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S-Chloroallyl Thiocarbamate Herbicides: Mouse Hepatic Microsomal Oxygenase and Rat Metabolism of *cis*- and *trans*-[^{14}C=O]Diallate

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Mouse hepatic microsomes metabolize *cis*- and *trans*-[^{14}C=O]diallate [*S*-(2,3-dichloroallyl) diisopropylthiocarbamate] in a NADPH-dependent reaction, yielding primarily $^{14}CO_2$ in the absence of glutathione (GSH) and $^{14}CO_2$ and *S*-(diisopropylcarbamoyl)-GSH in the presence of GSH. Although not detected, sulfoxides of the diallate isomers are likely intermediates in these reactions on analogy with previous studies on *S*-alkyl and *S*-benzyl thiocarbamates. Sulfoxides of the diallate isomers are more reactive and thermally unstable than other known thiocarbamate sulfoxides. The finding of carbonyl sulfide as an in vitro metabolite suggests that α-carbon hydroxylation of the 2,3-dichloroallyl group is an additional pathway for diallate degradation. Rats administered either diallate isomer excrete the *S*-diisopropylcarbamoyl derivatives of mercapturic acid (62%), cysteine (7%), and mercaptoacetic acid (1.5%) in addition to $^{14}CO_2$ (20%). The principal metabolic pathway in rats appears to involve sulfoxidation, nonenzymatic reaction of the sulfoxide with GSH, and mercapturic acid formation.

Thiocarbamate herbicides containing a *S*-alkyl, *S*-benzyl, or *S*-chlorobenzyl group are rapidly metabolized in mammals and plants by hydroxylation, sulfoxidation, and reaction of the sulfoxides with glutathione (GSH) (Casida et al., 1974, 1975a,b; Chen and Casida, 1978; DeBaun et al., 1978; Hubbell and Casida, 1977; Ishikawa et al., 1976; Santi and Gozzo, 1976). Little information is available on the metabolism of thiocarbamates with a *S*-chloroallyl moiety such as diallate [cis and trans isomers of *S*-(2,3-dichloroallyl) diisopropylthiocarbamate] and triallate [*S*-(2,3,3-trichloroallyl) diisopropylthiocarbamate]. In soils and plants, [^{14}C=O]diallate gives $^{14}CO_2$ and [^{14}C-trichloroallyl]triallate yields [^{14}C]trichloroallylsulfonic acid and $^{14}CO_2$ (Anderson, 1975; Schuphan and Ebing, 1979), but no mammalian metabolites are reported. Diallate and triallate are mutagenic agents in bacterial assays in the presence of hepatic microsomal oxygenase (MO) preparations (De Lorenzo et al., 1978; Sikka and Florczyk, 1978). It is therefore of interest to define the metabolic fate of the *S*-chloroallyl thiocarbamate herbicides in MO systems and in mammals. This report considers the metabolic reactions of the diisopropylcarbamoyl moiety of *cis*- and *trans*-diallate.

MATERIALS AND METHODS

Chemicals. Pure *cis*- and *trans*-diallate were isolated by a reported procedure (Schuphan and Ebing, 1977) from a 2:3 isomer mixture obtained from Chem Service (Westchester, PA). [^{14}C=O]Diallate (5 mCi/mmol) synthesized by Amersham-Buchler (Braunschweig, Germany) was separated into the individual isomers as described below.

S-Diisopropylcarbamoyl derivatives of GSH, cysteine, mercapturic acid, and mercaptoacetic acid were synthesized according to the general procedure of Hubbell and Casida (1977) using as carbamoylating agents *S*-(*n*-propyl) diisopropylthiocarbamate sulfoxide (PIPTC-SO) and the corresponding sulfone (PIPTC-SO_2) prepared by *m*-chloroperoxybenzoic acid (MCPBA) oxidation (Tilles and Casida, 1975) of *S*-(*n*-propyl) diisopropylthiocarbamate (PIPTC) (Tilles, 1959). The cited references give not only the reaction conditions but also the work-up procedures used. All products gave appropriate proton magnetic resonance spectra. Methyl esters of three compounds also gave suitable chemical ionization-mass spectra (CI–MS) (for conditions, see Hubbell and Casida, 1977) (*m/e*, relative intensity): *S*-(diisopropylcarbamoyl)cysteine, 263 (100) $[M + 1]^+$, 257 (7), 243 (7), 224 (7), 163 (11), 162 (24), 142 (11), 130 (10), 128 (41); *S*-(diisopropylcarbamoyl)-mercapturic acid, 305 (2) $[M + 1]^+$, 171 (5), 169 (10), 129 (9), 128 (100); *S*-(diisopropylcarbamoyl)mercaptoacetic acid, 234 (49) $[M + 1]^+$, 129 (8), 128 (100).

PIPTC [bp 121 °C (18 mm), mp ~−17 °C] was prepared in 84% yield by reacting *n*-propyl chlorothioformate with 2 molar equiv of diisopropylamine in ethyl ether. PIPTC was oxidized to PIPTC-SO (mp 67–68 °C, recrystallized from hexane) in 73% yield on reaction with 0.83 molar equiv of MCPBA in methylene chloride at −10 °C. The sulfoxide in turn was oxidized to PIPTC-SO_2 (mp 32–33 °C, crystallized from hexane) in 60% yield by adding 1.05 molar equiv of MCPBA in methylene chloride and holding for 30 min at 0 °C, followed by 1 h at 22 °C. Reactants for the conjugates were: 5 mmol of PIPTC-SO or PIPTC-SO_2, 6 mmol of GSH and 50 mL of triethylamine in 150 mL of methanol for the GSH derivative; 2 mmol of PIPTC-SO, 4 mmol of cysteine, and 2.1 mmol of triethylamine in 25 mL of methanol for the cysteine conjugate; 3 mmol each of mercapturic acid and triethylamine in methanol (40 mL) to which was added 7 mmol of PIPTC-SO_2 for the mercapturic acid conjugate; 10 mmol of mercaptoacetic acid and 6 mmol of triethylamine in 6 mL of methanol to which was added 2 mmol of PIPTC-SO for the mercaptoacetic acid conjugate.

Thin-Layer Chromatography (TLC). Chromatographic separations were accomplished with one-dimensional development on silica gel 60 F-254 precoated chromatoplates of 0.25-mm gel thickness. *cis*- and *trans*-[^{14}C=O]Diallate (5 mCi/mmol) were isolated by using diisopropyl ether/cyclohexane (1:3) (DC) (R_f 0.40 and 0.44, respectively). Diallate metabolite mixtures were separated for liquid scintillation counting (LSC) of individual components using the following solvent systems: DC; hexane/acetone (1:1) (HA); 1-butanol/glacial acetic acid/water (6:1:1) (BAW). Unlabeled standard compounds for cochromatography were detected with ninhydrin,

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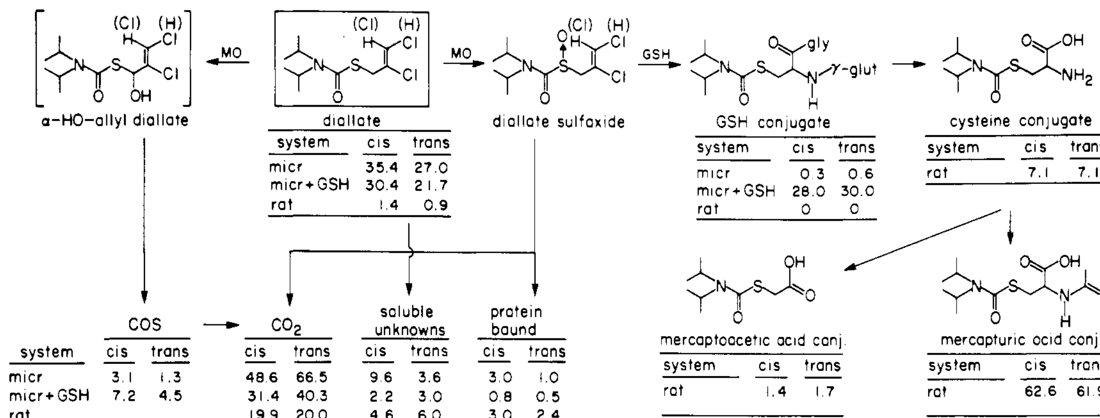

Figure 1. Metabolic pathways for the diisopropylcarbamoyl moiety of *cis*-diallate (structure shown) and *trans*-diallate [structure with substituents (Cl) and (H) replacing H and Cl]. Yields are percentages relative to starting *cis*- and *trans*-diallate in the mouse heptaic microsome–NADPH system with and without GSH and in the excreta of male rats treated orally at 0.32–0.65 mg/kg. In vivo metabolites tabulated as "protein bound" are ^{14}C compounds in the body at 30 h after dosing; however, this is not a specific category and may include other types of metabolites. An additional source of in vivo $^{14}CO_2$ is likely to be further metabolism of the GSH conjugate.

2′,7′-dichlorofluorescein (0.2% in ethanol), $KMnO_4$ (0.5% in 1% aqueous Na_2CO_3), iodine vapor, or under UV light as previously described (Chen and Casida, 1978; Stahl, 1969).

Metabolism in Mouse Hepatic Microsomal Preparations. *cis*- or *trans*-[^{14}C=O]Diallate (0.41 μmol) was incubated with hepatic microsomes from male albino mice [20% liver fresh weight equivalent; prepared according to Chen and Casida (1978)], reduced nicotinamide adenine dinucleotide phosphate (NADPH) (0 or 3.6 μmol) and GSH (0 or 1.5 μmol) in 0.1 M sodium phosphate buffer (pH 7.4) with a final volume of 1.5 mL for 40 min at 37 °C. $^{14}CO_2$ and ^{14}COS were trapped and analyzed as in our earlier report (Chen and Casida, 1978) with improvements by using suction for air movement into the isobutylamine traps and methanol to elute the mixture of diisobutylurea (from reaction of COS and isobutylamine) and isobutylamine carbonate (from CO_2) from the filter paper traps. The ^{14}C content of the methanol was determined before and after addition of concentrated HCl, the loss being considered as $^{14}CO_2$. The acidified methanol extract was mixed with two volumes of H_2O and extracted twice with ether to remove isobutylamine before confirmatory analysis of diisobutylurea as before (Chen and Casida, 1978).

The microsomal reaction mixtures were cooled to 0 °C and extracted with chloroform (2 × 1.5 mL) to remove all unmetabolized diallate and several relatively stable metabolites analyzed by TLC (HA) after drying the chloroform (Na_2SO_4). Precipitated protein was recovered by a reported procedure (Chen and Casida, 1978) for determination of protein-bound ^{14}C by combustion and LSC. The aqueous fraction was lyophilized to dryness and extracted with methanol (2 × 0.5 mL) affording complete ^{14}C recovery for analysis by TLC (BAW). All results are the average of two experiments.

Metabolism in Rats. Male albino Sprague-Dawley rats (160–180 g, Horton Laboratories, Inc., Oakland, CA) were individually treated orally by stomach tube with *cis*- or *trans*-[^{14}C=O]diallate (1–2 μCi; 0.32–0.65 mg/kg) or *trans*-[^{14}C=O]diallate (2 μCi; 90 mg/kg) in methoxytriglycol (30–50 μL). The stomach tube was then rinsed with 150 μL of methoxytriglycol. The rats were held in all-glass metabolism cages for 30–36 h prior to sacrifice with analyses of $^{14}CO_2$, total urinary and fecal ^{14}C, and tissue residues as previously described (Gaughan et al., 1977).

Urinary metabolites were separated by TLC (BAW) following direct spotting of 50–100 μL of urine. Feces were homogenized in methanol (5 mL × 2) with a Polytron homogenizer (Kinematica GmbH, Lucerne, Switzerland) to recover the methanol-soluble fraction for analysis by TLC (DC and BAW) and the unextractable portion for combustion and LSC. The data for 0–30 h composite samples are average results from two experiments.

Identification of Conjugates. *S*-(Diisopropylcarbamoyl)glutathione from in vitro metabolism and *S*-diisopropylcarbamoyl derivatives of cysteine and mercapturic acid from urine were tentatively identified by TLC cochromatography (BAW) with authentic unlabeled standards. Identities of the urinary metabolites were confirmed by methylation, followed by TLC cochromatography with methyl esters of the cysteine and mercapturic acid conjugates in acetone and HA (R_f values of 0.48 and 0.56, respectively, in acetone and 0.32 and 0.38, respectively, in HA) and of the mercaptoacetic acid conjugate in acetone (R_f 0.58) and ether/chloroform (3:2) (EC) (R_f 0.55). Prior to cochromatography the mercaptoacetic acid conjugate recovered by ether extraction of acidified (HCl) urine was subjected to methylation with diazomethane (Ueda et al., 1975) and TLC cleanup (HA, R_f 0.63). Methyl esters of the cysteine and mercapturic acid conjugates were suitable for TLC cochromatography on reacting a methanol extract of lyophilized urine with diazomethane. The identity of these two compounds as metabolites was then firmly established by isolating them from the 0–36 h urine of a rat treated with *trans*-diallate at 90 mg/kg for CI–MS examination of their methyl esters, prepared as above. This required sequential TLC purification with acetone, HA and EC (R_f 0.11 and 0.23 for the methylated cysteine and mercapturic acid derivatives, respectively). The methylated metabolites gave appropriate CI–MS spectra in comparison with those of authentic unlabeled *S*-(diisopropylcarbamoyl)cysteine and -mercapturic acid as their methyl esters.

RESULTS

Mouse Hepatic Microsomal Metabolism. Little or no diallate metabolism takes place in the absence of NADPH fortification since 95–97% of the substrate is recovered intact (R_f 0.65, HA). On NADPH fortification of the microsomes, large amounts of $^{14}CO_2$ are liberated (49–67%) and there is also formation of ^{14}COS (1–3%), five unidentified organosoluble metabolites (R_f 0.00, 0.05, 0.44, 0.54, and 0.80, HA; totaling 4–10%) and protein-bound derivatives (1–3%) (Figure 1). On adding GSH to the microsome–NADPH system, the GSH conjugate (R_f 0.21, BAW) becomes a major metabolite (28–30%) and the

amount of ^{14}COS is increased whereas the level of $^{14}CO_2$ and other metabolites is decreased. Preliminary rate studies indicate that *cis*-diallate is metabolized slightly faster than *trans*-diallate by the microsome–NADPH system.

Distribution and Metabolism in Rats. Radiocarbon from *cis*- and *trans*-[$^{14}C{=}O$]diallate is largely excreted or expired within 30 h after oral administration at 0.32–0.65 mg/kg with more in the urine (74–77%) than in the CO_2 (20%) or feces (1–3%). Relatively little of the ^{14}C is retained in the body at 30 h after treatment, i.e., 0.5% of the dose in the liver, 0.3% in blood, and 1.5–2.0% in other tissues. Radiocarbon from *cis*-diallate is eliminated slightly faster than that from *trans*-diallate.

A small portion (0.9–1.4%) of the diallate dose is excreted in feces without metabolism (TLC, DC) (Figure 1). *cis*-Diallate yields a minor (1.4% of the dose), unidentified (R_f 0.73, BAW and 0.00, DC) fecal metabolite (supplementary material). The major urinary metabolites are *S*-diisopropylcarbamoyl derivatives of cysteine (R_f 0.42, BAW), mercapturic acid (R_f 0.48, BAW), and mercaptoacetic acid (R_f 0.60, BAW) (Figure 1) but there are also two unknown (R_f 0.27 and 0.31, BAW), minor (0.5–5.2% of the dose) metabolites (see Supplementary Material Available paragraph). There is no major difference in urinary metabolite distribution when *trans*-diallate is administered at 0.59 or 90 mg/kg (see Supplementary Material Available paragraph).

DISCUSSION

The diallate isomers are rapidly metabolized in vitro by mouse hepatic microsomal oxidases and in vivo by rats utilizing pathways shown in Figure 1.

Sulfoxides of the diallate isomers are thermally unstable compounds that would decompose during the course of the isolation and analytical methods used in the present study (Schuphan and Casida, 1979). *cis*- and *trans*-Diallate sulfoxides, prepared by peracid oxidation, react rapidly with GSH in aqueous medium at pH 7.4 to yield the GSH conjugate. Sulfoxides are probably the major intermediates in metabolism of the diallate isomers since they can be trapped by reaction in vitro with added GSH and in vivo with endogenous GSH. Diallate sulfoxides also react readily with cysteine, penicillamine and probably other sulfhydryl-containing molecules. The diisopropylcarbamoyl derivative of GSH is further metabolized in vivo to the corresponding cysteine, mercapturic acid, and mercaptoacetic acid conjugates, by analogy with the findings of Hubbell and Casida (1977).

Two or more pathways are likely to contribute to the extensive $^{14}CO_2$ liberation both in vitro and in vivo. The first involves hydrolysis or other type of decomposition of the diallate sulfoxides which occurs most extensively in the absence of GSH. Another utilizes α-hydroxyallyl-[$^{14}C{=}O$]diallate as an intermediate, some of which decomposes to ^{14}COS which in turn is oxidized to $^{14}CO_2$ [for analogous reactions, see Chen and Casida (1978)]. Further, a portion of the $^{14}CO_2$ in vivo may result from metabolism of the GSH conjugate (Hubbell and Casida, 1977). There may also be other mechanisms for in vivo cleavage of the diallate ester group.

The diallate isomers undergo reactions in addition to sulfoxidation. There are two to four unidentified metabolites from each of *cis*- and *trans*-diallate both in vivo and in vitro, but they collectively account for $<10\%$ of the dose or substrate in each case. A portion of these metabolites may originate from initial hydroxylation on an isopropyl group. Protein binding probably involves carbamoylation via the sulfoxide since it requires NADPH fortification and is decreased by GSH.

There are large quantitative differences in the proportions of various types of metabolites originating from the carbamoyl moiety of *S*-chloroallyl thiocarbamates as compared to those of *S*-alkyl and *S*-chlorobenzyl thiocarbamates. These differences are attributable in part to the relative reactivity of the various sulfoxides. The diallate sulfoxides are not detected in microsomal systems, whereas sulfoxides are major metabolites (14–51%) of other thiocarbamates previously examined (Casida et al., 1975b; Chen and Casida, 1978). GSH *S*-transferases are involved in formation of GSH conjugates from *S*-alkyl and *S*-benzyl thiocarbamate sulfoxides (Casida et al., 1975b; Hubbell and Casida, 1977) but probably not from the diallate sulfoxides. The mercapturic acid derivative from the diallate isomers accounts for $\sim$62% of the administered dose, a yield greatly exceeding that with other thiocarbamates in rats (DeBaun et al., 1978; Hubbell and Casida, 1977). Thus, the diallate isomers are more efficiently sulfoxidized, relative to other sites of metabolism, and the sulfoxides appear to react readily with GSH under in vivo conditions. $^{14}CO_2$ release in MO systems is >37-fold more with the diallate isomers than with *S*-ethyl di-*n*-propylthiocarbamate (EPTC) (Chen and Casida, 1978). The $^{14}CO_2$ produced in vivo in rats corresponding to 20% of the diallate dose may originate from further metabolism of the GSH conjugate since related GSH conjugates injected into rats give 7–22% of the dose as $^{14}CO_2$ (Hubbell and Casida, 1977). The urinary ^{14}C from the diallate isomers is about twice that from EPTC or *S*-ethyl diisobutylthiocarbamate (butylate) but similar to that from the sulfoxides of EPTC and butylate (Hubbell and Casida, 1977). These various lines of evidence point to the dominance with the diallate isomers of the metabolic pathway involving sulfoxidation and GSH conjugation.

The reactivity and thermoinstability of *S*-chloroallyl thiocarbamate sulfoxides is discussed elsewhere (Schuphan and Casida, 1979).

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Supplementary Material Available: One table of spectroscopic data for *S*-(*n*-propyl) diisopropylthiocarbamate and its sulfoxide and sulfone and for the *S*-diisopropylcarbamoyl derivatives of GSH, cysteine, mercapturic acid, and mercaptoacetic acid. Three tables giving rates of ^{14}C elimination from treated rats and amounts of each metabolite in the excreta and in the in vitro systems (5 pages). Ordering information is given on any current masthead page.

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Crystal and Molecular Structure of Organophosphorus Insecticides. 12. Dowco 214

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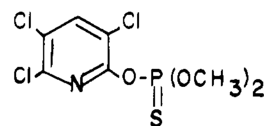
The crystal and molecular structure of Dowco 214 [*O,O*-dimethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate] has been determined by single crystal X-ray techniques. It crystallizes in space group $P\bar{1}$ with $a = 11.598$ (2), $b = 13.619$ (3), $c = 8.281$ (1) Å, $\alpha = 94.65$ (1), $\beta = 94.87$ (2), and $\gamma = 79.97$ (2)° with four molecules per unit cell (two per asymmetric unit). A modified Patterson superposition procedure yielded an initial model and subsequent least-squares refinement based on 3810 observed reflections ($|F_o| > 3\sigma_{F_o}$) gave a final residual index of $R = 0.078$. The geometry around the phosphorus is distorted tetrahedral with the P–O bond to the aryl group being somewhat elongated relative to the others, averaging 1.616 (4) Å vs. 1.560 (4) and 1.547 (4) Å. Charge densities as determined by CNDO methods are also presented, along with appropriate distances between positively charged centers.

Structural studies of various organophosphorus (OP) insecticides, with similar formulations but widely differing activities/toxicities, have been undertaken in this laboratory (Baughman and Jacobson, 1975, 1976, 1977, 1978; Baughman et al., 1978a,b; Gifkins and Jacobson, 1976; Rohrbaugh and Jacobson, 1976, 1977, 1978) via single-crystal X-ray diffraction techniques. These studies are part of a program to generate the necessary data base to correlate toxicity of insecticides, particularly of the organophosphorus type, and their structural and electronic features through generation of a body of precise structural parameters. Accurate structural determination of the relatively small OP insecticide molecules allows inferences to be drawn concerning the three-dimensional structure of the active sites on the complex acetylcholinesterase (AChE) molecule. As has been previously discussed (O'Brien, 1960; Fukuto and Metcalf, 1956; Fukuto, 1971; Hansch and Deutsch, 1966; Canepa et al., 1966), the effectiveness of the insecticide appears to depend on a favorable combination of gross topological features, relative charge densities on the sites that bond to the enzyme, and the esteratic–anionic site separations within a range that best accommodate the various AChE enzymes. It is hoped that such structural information will aid in the construction of more specific insecticides conforming to the most favorable configuration to interact with the target AChE molecule.

Among the crystal structures recently completed in this laboratory have been that of chlorpyrifos and its methyl oxon homologue, fospirate (the fourth and fifth references cited above) with LD_{50}'s of 163 and 869 mg/kg, respectively (Osborne, 1976). Continuing in this vein, we decided to carry out a crystal structure analysis of *O,O*-dimethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate, hereafter referred to as Dowco 214, the methyl homologue of chlorpyrifos. It has a much lower mammalian toxicity



(LD_{50} = 1500 mg/kg; Eto, 1974) than either chlorpyrifos or fospirate and yet is more effective against adult mosquitos.

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EXPERIMENTAL SECTION

Crystal Data. Samples of Dowco 214 were kindly supplied by D. W. Osborne of the Dow Chemical Co. A rectangular crystal of approximate dimensions 0.4 × 0.4 × 0.6 mm was mounted on the end of a glass fiber with Elmers Glue-All and attached to a standard goniometer head. Three preliminary ω-oscillation photographs, taken at various χ and ϕ settings on a four-circle diffractometer, provided the coordinates of 11 independent reflections which were input into an automatic indexing program (Jacobson, 1976). The resulting reduced cell and reduced cell scalars indicated triclinic symmetry. Observed layer line spacings on subsequent axial ω-oscillation photographs were equal within experimental error to those predicted by the indexing program.

Lattice constants were obtained by a least-squares refinement of the precise $\pm 2\theta$ ($|2\theta| > 25°$) measurements of 25 strong independent reflections using graphite monochromated Mo Kα radiation ($\lambda = 0.70954$), yielding a = 11.598 (2) Å, b = 13.619 (3) Å, c = 8.281 (1) Å, α = 94.65 (1)°, β = 94.87 (2)°, and γ = 79.97 (2)°.

Collection and Reduction of X-Ray Intensity Data. Data were collected at 27 °C on an automated four-circle diffractometer described previously (Rohrbaugh and Jacobson, 1974). All data within a 2θ sphere of 50° (5356

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