

Radiosynthesis of a Chloroacetanilide Herbicide ([*phenyl*-4-³H]Acetochlor)
and a Dichloroacetamide Safener for Herbicides ([2,2-*dimethyl*-³H]R-29148)

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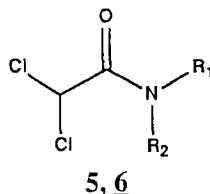
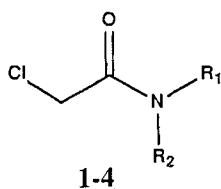
SUMMARY

2-Chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl)acetamide (the chloroacetanilide herbicide acetochlor) and 3-(dichloroacetyl)-2,2,5-trimethyl-1,3-oxazolidine (the dichloroacetamide safener R-29148) are required at high specific activity for studies on their metabolism and mode of action. [*phenyl*-4-³H]Acetochlor was obtained at 22 Ci/mmol in 71% yield by reductive dehalogenation of iodoacetochlor with tritium gas in ethanol in the presence of palladium on carbon and triethylamine. [2,2-*dimethyl*-³H]R-29148 was prepared at 15 Ci/mmol by treating acetone and 1-amino-2-propanol in pentane with two equivalents of NaOH in tritiated water (*i.e.* hydroxide ion-catalyzed enolization of acetone) followed by dichloroacetyl chloride.

Key words: acetochlor, chloroacetanilide, deuterium labeling, dichloroacetamide, herbicides, R-29148, safeners, tritiated water, tritium gas, tritium labeling

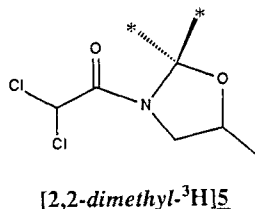
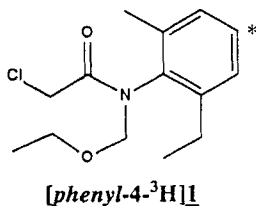
INTRODUCTION

Chloroacetanilides are one of the most important classes of herbicides because they provide selective control of annual grasses and many broad-leaved weeds in corn, soybean and cotton. The major compounds are acetochlor (1) ($R_1 = 2\text{-Et}, 6\text{-MePh}$; $R_2 = \text{CH}_2\text{OEt}$) (see below) and its homologs alachlor (2) ($R_1 = 2, 6\text{-Et}_2\text{Ph}$; $R_2 = \text{CH}_2\text{OMe}$) and metolachlor (3) ($R_1 = 2\text{-Et}, 6\text{-MePh}$; $R_2 = \text{CHMeCH}_2\text{OMe}$).¹ The chloroacetamide allidochlor (4) ($R_1 = R_2 = \text{CH}_2\text{CH}=\text{CH}_2$) was the first herbicide of this class but is no longer used.¹ The mechanism of herbicidal action of chloroacetanilides and chloroacetamides is not defined, although it may involve derivatization of a target thiol since they readily alkylate glutathione (GSH) in biological systems.²⁻⁴ The use of chloroacetanilide herbicides is restricted because they are carcinogens in laboratory animals and possible or probable carcinogens in humans.^{5,6} Their carcinogenic activity may be associated with derivatization of DNA by metabolites formed on oxidation of the R_1 or R_2 substituent.⁷⁻⁹



Dichloroacetamide safeners prevent injury to corn from chloroacetanilide and thiocarbamate herbicides. Two of the most effective safeners are R-29148 (5) (see below) and dichlormid (6) ($R_1 = R_2 = \text{CH}_2\text{CH}=\text{CH}_2$).^{10,11} They elevate the GSH level and GSH *S*-transferase activity in corn thereby facilitating herbicide detoxification and conferring crop safety.^{10,12} Metabolism of dichloroacetamide 6 by rat liver enzymes with GSH and NADPH yields the corresponding glycolamide, glyoxylamide and oxamic acid.¹³ Chloramphenicol, a dichloroacetamide antibacterial, although not an effective safener for thiocarbamate herbicides in corn,¹⁴ is metabolized by rat liver microsomes and NADPH to yield derivatized microsomal protein possibly via a reactive oxamyl chloride intermediate.¹⁵ It is not clear how these metabolic steps relate to safener action in plants and biochemical disruptions in mammals.

Progress in defining the mechanisms by which chloroacetanilides act as herbicides and carcinogens and dichloroacetamides act as herbicide safeners would be greatly facilitated by ³H-labeled compounds of high specific activity, e.g. [*phenyl*-4-³H]1 and [2,2-dimethyl-³H]5.



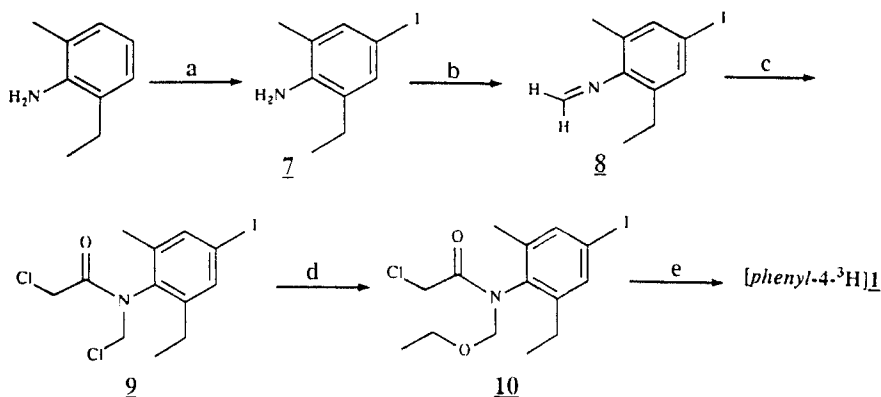
RESULTS AND DISCUSSION

[*phenyl*-4-³H]Acetochlor

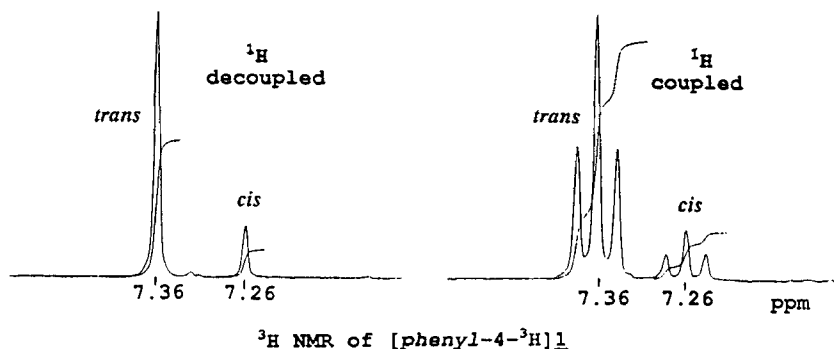
The ¹H NMR spectrum of 1 revealed *trans* (major) and *cis* (minor) rotational isomers for the chloromethyl group relative to the aniline ring resulting from restricted rotation of the chloroacetyl group by the *ortho* alkyl substituents^{16,17} with 15-20% of the *cis* isomer in methanol and 5-10% in chloroform. Heating a solution of 1 in deuterated methanol at 310 °K did not significantly change the rotational isomer ratio.

[*phenyl*-4-³H]1 was synthesized from 4-iodoacetochlor (10) via 2-ethyl-6-methylaniline and 2-ethyl-4-iodo-6-methylaniline (7) by described procedures^{17,18} in 58% overall yield (see scheme). The aniline was treated with iodine

monochloride in chloroform ¹⁹ to give iodoaniline 7 which was heated with paraformaldehyde in heptane in the presence of ethanol and triethylamine with continuous removal of water for 6 h. Enamine 8 was then reacted with chloroacetyl chloride in toluene to give *N*-chloromethyl intermediate 9 (which hydrolyzed easily in the presence of moisture). Freshly prepared 9 was treated with ethanol and triethylamine to obtain 10 which was isolated by preparative TLC. Tritium-iodine exchange in ethanol catalyzed by 10% palladium on carbon gave [phenyl-4-³H]1 (see ³H NMR which shows *trans* and *cis* rotational isomers) with a specific activity of 22 Ci/mmol calculated by HPLC analysis versus an unlabeled standard for amount and scintillation counting for radioactive content. There are also minor products from tritium exchange at aryl positions 3 and 5. Preparative HPLC gave [phenyl-4-³H]1 of >98% radiochemical purity.

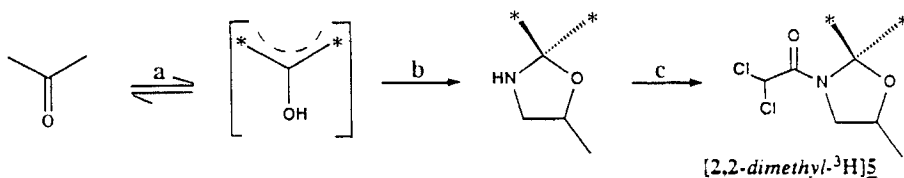


a: ICl, CHCl₃, 90%. b: (CH₂O)_n, heptane, 25% Et₃N, EtOH, Δ, 100%. c: ClCH₂C(O)Cl, toluene, 73%. d: 25% Et₃N, EtOH, CH₂Cl₂, 88%. e: ³H₂, Pd/C (10%), Et₃N, EtOH, 71%.

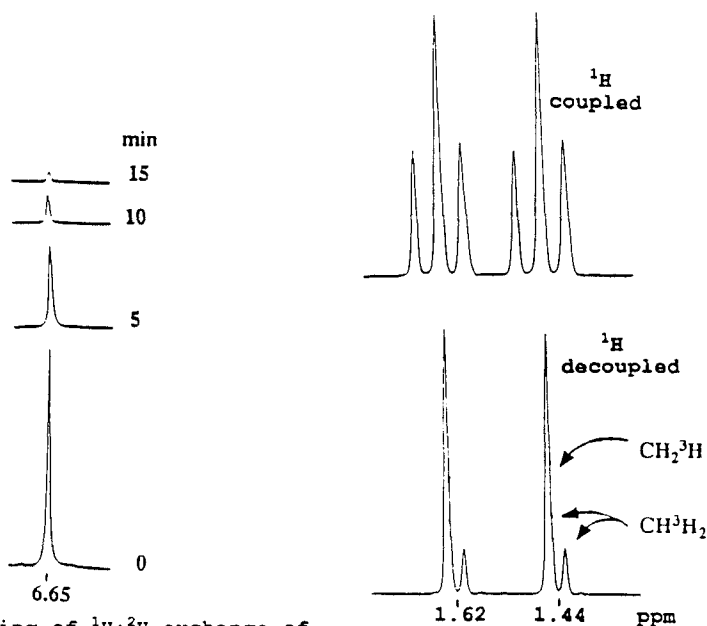


[2,2-dimethyl- ^3H]R-29148

Synthesis of 5 was achieved in 92% yield and >95% purity (NMR and TLC) by mixing acetone and 1-amino-2-propanol in pentane with one molar equivalent of 25% NaOH aqueous solution, then adding dichloroacetyl chloride (see scheme). Two strategies were considered for preparing [^3H]acetone at high specific activity as an intermediate: reduction of 1,3-dichloroacetone by tritium gas; hydroxide ion-catalyzed enolization of acetone (previously prepared at 1.2 Ci/mmol).²⁰ The first approach was abandoned once acetone- d_6 (NMR grade, 99.9% deuterium) was used to prepare [^2H]5 and most of the deuterium was lost, *i.e.* <10% of the product contained deuterium, even when 0.5 molar equivalent of acetone- d_6 was used. Accordingly, regular acetone was used with a fresh solution of NaOH dissolved in $^2\text{H}_2\text{O}$ resulting in >70% deuterium incorporation into [^2H]5.



a: NaOH, $^3\text{H}_2\text{O}$. b: DL-1-amino-2-propanol, pentane. c: $\text{Cl}_2\text{CHC}(\text{O})\text{Cl}$, pentane



^1H NMR monitoring of $^1\text{H}:^2\text{H}$ exchange of $\text{Cl}_2\text{CHC}(\text{O})\text{NR}_2$ proton of 5 in $\text{C}^2\text{H}_5\text{O}^2\text{H}$ using 1.2 equiv. 25% aqueous NaOH in $^2\text{H}_2\text{O}$.

^3H NMR of [2,2-dimethyl- ^3H]5

To synthesize [2,2-dimethyl- ^3H]5, tritiated water (2.5-3.0 Ci/mmol) was mixed with 50% NaOH solution and then with acetone and 1-amino-2-propanol in pentane followed by dichloroacetyl chloride. The product had a specific activity of 15 Ci/mmol calculated from ^1H and ^3H NMRs and was more than 98% pure as judged by reverse phase HPLC. The major labelled species was CH_2^3H plus significant amounts of CH^3H_2 and even C^3H_3 (see ^3H NMR). The proton in the dichloroacetyl group is very acidic and exchanges in the process with ^2H and ^3H (see ^1H NMR).

Dichloroacetamide 5 has a chiral center at C-5 so, although not detailed here, the individual enantiomers were prepared from (R)-(-)- and (S)-(+)-1-amino-2-propanol (Aldrich), but no difference was observed in their activity for elevating GSH levels in corn seedlings (procedure of Lay and Casida¹⁴).²¹ Accordingly, racemic [^3H]5 was prepared for mode of action research.

EXPERIMENTAL

Preparation of [phenyl-4- ^3H]1

2-Ethyl-4-iodo-6-methylaniline (7): to a solution of 2-ethyl-6-methylaniline (1.35 g, 10 mmol) in chloroform (10 mL) was added iodine monochloride (1.62 g, 10 mmol). The resulting dark solution was stirred overnight before it was diluted with chloroform, washed with a saturated solution of NaHSO_3 , dried (MgSO_4), filtered and concentrated in vacuo to give 2.33 g of an oil which was used in the next step without further purification. ^1H NMR (CDCl_3) δ : 7.23 (s, 2H), 3.59 (s, 2H, exchangeable), 2.46 (q, $J=7.02$ Hz, 2H), 2.15 (s, 3H), 1.22 (t, $J=7.02$ Hz, 3H). ^{13}C NMR (CDCl_3) δ : 141.8, 136.2, 134.4, 129.7, 124.3, 79.5, 23.8, 17.2, 12.7.

2-Ethyl-4-iodo-6-methyl-N-methylethaniline (8): a suspension of 7 (1.3 g, 5 mmol) and paraformaldehyde (0.2 g, 6 mmol) and a solution of triethylamine (25%) in ethanol (50 μL) in heptane (50 mL) was heated overnight using a Dean-Stark distilling receiver for continuous removal of water. Then it was filtered and concentrated in vacuo to give 1.36 g of a dark brown oil which was used without further purification. ^1H NMR (CDCl_3) δ : 7.68 (s, 1H, $=\text{CH}_2$), 7.37 (br s, 3H, phenyl, $=\text{CH}_2$), 2.41 (q, $J=7.02$ Hz, 2H), 2.07 (s, 3H), 1.11 (t, $J=7.02$ Hz, 3H). ^{13}C NMR (CDCl_3) δ : 156.5, 150.9, 136.5, 134.9, 134.7, 128.4, 88.0, 24.2, 17.8, 14.4.

2-Chloro-N-(chloromethyl)-N-(2-ethyl-4-iodo-6-methylphenyl)acetamide (9): to imine 8 (0.63 g, 2.3 mmol) in toluene (10 mL) was added chloroacetyl chloride (284 mg, 2.5 mmol) in toluene (5 mL). After stirring for 2 h at room temperature, it was concentrated in vacuo and purified by flash chromatography on silica gel using chloroform as eluent to give 0.65 g of a yellowish oil. ^1H

NMR (CDCl₃) δ : 7.60 (s, 1H), 7.57 (s, 1H), 5.41 (s, 2H), 3.72 (s, 2H), 2.53 (m, 2H), 2.26 (s, phenyl-CH₃, trans), 2.19 (s, phenyl-CH₃, cis), 1.26 (t, $J=7.02$ Hz, phenyl-CH₂CH₃, trans), 1.15 (t, $J=7.02$ Hz, phenyl-CH₂CH₃, cis). ¹³C NMR (CDCl₃) δ : 166.7, 144.0, 138.3, 137.6, 136.6, 136.0, 96.0, 58.6, 41.0, 23.8, 18.3, 14.9.

2-Chloro-N-(ethoxymethyl)-N-(2-ethyl-4-iodo-6-methylphenyl)acetamide (10): to a solution of chloromethyl derivative 9 (0.34 g, 0.88 mmol) in methylene chloride (5 mL) was added a solution of triethylamine in ethanol (25%, 1 mL) after which it was stirred for 24 h at room temperature, concentrated and diluted in methylene chloride. The solution was washed with H₂O, dried (MgSO₄), filtered and concentrated in vacuo. Preparative TLC purification (silica gel, 1 mm plate) with chloroform gave 310 mg of the desired product. ¹H NMR (CDCl₃) δ : 7.55 (s, 1H), 7.53 (s, 1H), 4.98 (dd, $J=10.02$, 4.9 Hz, NCH₂O, trans), 4.90 (dd, $J=10.02$, 16.58 Hz, NCH₂O, cis), 3.70 (m, CH₂Cl and OCH₂, trans), 3.52 (q, $J=7.02$ Hz, OCH₂, cis), 2.52 (m, 2H), 2.26 (s, phenyl-CH₃, trans), 2.22 (s, phenyl-CH₃, cis), 1.23 (t, $J=7.56$ Hz, phenyl-CH₂CH₃), 1.16 (t, $J=7.02$ Hz, OCH₂CH₃). ¹³C NMR (CDCl₃) δ : 167.3, 144.1, 138.5, 137.9, 137.2, 136.2, 95.2, 78.4, 65.9, 41.7, 23.6, 18.0, 15.0, 14.1. Fast atom bombardment-high resolution mass spectrum (FAB-MS) MH⁺: C₁₄H₂₀ClINO₂, calc. 396.02273, found 396.02229. Analytical reverse phase HPLC, Supelco 0.25 x 20 cm, λ = 205 nm, 75% methanol in water, flow 1 mL/min, R_t = 13 min.

1: a suspension of 10 (20 mg, 0.05 mmol), triethylamine (10 μ L, 0.07 mmol) and palladium on carbon (10%, 10 mg) in ethanol (3 mL) was degassed three times and then stirred under slight positive pressure of hydrogen. After 2 h the suspension was filtered and concentrated in vacuo. Preparative TLC (silica gel, chloroform) gave 14 mg of 1. R_t = 7.3 min, analytical HPLC as above. ¹H NMR (CD₃OD) δ : 7.20-7.32 (m, phenyl), 4.99 (s, NCH₂O, trans, 85%), 4.59 (s, NCH₂O, cis, 15%), 3.78 (s, CH₂Cl), 3.66 (q, $J=7.04$ Hz, OCH₂, trans), 3.52 (q, $J=7.04$ Hz, OCH₂, cis), 2.59 (m, phenyl-CH₂), 2.26 (s, phenyl-CH₃, trans), 2.19 (s, phenyl-CH₃, cis), 1.24 (t, $J=7.52$ Hz, phenyl-CH₂CH₃), 1.18 (t, $J=7.04$ Hz, OCH₂CH₃). ¹H NMR (CDCl₃) δ : 7.14-7.30 (m, phenyl), 5.02 (dd, $J=10.03$, 4.92 Hz, NCH₂O, trans, 93%), 4.90 (dd, $J=10.03$, 16.58 Hz, NCH₂O, cis, 7%), 3.74 (q, $J=7.02$ Hz, OCH₂, trans), 3.70 (s, CH₂Cl), 3.50 (q, $J=7.02$ Hz, OCH₂, cis), 2.57 (m, phenyl-CH₂), 2.26 (s, phenyl-CH₃, trans), 2.22 (s, phenyl-CH₃, cis), 1.25 (t, $J=7.57$ Hz, phenyl-CH₂CH₃), 1.19 (t, $J=7.02$ Hz, OCH₂CH₃).

[phenyl-4-³H]1: a solution of 10 (20 mg, 0.05 mmol) and triethylamine (10 μ L, 0.07 mmol) in absolute ethanol (3 mL) was degassed with three freeze, pump, thaw cycles and then a mixture of 10% palladium on carbon (10 mg) was added during the last thaw. The mixture was stirred under slight negative pressure of

tritium gas for 3 h at room temperature. After freeze degassing three times to remove the tritium gas, the mixture was filtered through a polytetrafluoroethylene membrane and lyophilized to give 1.27 Ci of residue. Purification involved HPLC (HP 1040A equipped with diode array UV and β -ram ^3H detectors and Waters pumps and controllers) on a semi-preparative column (Supelco 0.5 x 20 cm, LC 18 DB) using 85% methanol in water with a flow of 2.5 mL/min, R_t =9.05 min. The combined fractions were lyophilized, dissolved in 2.0 mL of methanol and counted. A total of 800 mCi of pure product was obtained in 71% radiochemical yield at a specific activity of 22 Ci/mmol. ^1H NMR (CD_3OD) δ : 7.27 (d, J =8.25 Hz, phenyl, trans), 7.20 (d, J =8.25 Hz, phenyl, trans), 7.14 (d, J =8.25 Hz, phenyl, cis), 7.11 (d, J =8.25 Hz, phenyl, cis), 5.03 (s, NCH_2O , trans, 85%), 4.54 (s, NCH_2O , cis, 15%), 3.78 (s, CH_2Cl), 3.66 (q, J =7.02 Hz, OCH_2 , trans), 3.52 (q, J =7.02 Hz, OCH_2 , cis), 2.56 (m, phenyl- CH_2), 2.26 (s, phenyl- CH_3 , trans), 2.19 (s, phenyl- CH_3 , cis), 1.24 (t, J =7.51 Hz, phenyl- CH_2CH_3), 1.16 (t, J =7.02 Hz, OCH_2CH_3). ^3H NMR (^1H -decoupled, CD_3OD) δ : 7.36 (s, trans, 85%), 7.32 (1% ^3H on phenyl positions 3 and 5), 7.26 (s, cis, 15%). ^3H NMR (^1H -coupled, CD_3OD) δ : 7.36 (t, J =8.12 Hz, trans), 7.26 (t, J =8.12 Hz, cis).

Preparation of [2,2-dimethyl- ^2H and ^3H]5.

[^2H]5: acetone (11 μL , 0.15 mmol, HPLC grade) was diluted in pentane (0.3 mL) in a small vial. To this, DL-1-amino-2-propanol (23 μL , 0.3 mmol) and a freshly-made aqueous solution of NaOH in $^2\text{H}_2\text{O}$ (99.8 atom % ^2H , 25%, 47 μL , 0.3 mmol) were added and the biphasic solution was stirred for 2 h at 25°C. Then it was cooled to 0°C in an ice bath and dichloroacetyl chloride (30 μL , 0.3 mmol) in pentane (0.3 mL) was added dropwise. A precipitate formed immediately and the mixture was stirred overnight. Water (1 mL) was added and the mixture was extracted with pentane (2 mL x 2), which was then dried (MgSO_4), filtered and concentrated in vacuo to give 20 mg of a white solid. ^1H NMR (CDCl_3) δ : 6.03 (s, 0.4 H, 0.6 ^2H), 4.28 (dq, J =5.6, 9.5 Hz, 1H), 3.98 (dd, J =5.6, 9.5 Hz, 1H), 3.28 (t, J =9.5 Hz, 1H), 1.64 (m, 1.3H corresponding to 79% deuterium incorporation into the methyl groups of acetone), 1.38 (d, J =5.6 Hz, 3H). ^2H NMR (C_6D_6) δ : 5.6 (s), 1.59 (s), 1.42 (s). ^{13}C NMR (CDCl_3) δ : 159.2, 95.5, 70.3, 66.5, 51.8, 24.5 (m), 22.2 (m), 17.4. FAB-MS MH^+ : $\text{C}_8^1\text{H}_{10}^2\text{H}_4\text{Cl}_2\text{NO}_2$ as the major product: calc. 230.06527, found: 230.06466.

[^3H]5: platinum oxide (63 mg, 0.27 mmol) was placed in a side-arm round-bottom flask. Carrier free tritium gas was passed in and $^3\text{H}_2\text{O}$ (2.5–3.0 Ci/mmol) was condensed into another vessel and kept under nitrogen atmosphere. An aqueous solution of NaOH in water (50%, 27 μL , 0.33 mmol) was added at 0°C followed by pentane (0.3 mL), acetone (11 μL , 0.15 mmol) and DL-1-amino-2-propanol (23 μL ,

0.3 mmol). The mixture was stirred at 25°C for 2 h then cooled again to 0°C and dichloroacetyl chloride (30 μ L, 0.3 mmol) in pentane (0.3 mL) was added. The reaction was warmed to 25°C and stirred overnight. Most of the pentane was evaporated leaving an orange-colored slurry to which pentane (1 mL) and water (0.5 mL) were added. The upper colorless organic phase was transferred by a double-ended needle to a tube containing MgSO_4 (0.5 g). The aqueous phase was extracted twice with pentane (2.5 mL). The combined organic extracts were transferred to another tube containing MgSO_4 . Then the mixture and a pentane rinse (1 mL) were filtered through glass wool into a conical flask and lyophilized under static pressure to give a white solid, which was more than 98% pure as judged by HPLC on an aliquot in a reverse phase Supelco column as above at λ 216 nm and using 75% methanol in water at 1.6 mL/min, R_t = 4.52 min. No further purification was necessary. The product (700 mCi) had a specific activity of 15 Ci/mmol. ^1H NMR (^1H -coupled, C_6D_6) δ : 5.58 (s), 3.60 (dq, $\underline{J}$ =5.6, 9.5 Hz), 3.06 (dd, $\underline{J}$ =5.6, 9.5 Hz), 2.53 (t, $\underline{J}$ =9.5 Hz), 1.65 (s, CH_3), 1.61 (s, CH_2^3H), 1.47 (s, CH_3), 1.42 (s, CH_2^3H). ^3H NMR (^1H -decoupled, C_6D_6) δ : 5.55 (s, C^3HCl_2), 1.65 (s, CH_2^3H), 1.62 (d, $\underline{J}$ =9.7 Hz, CH^3H_2), 1.47 (s, CH_2^3H), 1.44 (d, $\underline{J}$ =9.7 Hz, CH^3H_2). ^3H NMR (^1H -coupled, C_6D_6) δ : 5.55 (s), 1.65 (t, $\underline{J}$ =13.88 Hz), 1.47 (t, $\underline{J}$ =13.88 Hz).

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REFERENCES

1. Worthing, C.R. and Hance, R.J., Eds. -The Pesticide Manual, 9th Edition, The British Crop Protection Council, Unwin Brothers Limited, Old Woking, Surrey, UK (1991).
2. Devine, M., Duke, S.O. and Fedtke, C. -Physiology of Herbicide Action, P T R Prentice-Hall, Inc., Englewood Cliffs, N.J. (1993).

3. Sharp, D.B. -In Herbicides: Chemistry, Degradation, and Mode of Action (Kearny, P.C. and Kaufman, D.D., Eds.), Marcel Dekker, New York, Vol. 3, pp.301-333 (1988).
4. LeBaron, H.M., McFarland, J.E., Simoneaux, B.J., and Ebert, E. -In Herbicides: Chemistry, Degradation, and Mode of Action (Kearny, P.C. and Kaufman, D.D., Eds.), Marcel Dekker, New York, Vol. 3, pp.335-382 (1988).
5. Stevens, J.T. and Sumner, D.D. In Handbook of Pesticide Toxicology (Hayes, W.J., Jr. and Laws, E.R., Jr., Eds.) Academic Press, New York, Vol. 3, pp. 1341-1345 (1991).
6. Hanson, D. -Chem. Eng. News, p.5, March 21, 1994.
7. Brown, M.A., Kimmel, E.C., and Casida J.E. -Life Sci. 43:2087 (1988) and 44:1325 (1989).
8. Jacobsen, N.E., Sanders, M., Toia, R.F., and Casida, J.E. -J. Agric.Food Chem. 39:1342 (1991).
9. Feng, P.C.C. and Patanella, J.E. -Pestic. Biochem. Physiol. 33:16 (1989).
10. Hatzios, K.K. -In Crop Safeners for Herbicides: Development, Uses, and Mechanisms of Action (Hatzios, K.K. and Hoagland, R.E., Eds.), Academic Press, New York, pp.3-45 and 65-101 (1989).
11. Herbicide Handbook, Sixth Edition, Weed Science Society of America, Champaign, IL. (1989).
12. Lay, M.-M., Hubbell, J.P., and Casida, J.E. -Science 189:287 (1975).
13. Miaullis, J.B., Thomas, V.M., Gray, R.A., Murphy, J.J., and Hollingworth, R.M. -In Chemistry and Action of Herbicide Antidotes (Pallos, F.M. and Casida, J.E., Eds.), Academic Press, New York, pp.109-131 (1978).
14. Lay, M.-M. and Casida, J.E. -Pestic. Biochem. Physiol. 6:442 (1976)
15. Pohl, L.R., Nelson, S.D., and Krishna, G. -Biochem. Pharmacol. 27:491 (1978).
16. Chupp, J.P. and Olin, J.F. -J. Org. Chem. 32:2297 (1967).
17. Chupp, J.P., Olin, J.F., and Landwehr, H.K. -J. Org. Chem. 34:1192 (1969).
18. Ratts, K.W. and Chupp, J.P. -J. Org. Chem. 39:3745 (1974).
19. Latli, B., Greenfield, L.J., and Casida, J.E. -J. Labelled Compd. Radiopharm. 33:613 (1993).
20. Chiang, Y., Kresge, A.J., Morimoto, H., and Williams, P.G. -J. Am. Chem. Soc. 114:3981 (1992).
21. Walton, J.D., personal communication.