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Pyrethroid Chemistry: Reactive α,β-Unsaturated Keto Aldehydes from Peracid Oxidation, Oxidative Photodecomposition, and Metabolism of 5-Benzyl-3-furylmethyl Derivatives

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Oxidation of 5-benzyl-3-furylmethyl 2,2,3,3-tetramethylcyclopropanecarboxylate or the analogous methyl ether with 1.5 equiv of *m*-chloroperoxybenzoic acid proceeds by 4,5-addition, furan ring opening, and rearrangement to form the (*Z*)-2-[(acyloxy)methyl]- or (*Z*)-2-(methoxymethyl)-4-keto-5-phenyl-2-pentenal, respectively, together with small amounts of the corresponding carboxylic acids. The 2-methoxymethyl keto aldehyde also forms in small yield on oxidative photodecomposition and microsomal metabolism. In biomimetic systems, both this methoxymethyl α,β-unsaturated keto aldehyde and peracid-oxidized 5-benzyl-3-furylmethyl *cis*-chrysanthemate (resmethrin) form covalent derivatives with bovine serum albumin and the methoxymethyl keto aldehyde also forms a thioether derivative with 3,4-dichlorobenzenethiol. Oxidative furan ring opening of 5-benzyl-3-furylmethyl derivatives, including pyrethroids, may therefore contribute to their photochemical and metabolic lability and to tissue binding and persisting fragments in mammals. The α,β-unsaturated keto aldehyde products are not detected as mutagens in several types of *Salmonella typhimurium* assays.

The pyrethroid insecticides resmethrin (**1A**, Figure 1) (Elliott et al., 1967), kadethrin (Martel and Buendia, 1974), and tetramethylcyclopropanecarboxylate **1B** (Figure 1) (Berteau and Casida, 1969) are esters of 5-benzyl-3-furylmethyl alcohol. **1A** and kadethrin undergo a variety of photoreactions including extensive oxidative opening of the furan ring probably via an ozonide-type cyclic peroxide (Ueda et al., 1974; Ohsawa and Casida, 1979). Metabolism of **1a** and kadethrin in rats and/or hepatic microsomal oxidase systems involves hydrolysis of the cyclopropanecarboxylate linkage and hydroxylation at the 4′- and α-methylene positions of the alcohol moiety in both cases, hydroxylation of the isobutenyl methyl groups in resmethrin, and oxidative cleavage of the thiolactone ring in kadethrin (Miyamoto et al., 1971; Ueda et al., 1975a,b; Ohsawa and Casida, 1980). An additional minor pathway proposed for metabolism of **1A** involves hydroxylation at C-4 of the furan (Miyamoto et al., 1971). **1A** also yields bound metabolites on activation in hepatic microsomal oxidase systems (Ueda et al., 1975b) and in the liver of treated rats (Ueda et al., 1975a; Graillot and Hoellinger, 1982; Hoellinger et al., 1983) with higher binding for the alcohol than the acid moiety. It has recently been reported that **1a** (1(*R*),trans and 1(*R*),cis isomers) and 5-benzyl-3-furylmethyl alcohol bind covalently to protein after oxidative in vitro metabolism (Hoellinger et al., 1985). The reactive intermediate in **1A** metabolism is tentatively proposed to be 5-benzyl-3-furylcarboxaldehyde (Ueda et al., 1975b).

Substituted-furans undergo epoxidation on photolysis (Karminski-Zamola et al., 1982) and oxidative ring opening on peracid treatment (Kobayashi et al., 1983; Ravindranath et al., 1984) and on metabolism involving cytochrome P-450 monooxygenases (Ravindranath et al., 1984). The keto aldehydes from microsomal oxidation of methylfurans are proposed to contribute to their toxicity and tissue binding (Ravindranath et al., 1984).

This study examines the chemical, photochemical, and microsomal oxidative reactions of the 5-benzyl-3-furylmethyl moiety and the possible toxicological significance of the resulting products.

MATERIALS AND METHODS

Analytical Procedures. Nuclear magnetic resonance (NMR) spectroscopy was carried out with a Bruker WM 300 instrument at 300 MHz (^{1}H), 75.5 MHz (^{13}C), or 47 MHz (^{2}H). ^{2}H spectra were obtained in the unlocked mode

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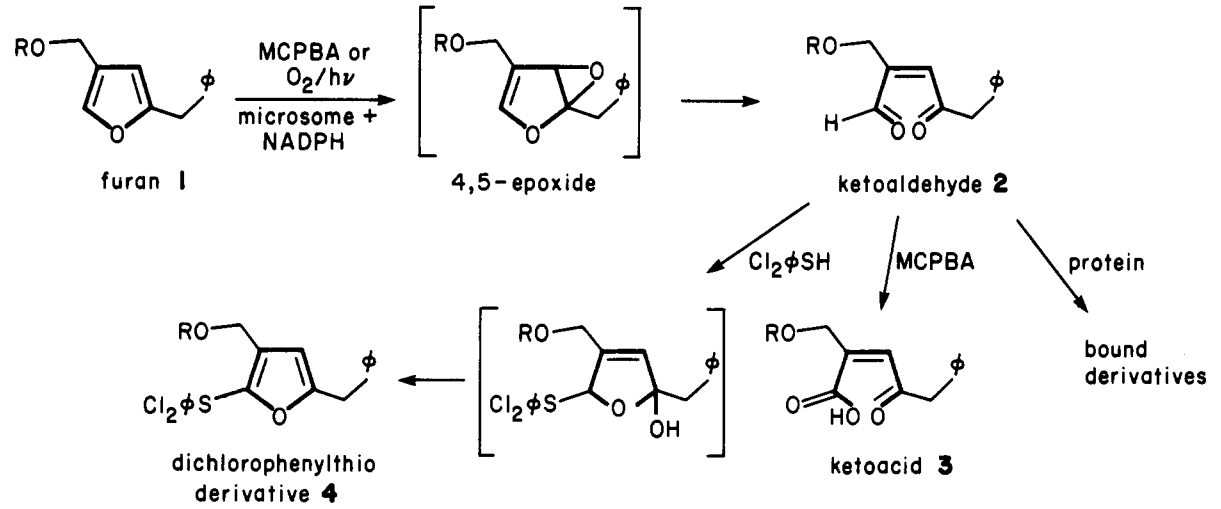


Figure 1. Oxidative conversion of 5-benzyl-3-furylmethyl chrysanthemate (**1A**), tetramethylcyclopropanecarboxylate (**1B**), and methyl ether (**1C**) to reactive keto aldehydes **2A–C**. The indicated reactions are defined with **1C**. Further reactions of the keto aldehydes are established for the conversion with MCPBA of **2B** and **2C** to **3B** and **3C** and protein binding for a reaction product of **1A** and MCPBA. R substituents: **A**, [^{14}C-*carboxyl*]1(*R*),cis-chrysanthemate or unlabeled 1(*RS*),*cis*,*trans*-chrysanthemate; **B**, 2,2,3,3-tetramethylcyclopropanecarboxylate; C, methyl ether.

with reference to external deuteriochloroform ($CDCl_3$). Samples were dissolved in $CHCl_3$ or $CDCl_3$ as appropriate and chemical shifts (δ) are reported as ppm downfield from tetramethylsilane. Coupling constants (J) are given in hertz.

Mass spectrometry (MS) utilized a Hewlett Packard 5985B system operated under electron impact (EI) or chemical ionization (CI) conditions at 70 and 230 eV, respectively. CI relied on methane as the reactant gas at a pressure of 0.8 torr. Molecular ($M^{+\cdot}$) and quasimolecular (MH^+) ions and significant fragments are reported as m/z units, with relative intensities given in parentheses. Gas chromatography (GC) was used in combination with MS on a 5840A Hewlett Packard instrument operated with temperature programming (120–220 °C, 20 °C/min). Separations were accomplished on a high performance methyl silicone capillary column (10 m) with helium as the carrier gas at 1 mL/min. Retention times (R_t) are given in minutes.

Chemicals. The structures and designations of relevant compounds are given in Figure 1. **1A** from Sumitomo Chemical Co. (Takarazuka, Japan) was a racemic cis,trans mixture unless specified otherwise. **1B** from an earlier synthesis (Berteau and Casida, 1969) was recrystallized from ethanol. **1b**: ^{1}H NMR 1.15–1.25 (4 CH_3), 1.27 (CHCOO), 3.93 (CH_2Ph), 4.88 (OCH_2), 6.04 (CH=), 7.30 (OCH=), 7.15–7.30 (C_6H_5); EI-MS 312 ($M^{+\cdot}$, 7), 171 (78), 143 (46), 125 (100), 97 (69); CI-MS 313 ([MH]$^+$, 100) and corresponding M + 29 and M + 41 signals. **1C** was prepared by treatment of 5-benzyl-3-furylmethyl alcohol (Sumitomo) with methyl iodide and silver oxide (5 equiv) in chloroform. **1C**: ^{1}H NMR 3.32 (CH_3O), 3.93 (CH_2Ph), 4.25 (CH_2O), 6.02 (CH=), 7.29 (OCH=), 7.15–7.30 (C_6H_5); ^{13}C NMR 34.1 (CH_2Ph), 57.2 (CH_3O), 65.5 (OCH_2), 106.7 (CH=), 122.6 (>C=), 126.1 (C-4 of C_6H_5), 128.1 and 128.3 (C-2 and C-3 of C_6H_5), 137.5 (C-1 of C_6H_5), 139.0 (OCH=), 155.0 (>C=); EI-MS 202 ($M^{+\cdot}$, 96), 172 (100), 141 (52), 128 (58); CI-MS 203 ([MH$^+$], 68), 187 (18), 172 (100). Deuteration of **1C** was accomplished by acid-catalyzed exchange (Elliott et al., 1973) but the reported procedure yielded 35% deuteration at the benzylic position in addition to 98% deuteration at C-2 of the furan ring: ^{2}H NMR 7.30 (OCD=), 3.93 (CHDPh). EI-MS as with **1C** but $M^{+\cdot}$ at 203 and 204 (35%). 1(*R*),*cis*-Allethrin was provided by Roussel-Uclaf (Paris, France). [^{14}C]**1A** and [^{14}C]allethrin, each 1(*R*),cis preparations labeled in the carboxyl carbon, were from previously described syntheses (Yamamoto and Casida, 1968; Ueda et al., 1974). *m*-Chloroperoxybenzoic acid (MCPBA) was always purified to >99% before use (Fieser and Fieser, 1967) and [^{18}O]-MCPBA (35% enrichment) was a gift from Dr. William Wagner (Wagner and Rastetter, 1983).

Peracid, Photochemical, and Metabolic Oxidations. Furans **1A–C** (0.1 mmol) were individually mixed with MCPBA or [^{18}O]MCPBA (1.5 equiv) in $CDCl_3$ (0.5 mL) and the reaction was monitored by ^{1}H NMR spectroscopy. Optimal yields of **2B** and **2C** were obtained at ~50% conversion in 0.5 h at 5–10 °C. Reaction mixtures were washed twice with saturated aqueous sodium thiosulfate, water, and finally with saturated sodium bicarbonate. The organic layer was dried over magnesium sulfate.

Photooxidation of **1A–C** and **2C** was accomplished as 0.2 M solutions in oxygen-saturated $CDCl_3$ at 360 nm (Rayonette photoreactor, RPR 3500 lamps) for 2 h with inspection of product formation by ^{1}H NMR.

Biooxidation used liver microsomes (2 mg of protein, from rats without inducer pretreatment) and reduced nicotinamide–adenine dinucleotide phosphate (NADPH, 0–2 μmol) in 200 mM pH 7.4 phosphate buffer (2 mL) with incubation for 30 or 60 min at 37 °C. **1C** was added at 5–30 μg in ethanol (50 μL) as the carrier vehicle. No reaction was observed in the absence of NADPH or with heat-inactivated microsomes. Following incubation the samples were saturated with sodium chloride and extracted with ether (2 × 2 mL) and the organic layer was concentrated and analyzed by GC–EI-MS.

Reactions of Keto Aldehydes 2B and 2C. The reaction of **2C** with equimolar 3,4-dichlorobenzenethiol or *N*-acetylcysteine in $CDCl_3$ was monitored by ^{1}H NMR.

Binding to bovine serum albumin (BSA) was examined colorimetrically with **2C** and radiometrically with a reaction mixture containing **2A**. In the former case, **2C** (50 μg) was incubated with BSA (2 mg) in 1.0 mL of 200 mM pH 7.4 sodium phosphate buffer. At 15-min intervals the protein was precipitated with 10% trichloroacetic acid (TCA) with centrifugation and the supernatant was added to 1 mL of 0.1% 2,4-dinitrophenylhydrazine (DNP) solution in 2 N hydrochloric acid. The absorbance of the DNP derivative was recorded at 456 nm after addition of 7 mL of 1 N sodium hydroxide to determine the unreacted al-

dehyde(s) by comparison with a standard curve (Hodgson and Casida, 1962).

Alternatively, [^{14}C]**1A** or [^{14}C]allethrin (16 μg) was reacted with 5 equiv of MCPBA in 100 μL of $CDCl_3$. After 10 min the solvent was evaporated and BSA (2.7 mg) was added as a solution in 200 mM pH 7.4 phosphate buffer (1 mL). The mixture was vigorously shaken and incubated at 37 °C for 1 h. The protein was precipitated with TCA and centrifuged as above, and the pellet was washed with acetonitrile (1 mL × 2). The supernatant, washes, and pellet were assayed by liquid scintillation counting. In separate experiments 3,4-dichlorobenzenethiol (1 μL) was added before BSA or the BSA was incubated for varying times between 0 and 60 min with synthetic **2C** (50 μg).

Mutagenesis Assays. Three strains of *Salmonella typhimurium* were used: TA100 to detect mutagens causing base pair substitution (Maron and Ames, 1983); TA102 with adenine–thymine base pairs at the site of mutation assayed as with the TA100 strain and also under photomutagenesis conditions (Levin et al., 1982; Maron and Ames, 1983); *his*D3052 sensitive to malondialdehyde and related acroleins (Basu and Marnett, 1984). Potential activation was examined on coincubation with the S9 mix for metabolism (Maron and Ames, 1983), following partial photodecomposition on exposure as thin films to sunlight or 360-nm light, and after treatment with 1–10 equiv of MCPBA in tetrahydrofuran followed by quench of the unreacted MCPBA with dimethyl sulfoxide.

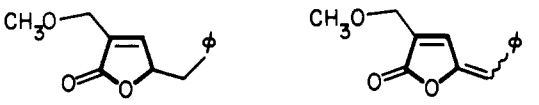
RESULTS AND DISCUSSION

Conversion of Furans 1B and 1C to Keto Aldehydes 2B and 2C with MCPBA. Furans **1B** and **1C** are converted to keto aldehydes **2B** and **2C** in >90% yield based on the reacted material on treatment with 1.5 equiv of MCPBA in $CDCl_3$. Keto aldehyde **2b**: ^{1}H NMR 1.15–1.25 (4 CH_3), 1.26 (cyclopropyl H), 3.91 (CH_2Ph), 4.78 (OCH_2, d, J = 1.7), 6.94 (CHCO, t, J = 1.7), 7.15–7.30 (C_6H_5), 10.15 (HCO); CI-MS 357 ([M + 29]$^+$, 11), 329 ([MH]$^+$, 96), 311 ([MH − H_2O]$^+$, 18), 187 (42), 171 (100), 143 (52), 125 (44). Keto aldehyde **2C**: ^{1}H NMR 3.35 (CH_3O), 3.88 (CH_2Ph), 4.14 (OCH_2, d, J = 2.1), 7.07 (CHCO, t, J = 2.1), 7.15–7.30 (C_6H_5), 10.15 (HCO); EI-MS 218 (M$^+$·, 92), 200 (8), 186 (100), 158 (69), 141 (46), 129 (98); CI-MS 247 ([M + 29]$^+$, 8), 219 ([MH]$^+$, 62), 201 ([MH − H_2O]$^+$, 38), 187 (100). The presence of carbonyl groups was also supported by ^{13}C NMR (92.18 and 92.10 ppm) and ^{2}H NMR (DCO at 10.15 ppm). GC–MS examination (with partial decomposition) gave R_t 13.0 min for keto aldehyde **2B** and 6.4 min for keto aldehyde **2C**. Formation of keto aldehyde **2A** was only monitored by its ^{1}H NMR signal (HCO, 10.15 ppm) due to the complexity of the mixture obtained. In subsequent experiments the keto aldehydes were generally used as mixtures with their corresponding furans (**1B** and **1C**).

The mechanism of ring opening was examined by oxidizing furans **1B** and **1C** with [^{18}O]MCPBA and GC–CI-MS analysis of keto aldehydes **2B** and **2C** to differentiate initial addition of oxygen to the 2,3- or 4,5-double bond. CI of aldehydes yields intense and abundant [MH − H_2O]$^+$ fragments (Harrison, 1983) which can be used to determine the site of oxygen addition to the furan ring. Thus, epoxidation with [^{18}O]MCPBA may yield the keto aldehyde with [^{18}O] at the aldehyde or at the ketone group. Comparison of the $^{18}O/^{16}O$ ratios in the [MH]$^+$ and [MH − H_2O]$^+$ signals gives the percentage of 2,3-addition leading to [^{18}O]aldehyde and 4,5-addition yielding [^{18}O]ketone. Both **2B** and **2C** had identical $^{18}O/^{16}O$ ratios in their [MH]$^+$ signals and [MH − 18]$^+$ fragments, indicating that oxidation occurs by 4,5-addition, since ^{18}O is retained in the molecule.

Reactions of Keto Aldehydes 2B and 2C. Oxidation of **1B** and **1C** yields not only keto aldehydes **2B** and **2C** but also keto acids **3B** and **3C**. **3B**: ^{1}H NMR 1.15–1.25 (4 CH_3), 3.22 (CH_2Ph), 4.81 (OCH_2, d, J = 1.7), 6.97 (CHCO, t, J = 1.7). CI-MS gave a quasi-molecular ion at 345 ([MH]$^+$). **3C**: ^{1}H NMR 3.23 (CH_2Ph), 3.33 (CH_3O), 4.10 (OCH_2, d, J = 1.7), 7.02 (CHCO, t, J = 1.7). Molecular (M$^+$·, 234) and quasi-molecular ions ([MH]$^+$, 235) support the structural assignment.

The lactone and benzylidene lactone derivatives (see below), tentatively identified by MS, are obtained from keto acid **3C** and keto aldehyde **2C**, respectively, on thermal decomposition (GC–MS) or prolonged standing. Similar products are reported in the MCPBA oxidation of other furans (Kobayashi et al., 1983).



lactone benzylidene-lactone

2C reacts readily with 3,4-dichlorobenzenethiol yielding a complex mixture of products (NMR) the major one (~50% yield) of which is tentatively characterized as **4C** (Figure 1): ^{1}H NMR δ 3.29 (CH_3O), 3.95 (CH_2Ph), 4.30 (OCH_2), 6.20 (CHCO), 6.9–7.5 (aromatics); GC–CI-MS (19 min, R_t) 407 ([M + 29]$^+$, 8), 379 ([MH]$^+$, 22), 347 ([MH − OCH_3]$^+$, 92), 301 ([M − C_6H_5]$^+$, 100), 201 (86). No attempt was made to identify the product(s) formed rapidly on reaction of **2C** and *N*-acetylcysteine.

Photochemical Formation of Keto Aldehydes. Keto aldehyde **2C** is detected (^{1}H NMR) in ~2% yield on photodegradation of **1C** in oxygenated $CDCl_3$ with irradiation for 2 h. **2C** is quite unstable and on direct photolysis it yields a great variety of unidentified products. Keto aldehydes are not detected with comparable irradiations of **1A** and **1B**. The benzylidene lactone chrysanthemate was previously identified in photodegradation studies on **1A** (Ueda et al., 1974).

Metabolic Formation of Keto Aldehydes and Their Reactions with BSA. Keto aldehyde **2C** was observed (GC–EI-MS) on incubation of furan **1C** in the presence of microsomes plus NADPH, but not in the absence of NADPH, in yields ranging from 0.1 to 0.5%. The 0.5% yield was with 30 μg of substrate and 30 min of incubation and the lower yields at lower substrate levels or on longer incubation times. No other products were observed by GC–CI-MS but upon methylation (CH_2N_2) of the mixture trace amounts of the methyl ester of **3C** were detected (R_t 4.6).

Colorimetric analysis revealed more rapid disappearance of the DNP-reactive component(s) of MCPBA-oxidized **1C**, including some **2C**, in pH 7.4 phosphate buffer (37 °C) in the presence of BSA than in its absence. The BSA-dependent reaction was pseudo first order with 30% reaction in 60 min after correction for 10% loss in the absence of BSA.

Radioactive assay revealed 5-fold higher radiocarbon binding to BSA with peracid-activated [^{14}C]**1A** than with **1A** per se (Table I). Pretreatment of the samples with 3,4-dichlorobenzenethiol (Table I) or with **2C** resulted in a considerable decrease of radiocarbon binding (from 7.2 to 1.8%). As a non-furan control there was very little binding of radiocarbon from [^{14}C]allethrin to BSA with or without peracid pretreatment.

Mutagenesis of 1A–C and Their Degradation Products. The 5-benzyl-3-furylmethyl derivatives and their degradation products considered here were subjected

Table I. Reaction of MCPBA-Oxidized Resmethrin and Allethrin with Bovine Serum Albumin

reaction mixture	protein binding, %[a] resmethrin	allethrin
[^{14}C]pyrethroid	1.5 ± 0.5	1.5 ± 1.2
oxidized [^{14}C]pyrethroid[b]		
alone	7.2 ± 1.8	1.0 ± 0.5
with thiol[c]	1.8 ± 0.4	1.3 ± 1.0

[a] Mean and standard deviation for five determinations with resmethrin and three with allethrin. [b] Reaction mixture of pyrethroid with 5 equiv of MCPBA in $CDCl_3$. The resmethrin and allethrin products include epoxychrysanthemates (Ueda et al., 1974; Ruzo et al., 1980). Additional minor products with resmethrin are keto aldehydes such as **2A** with modified acid moieties. [c] 3,4-Dichlorobenzenethiol in sufficient amount to react with any ketoaldehydes present.

to a variety of *S. typhimurium* assays with strains sensitive to different types of mutagens. No significant mutagenic activity was detected with the following *S. typhimurium* strains, compounds, and conditions: TA100 for **1A** (1-(*RS*),cis,trans, 1(*R*),cis, 1(*R*),trans) direct, photodecomposed, with peracid, with S9, and photodecomposed with S9 (each up to 1000 μg per assay); TA100 for **1B** direct (100 μg) and with peracid (1000 μg); TA102 for 1(*R*),cis-**1A** direct (1000 μg) or as a photomutagenesis assay (100 μg); *his*D3052 for **1B** and **1C** direct (100 μg). As the only exception, 5-benzyl-3-furancarboxaldehyde gave 0.6 revertant/μg in the TA100 assay direct and 0.2 revertant/μg with S9 as expected for a very weak, biodegradable mutagen. Resmethrin per se is also noted to be inactive in a variety of other mutagenesis assays (Miyamoto, 1976).

Possible Significance of Reactive α,β-Unsaturated Keto Aldehyde Intermediates in Pyrethroid Photodecomposition and Metabolism. Furan epoxidation and ring cleavage reactions appear to contribute to the photochemical and metabolic breakdown of resmethrin and probably related pyrethroids. They provide a process in addition to cyclic peroxide formation for photooxidative ring cleavage. They also lead under metabolic conditions to keto aldehydes which are more plausible agents than the benzylfurancarboxaldehyde to derivatize proteins and explain the tissue binding and persisting fragments from the alcohol moiety of **1A**.

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Registry No. **1A**, 10453-86-8; **1B**, 18877-89-9; **1C**, 96666-90-9; **2A**, 96666-91-0; **2B**, 96666-92-1; **2C**, 96666-93-2; **3B**, 96666-94-3; **3C**, 96666-95-4; **4C**, 96666-96-5; NADPH, 53-57-6; 3,4-dichlorobenzenethiol, 5858-17-3; 5-benzyl-3-furylmethyl alcohol, 20416-09-5; 1(*R*),*cis*-allethrin, 61009-23-2; *m*-chloroperoxybenzoic acid, 937-14-4.

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