn (*Zea mays*; CN).

Preemergence application was effected, by applying the composition in a dosage of 0.2 kg/ha, 24 h after seed planting. Postemergence treatment was effected by applying the composition in a dosage of 0.1 kg/ha when the soybean, corn, and weeds were, respectively, at the 2–3-leaf stage, 3–4-leaf stage, and 2–2.5-leaf stage. All treatments were replicated three times. Herbicidal effect on weeds was observed on day 14 after treatment. Degree of injury to crop plants was observed on day 21. The observed herbicidal effects and crop injury were both classified by growth inhibition, on a scale of 5: 5, more than 90% (substantial suppression); 4, 70–90%; 3, 40–70%; 2, 20–40%; 1, 5–20%; 0, less than 5% (nonherbicidal effect).

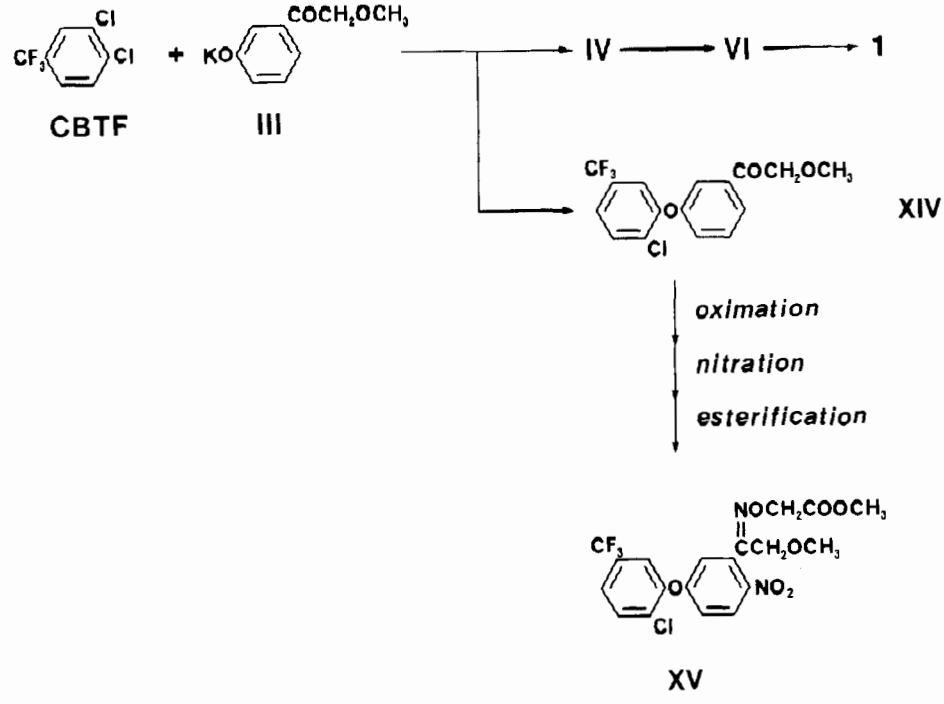
Five of the compounds were selected on the basis of the pot test results, for further evaluation of postemergent herbicidal effects at a field test in Yokohama, Kanagawa, Japan, in June 1986. In the soil of each plot (1–2 m^2) cocklebur (*Xanthium strumarium*; CB), morningglory (*Ipomoea spp.*; MG), sicklepod (*Cassia obtusifolia*; SP), pigweed (*Amaranthus retroflexus*; PW), jimsonweed (*Datura stramonium*; JW), hemp sesbania (*Sesbania exaltate*; HS), prickly sida (*Sida spinosa*; PS) and the weeds described in the pot test and soybean were sown as seeds and allowed to grow. At the time of application in the dosage shown in Table II, the weed leaf stage and height were 2–10 and 3–20 cm, respectively, and the crop leaf stage and height were trifoliates 1.2–2 and 13–16 cm. All treatments were replicated three times. On day 14, percent weed control was determined by visual estimation of percent plant growth reduction in treated as compared with nontreated plots. On day 21, percent crop injury was determined in the same manner.

RESULTS AND DISCUSSION

Syntheses. The intermediate and end compounds shown in Scheme I were readily and effectively synthesized with compound II as the starting material.

Synthesis with 3,4-dichlorobenzotrifluoride (CBTF) as

Scheme II. Process of Formation of Methyl (*E,Z*)-[[[1-[5-[2-Chloro-5-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetate, as an Impurity in AKH-7088

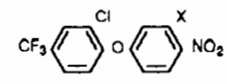
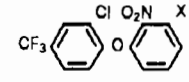
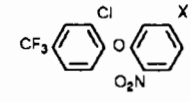
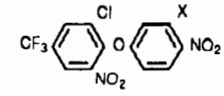


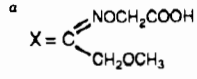
the starting material was also investigated, because of its ready availability and low price. In the synthesis of compound IV from this material, however, a competing isomeric side reaction was observed to result in the formation of 3′-[2-chloro-5-(trifluoromethyl)phenoxy]-2-methoxyacetophenone (XIV), apparently as indicated in Scheme II, as 8–10% by weight of the total reaction product. The selectivity of the coupling reaction was apparently temperature dependent. The two isomers were very similar in physicochemical properties, and attempts to separate compound XIV by the standard methods proved ineffective. It was found, furthermore, that compound XIV underwent the series of oximation, nitration, and esterification reactions indicated in Scheme II upon addition of compound V, mixed acid, and alcohol, respectively, resulting in the formation of methyl (*E,Z*)-[[[1-[5-[2-chloro-5-(trifluoromethyl)phenoxy]-2-nitrophenyl]-2-methoxyethylidene]amino]oxy]acetate (XV), mp 83–85 °C. It therefore appeared that effective removal of compound XIV derivatives at some later stage of the overall synthesis scheme would be necessary in order to obtain AKH-7088 in sufficiently pure form.

Nitration of compound VI in the presence of compound XIV oximation products was observed to result in a number of isomeric reaction products at various reaction temperatures. The principal isomers of compound 1 at temperatures of 0 and −20 °C are shown in Table VI. As indicated by the increased yield of compound 1 at −20 °C, the selectivity of the reaction for nitration at the position shown in compound 1 apparently increased at lower temperatures. It was also found that the presence of water, whether as an initial ingredient or an intermediate product, tended to decrease this selectivity.

Addition of methanol to the reaction mixture following nitration, however, was found to result in the formation of a white precipipate containing compound 1 as its main component and was substantially free of any other isomeric products. This is apparently attributable to the preferential formation of a molecular complex between

Table VI. Principal Isomers in Nitration To Obtain Compound 1

structure[a]	crude, % 0 °C	crude, % −20 °C
	85	92
	10	6.5
	2.5	0.5
	0.5	trace
other miscellaneous	2	1

[a] 

compound 1 and methanol, which thus facilitates the recovery of compound 1 in pure form even where CBTF is used as the starting material. AKH-7088 from CBTF exhibited the same NMR spectral and physicochemical properties as those of AKH-7088 from compound II. Its biological activities were also found to be virtually the same as those described below for the latter. Industrial production from CBTF thus appears both attractive and effective.

Biological Activity. Analysis of the structure–activity relationships of all 22 of the compounds I subjected to the pot and field test indicated compound **3**, AKH-7088, to be clearly superior to the others in both strength and selectivity of herbicidal action.

The influence of the substituent R on the relationship was clear and remarkable. As shown Tables IV and V,

the herbicidal activity of the compounds, as classified by this substituent, was in decreasing order ester, thioester, and amide. With those having R^1 consisting of a methyl, ethyl, ally, 2-chloroethyl, or phenyl (compounds **3**, **4**, **6**, **9**, and **10**, respectively), the activity against broadleaf weeds was strong even at postemergence dosages of 0.05–0.2 kg/ha. With those having R^1 consisting of a hydrogen or sodium atom, the activity was very low even at 0.8–1.2 kg/ha. In addition, compound XV, derived from the coupling isomer, and the compounds derived from the main isomers formed during nitration for compound **1** exhibited almost no herbicidal activity against the weeds tested.

The wide variety of acid derivatives in the compound I series exhibiting herbicidal activity and the particularly strong activity exhibited by those which, on the basis of their R^1 substituent structure, may be presumed to be most readily hydrolyzed suggest that the free acid form, compound **1**, is the essential mediator of the herbicidal effect. The low observed herbicidal activity of compounds **1** and **2** themselves, on the other hand, may reasonably be attributed to relative difficulty in the transport of such free acids into the plant. it thus appears that the two main determining factors for herbicidal effect by the compounds of this series are (1) a log *P* value appropriate for rapid transparent into the plant and (2) ready conversion to free acid at the receptor site by hydrolysis of the ester.

The chemical structure of AKH-7088 would appear to satisfy both of these requirements, and the results of the field test, as shown in Tables IV and V, bear this out. It was found to be highly effective in postemergent application particularly against many broadleaf weeds, including current problem weeds such as velvetleaf, cocklebur, and jimsonweed. The observed efficacies may be summarized as follows. Full control: Velvetleaf, cocklebur, jimsonweed, smartweed, pigweed, prickly sida, hempsesbania. Conditional control: Lambsquarter, morningglory, sicklepod. Limited suppression: Annual grasses.

Velvetleaf, smartweed, jimsonweed, and prickly sida were particularly sensitive to AKH-7088 and were controlled by postemergent dosages as low as 0.05 kg/ha. Cocklebur and hemp sesbania were readily controlled at 0.1–0.2 kg/ha. Lambsquarter was slightly less sensitive but was controlled if treated early (2–3 cm) with 0.2–0.25 kg/ha. Morningglory and sicklepod were controlled at high dosages. Annual grasses were only partially suppressed, even at high dosages.

Soybean at all growth stages, including preemergence, was highly tolerant to AKH-7088. Injury that was observed was localized and temporary. It occurred as leaf crinkling and speckling soon after application, particularly on the youngest leaves, but then disappeared rapidly. Corn, rice, and wheat were also observed to be tolerant to pre- and postemergence AKH-7088.

AKH-7088 was also found to be active in preemergence application, but higher dosages were required for effective control. AKH-7088 is clearly a fast-acting contact herbicide. Maximum activity was usually manifested at 3–10 days after application.

Separate experiments have indicated that AKH-7088 would be safe in practical use as a herbicide. Its acute oral LD_{50} and acute dermal LD_{50} in male and female albino rats have been found to be >5000 and >2000 mg/kg, respectively. It has also been found nonmutagenic in the Ames *Salmonella* assay either in the presence or in the absence of rat S-9 metabolic activation.

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