Identification of [^{14}C]Quizalofop-P-tefuryl Metabolites in Goat Urine by Nuclear Magnetic Resonance and Mass Spectrometry

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The urinary metabolites of [^{14}C]quizalofop-P-tefuryl, (*R*,*S*)-tetrahydrofurfuryl (*R*)-2-[4-[(6-chloro-2-quinoxalinyl)oxy]phenoxy]propanoate, were identified. A lactating goat received three consecutive daily oral doses of quizalofop-P-tefuryl, equivalent to 330 ppm in the daily diet. The animal was sacrificed 24 h after the last administration. A major route of elimination was found to be via the urine, where two metabolites were observed by HPLC. The major metabolite was identified by mass and NMR spectrometry as quizalofop, a compound resulting from hydrolysis of the tetrahydrofurfuryl alcohol moiety of quizalofop-P-tefuryl. The minor metabolite was more polar than quizalofop, and its molecular weight was 16 amu higher than that of quizalofop. This metabolite was identified as a hydroxy derivative of quizalofop. Cochromatographic comparison of the minor metabolite with synthetic (*R*)-2-[4-[(6-chloro-3-hydroxy-2-quinoxalinyl)oxy]phenoxy]propanoic acid, prepared in three steps, revealed that hydroxylation had occurred at the 3-position of the quinoxaline ring.

INTRODUCTION

Quizalofop-P-tefuryl, (*R*,*S*)-tetrahydrofurfuryl (*R*)-2-[4-[(6-chloro-2-quinoxalinyl)oxy]phenoxy]propanoate, is a new herbicide developed by Uniroyal Chemical Co. and registered as Pantera. It is a specific postemergence herbicide that effectively controls both annual and perennial grasses in tolerant broadleaf crops, such as cotton, soybean, peanut, canola, and sugar beet. It is particularly efficacious against Johnson grass and quackgrass and is most efficacious when target grasses are actively growing and are not being stressed. The metabolism of phenoxy propanoates by plants has been described (Shimabukuro, 1990) including the ethyl ester of quizalofop (Koeppe et al., 1991). The only information available concerning animal metabolism of chloroquinoxalinyloxyphenoxy propanoates is provided in a review by Suzuki et al. (1991). The mechanism of action of the ethyl ester of quizalofop was investigated by Nakahira et al. (1990), and the mode of action and the basis for selectivity of the related phenoxy propanoates have been reviewed by Shimabukuro (1990).

The metabolism of quizalofop-P-tefuryl in animals and plants has been extensively investigated in our laboratories. A lactating goat that received three consecutive daily oral doses of quizalofop-P-tefuryl excreted approximately 19% of the administered dose in urine and about 10% in feces. Less than 1% was found in the milk and edible tissues. Most of the test material is presumed to have remained in the gastrointestinal tract at sacrifice.

This paper describes the isolation and identification of the metabolites of quizalofop-P-tefuryl in the urine of the lactating goat. In addition, the chemical synthesis of a hydroxylated metabolite is described. The structure of quizalofop-P-tefuryl and the location of radiolabel (designated by an asterisk) are shown in Figure 1.

EXPERIMENTAL PROCEDURES

Test Material. Quizalofop-P-tefuryl uniformly labeled with ^{14}C at positions 4a, 5, 6, 7, 8, and 8a of the quinoxaline ring (Figure 1) with a specific activity of 45.5 mCi/mmol and a radiochemical purity of greater than 99% was synthesized by Chemsyn Science Laboratories, Lenexa, KS. The radiolabeled material was diluted with cold quizalofop-P-tefuryl to a specific activity of about 1 mCi/mmol prior to dosing.

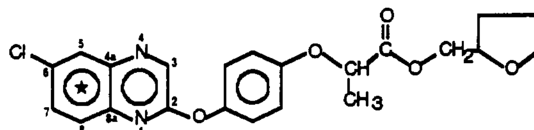

Figure 1. Structure of quizalofop-P-tefuryl and location of radiolabel (*).

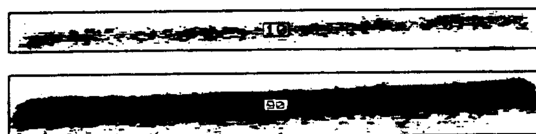

Figure 2. Autoradiogram of goat urine metabolites separated on a reversed-phase TLC plate. Numbers in the bands indicate relative percentages of radioactivity as determined by the AMBIS system. The origin is marked by the letter O. The R_f values are 0.56 (band 1) and 0.42 (band 2).

Animal Treatment and Sample Collection. A lactating Nubian/Alpine goat (approximately 7 years old and weighing 47 kg) received three consecutive daily capsules via a balling gun after each morning milking. Each capsule contained approximately 17 mg of labeled and 689 mg of nonradioactive quizalofop-P-tefuryl, giving a dose equivalent to 330 ppm in the daily diet. The animal was maintained in a metabolism stall that allowed for the separate collection of urine and feces. Water and feed were provided ad libitum.

Urine was collected daily during the treatment period, and the animal was sacrificed approximately 24 h following the last dose.

Analytical Methods. High-performance liquid chromatography (HPLC), on-line radioactivity monitoring, data acquisition, and fraction collection were performed with instrumentation previously described (Banijamali et al., 1991). Separation was achieved on a Phenomenex C_8 Spherex column, 5-μm particles, 150 × 4.6 mm. The guard column was a Brownlee Spheri-10, 30 × 4.6 mm, C_8 cartridge. The solvents were acetonitrile and 50 mM ammonium formate, pH 6.5. The gradient was linear from 10 to 40% acetonitrile over 40 min followed by a steep rise to 100% acetonitrile in 5 min, which was maintained for 5 min (total run was 50 min) at a flow rate of 1 mL/min. All runs were at ambient temperature.

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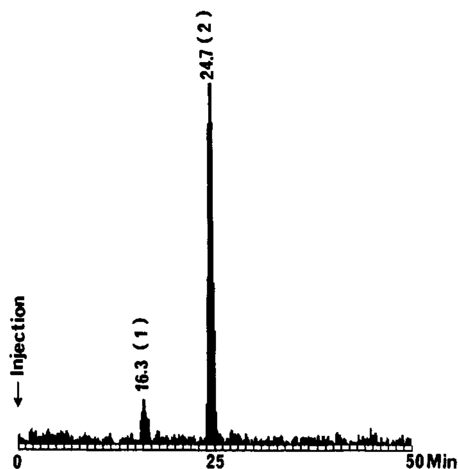

Figure 3. HPLC radiochromatogram of quizalofop-P-tefuryl metabolites in goat urine. Metabolite numbers and retention times are shown. The distributions of radioactivity in percent total radioactive residue as determined by HPLC fraction collection and LSC are, for peak 1, 5.8%, and for peak 2, 84.1%.

The radioactivity on TLC plates was visualized on an AMBIS radioanalytic imaging system, with AST computer and color probe software (V.1.74).

Radiocarbon was quantitated in 10 mL of Ultima Gold (Packard) by dissolving an aliquot of the sample and counting in a Beckman Model LS 7500 liquid scintillation counter (LSC).

Nuclear magnetic resonance (NMR) spectra were obtained on a Varian XL-300 spectrometer using the manufacturer's supplied version 6.2 software. Solvents were evaporated from TLC-purified metabolites under a stream of dry nitrogen; metabolites were dissolved in $CDCl_3$ or DMSO-d_6 and were placed in 5-mm NMR tubes. Chemical shifts were recorded as parts per million (δ) relative to TMS (multiplicity: s, singlet; m, multiplet; d, doublet; q, quartet). THFyl assignment refers to tetrahydrofuranyl.

Infrared (IR) spectra were obtained with a Perkin-Elmer 1420 infrared spectrometer on samples prepared as KBr disks. Bands are reported as cm^{-1} and described as strong (s), medium (m), weak (w), or broad (br).

Both electron impact (EI) and negative ion chemical ionization (NICI) mass spectra (MS) were obtained on a Finnigan 4500 GC/MS with a direct exposure probe (DEP) for sample introduction. The metabolites were placed as 1 μg/μL acetonitrile solutions on the probe. The solvent was evaporated before the sample was introduced into the MS. The spectrometer was set to scan up to 500 Da at a rate of 0.45 scan/s. Fast atom bombardment mass spectrometry (FABMS) was performed with a Kratos MS 890 hybrid mass spectrometer in the EBQQ configuration on samples dissolved in 1:2 methanol–glycerol.

Extraction, Separation, and Purification of Metabolites. LSC indicated that 19.1% of the administered dose was excreted in urine. Quantitative separation and purification of the urinary metabolites were achieved through a series of steps as follows.

1. Amberlite XAD-4. The preliminary extraction/cleanup of urinary metabolites consisted of adsorption onto activated Amberlite XAD-4 resin. Approximately 50 g of resin was activated by washing with methanol, acetonitrile, and water (twice with approximately 100 mL of each solvent), sequentially prior to use. The pooled urine sample (30 mL) was diluted with water (1:1), mixed with activated resin, and stirred for about 16–20 h. After filtration, the resin was washed with water and dried at room temperature. Samples were eluted from the resin by washing three times with acetonitrile (total 135 mL), and quantitative recovery of radioactivity was obtained.

2. TLC. The concentrated acetonitrile extract from the resin (approximately 15 million dpm in 15 mL) was applied to five preparative reversed-phase TLC plates (Whatman PLKC18F, 20 × 20 cm, 1000 μm) and developed in acetonitrile–50 mM ammonium formate, pH 6.5 (30:70 by volume). The plates were dried, and two distinct zones of radioactivity were observed by autoradiography after scanning for 20 min (Figure 2). The plates were sprayed with water, and the radioactive bands were carefully scraped and extracted by stirring with methanol. Extracts were filtered and concentrated, and the radioactivity was quantitated. The individual bands [approximately 8 million dpm of band 1 (R_f 0.56) in 4 mL of methanol and nearly 1 million dpm of band 2 (R_f 0.42) in 2 mL of methanol] were applied to separate preparative silica gel TLC plates (Whatman PLK5F, 20 × 20 cm, 1000 μm) and developed in methanol–chloroform (30:70 by volume). After the plates were dried and autoradiographed, the radioactive bands on each plate were scraped and extracted with methanol. The amount of radioactivity isolated was quantitated by LSC.

SYNTHESIS

(*R,S*)-(Tetrahydro-2-furanyl)methyl (*R*)-2-[4-[(6-Chloro-2-quinoxalinyl)oxy]phenoxy]propanoate 4-Oxide (2). A mixture of (*R,S*)-(tetrahydro-2-furanyl)methyl (*R*)-2-[4-[(6-chloro-2-quinoxalinyl)oxy]phenoxy]propanoate (1) (Davis et al., 1992) (3.0 g, 7.0 mmol) and Oxone, monopersulfate compound (4.5 g, 7.3 mmol), in 35% aqueous acetic acid (70 mL) was stirred at room temperature for 5 days. The reaction mixture was partitioned between dichloromethane (200 mL) and water (400 mL). The organic layer was separated, washed with 5% $NaHCO_3$ (100 mL), and dried ($MgSO_4$). Solvent was evaporated to yield a light amber oil (2.7 g). Product was separated from the unoxidized ester by flash chromatography (Still et al., 1978) using ethyl acetate–hexane (2:3) as eluent. Evaporation of solvent from combined like fractions gave an oily solid (2.3 g). The latter, on crushing in ethyl acetate–hexane (2:98), yielded a white powder (2.1 g; 67%): mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (m, d, J = 6.8 Hz, 4H, 3-THFylCH, CH_3), 1.88 (m, 3H, 3-THFylCH and 4-THFylCH$_2$), 3.80 (m, 2H, 5-THFylCH$_2$), 4.13 [m, 2H, CH$_2$OC(O)], 4.27 (m, 1H, 2-THFylCH), 4.81 (q, J = 6.8 Hz, 1H, CH), 6.97 (AA′BB′, J = 9.0 Hz, 2H, aromatic), 7.14 (AA′BB′, J = 8.8 Hz, 2H, aromatic), 7.64 (dd, $J_{7,8}$ = 8.8 Hz, $J_{5,7}$ = 2.2 Hz, 1H, H_7), 7.70 (d, $J_{7,8}$ = 8.8 Hz, 1H, H_8), 8.19 (s, 1H, H_3), 8.48 (d, $J_{5,7}$ = 2.2 Hz, 1H, H_5); IR 1740s, 1555m, 1505s, 1460m, 1410m, 1355m, 1210s, 1140s, 1100m, 840m, 820s; EIMS m/z 444 (M^+).

(*R,S*)-(Tetrahydro-2-furanyl)methyl (*R*)-2-[4-[(6-Chloro-3,4-dihydro-3-oxo-2-quinoxalinyl)oxy]phenoxy]propanoate (3). To a stirred solution of 2 (0.80 g, 1.8 mmol) in dichloromethane (20 mL), cooled to 5 °C by an ice–water bath, was added trifluoroacetic anhydride (8.0 mL, 57 mmol) over 15 min. The reaction mixture was stirred for 1 h at 5 °C and allowed to warm to room temperature over 1.5 h. Evaporation of volatiles left a yellow viscous oil which crystallized on standing (1.1 g). Two recrystallizations from ethyl acetate–hexane (3:2) gave product 3 (250 mg, 31%) as fine colorless needles: mp 175–176 °C; ^{1}H NMR ($CDCl_3$) δ 1.66 (m, d, J = 6.8 Hz, 4H, 3-THFylCH,-CH$_3$), 1.88 (m, 3H, 3-THFylCH and 4-THFylCH$_2$), 3.80 (m, 2H, 5-THFylCH$_2$), 4.14 [m, 2H, CH$_2$OC(O)], 4.27 (m, 1H, 2-THFyl-CH), 4.82 (q, J = 6.8 Hz, 1H, CH), 6.95 (AA′BB′, J = 9.1 Hz, 2H, aromatic), 7.21 (AA′BB′, J = 9.1 Hz, dd, $J_{7,8}$ = 8.6 Hz, $J_{5,7}$ = 2.2 Hz, 3H, aromatic + H_7), 7.40 (d, $J_{7,8}$ = 8.6 Hz, 1H, H_8), 7.47 (d, $J_{5,7}$ = 2.2 Hz, 1H, H_5), 12.5 (br s, 1H, NH); IR 3440w, 3180w, 2940m, 1740s, 1690vs, 1615s, 1575s, 1502vs, 1290s, 1220vs, 1185s, 1130s, 1085s; EIMS m/z 444 (M^+).

(*R*)-2-[4-[(6-Chloro-3,4-dihydro-3-oxo-2-quinoxalinyl)oxy]-phenoxy]propanoic acid (4). A mixture of 3 (250 mg, 0.56 mmol), 0.01 N NaOH (56 mL), and methanol (10 mL) was stirred at room temperature for 18 h and heated to 80 °C for 1 h. On cooling to 25 °C, unreacted 3 (50 mg) was filtered and the filtrate concentrated to 30 mL using a rotary evaporator. Acidification of the concentrate with 1 N HCl followed by filtration of the suspension gave a beige solid (100 mg; 62%): mp 265 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.55 (d, J = 6.6 Hz, 3H, CH$_3$), 4.86 (q, J = 6.6 Hz, 1H, CH), 6.96 (AA′BB′, J = 8.8 Hz, 2H, aromatic), 7.12–7.27 (AA′BB′, J = 8.8 Hz, dd, $J_{7,8}$ = 8.6 Hz, $J_{5,7}$ = 1.5 Hz, d, $J_{5,7}$ = 1.5 Hz, 4H, aromatic + H_7 + H_5), 7.36 (d, $J_{7,8}$ = 8.6 Hz, 1H, H_8), 12.6 (s, 1H, NH); IR 3600–2500br, 1755s, 1685vs, 1640s, 1620vs, 1575s, 1508vs, 1295s, 1225vs, 1185s, 1130s; EIMS m/z 360 (M^+).

RESULTS AND DISCUSSION

Distribution of Radioactivity in Urine. The HPLC radiochromatogram of urine without prior extraction

Figure 4. Mass spectra of the peak 2 urinary metabolite obtained under EI (a) and FAB (b) conditions.

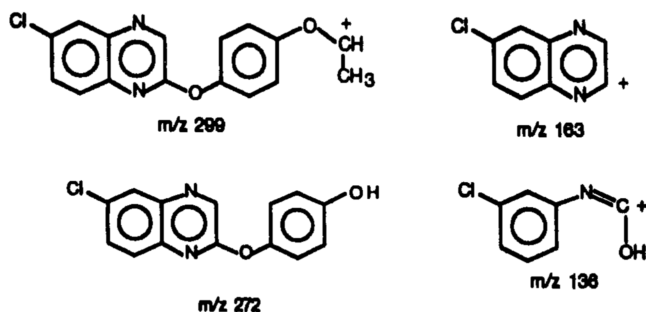

Figure 5. Structures of the major fragments in EIMS of the peak 2 urinary metabolite.

showed two radioactive peaks (Figure 3). The distribution of radioactivity in this chromatogram, determined by fraction collection and LSC, is indicated. Approximately 85% of the total radioactive residue in urine resided in peak 2 (tr = 24.7 min), and about 6% of the total radioactive residue was accounted for in peak 1 (tr = 16.3 min). No starting material, [^{14}C]quizalofop-P-tefuryl, was observed in the urine. (Quizalofop-P-tefuryl eluted with a retention time of about 48 min in this HPLC system.)

Isolation and Purification of Peaks from Urine. The preliminary extraction/cleanup of quizalofop-P-tefuryl urinary metabolites consisted of adsorption onto activated Amberlite XAD-4 resin. Over 95% of the radioactivity in urine was adsorbed onto the resin and subsequently eluted from it by washing with acetonitrile and methanol. The concentrated extracts from the Amberlite XAD-4 resin were applied to preparative reversed-phase TLC plates and developed in acetonitrile–50 mM ammonium formate as described under Experimental Procedures. Areas from the preparative TLC plates containing radioactivity were removed and the radioactivity eluted from the C_{18} material with acetonitrile and methanol. Metabolites obtained from the initial preparative reversed-phase TLC separation required additional TLC cleanup to remove unlabeled contaminants, prior to spectral analyses. This was achieved for each

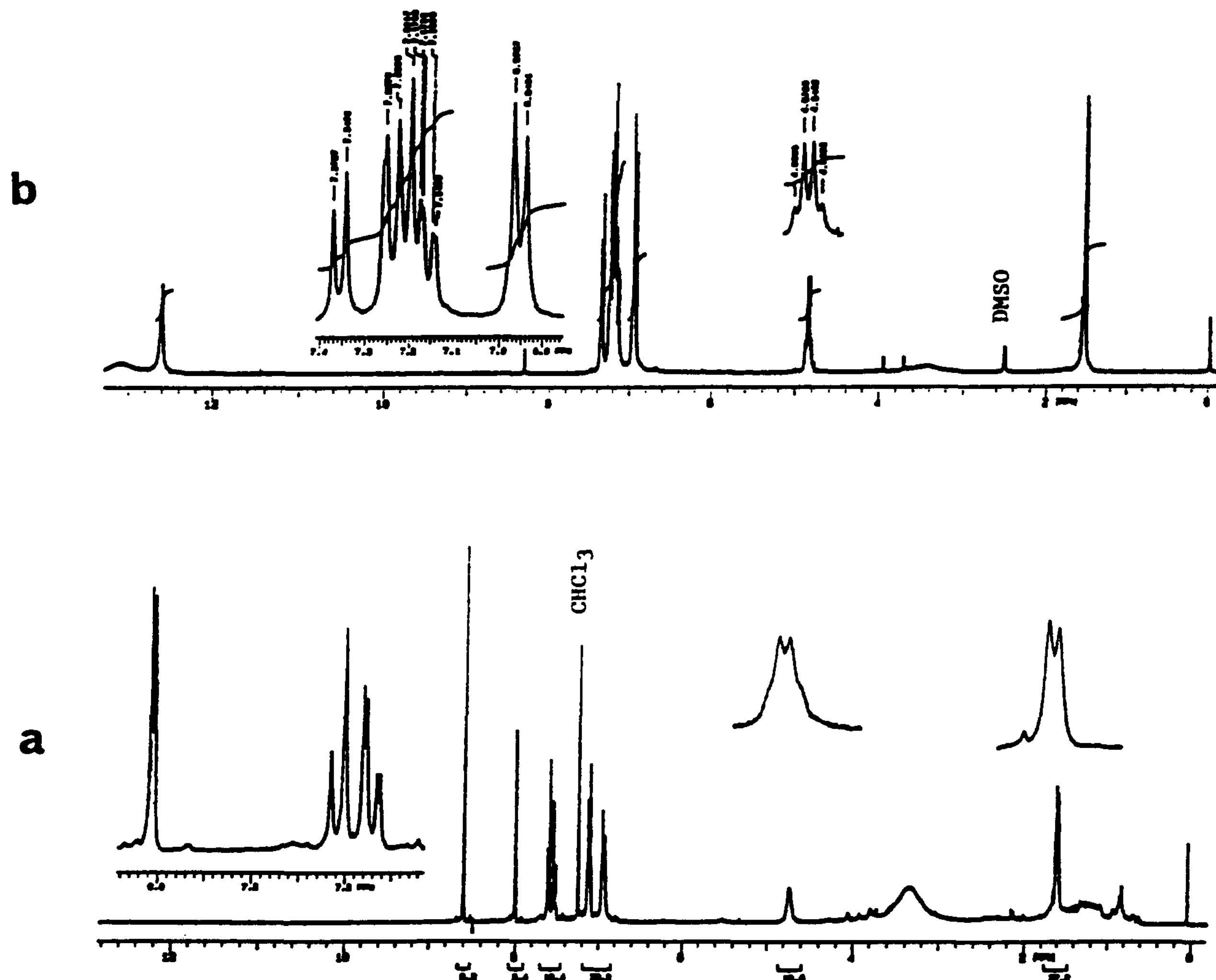

Figure 6. ^{1}H NMR (300 MHz) spectra of the peak 2 urinary metabolite (a) and synthetic 3-hydroxyquizalofop (b).

band on preparative silica gel TLC plates developed in methanol–chloroform. In this manner approximately 3 mg of peak 2 and 100 μg of peak 1 were obtained. The HPLC radiochromatogram and UV chromatogram of each peak after final purification indicated high-purity samples suitable for spectral analyses.

Identification of Peak 2 Urinary Metabolite. The identification of peak 2 was achieved by high-resolution FT-NMR and mass spectrometry. The latter provided molecular weight and some structural information. Mass spectra obtained under EI, NICI (using ammonia as the reagent gas), and FAB conditions gave the molecular weight and fragmentation pattern. The EIMS of this urinary metabolite (Figure 4a) displayed the molecular ion peak at 344 amu. In addition, a prominent ion at m/z 299, 45 amu lower than the molecular ion peak, is characteristic of loss of a carboxyl group, and the ion at m/z 272 can be attributed to 4-[(6-chloro-2-quinoxalinyl)-oxy]phenol (CQOP) formed upon loss of propanoic acid (m/z 72) from the molecular ion. Other significant ions at m/z 163 and 136 are attributed to chloroquinoxaline and subsequent loss of a cyano group from it, respectively (Figure 5). The FAB spectrum of peak 2 obtained under negative ion conditions displayed an M − 1 peak at 343 amu (Figure 4b). The other characteristic peaks were assigned to CQOP − 1 at m/z 271, chlorohydroxyquinoxaline (CHQ − 1) at m/z 179, and the sodium adduct of the molecular ion (M − 1 + Na) at m/z 366. In addition, losses of water and chlorine from the molecular ion were observed at m/z 325 and 308, respectively. Similarly, a loss of chlorine from CQOP was seen at m/z 236. Although the fragments described above are well characterized, the single chlorine isotopic peaks appearing as $X + 2$ with the characteristic abundance of ^{37}Cl provided additional evidence for the structural assignments in the mass spectrum.

The absence of proton signals corresponding to the tetrahydrofurfuryl group in the ^{1}H NMR spectrum of peak 2 indicated metabolic de-esterification of quizalofop-P-tefuryl and confirmed that peak 2 is quizalofop (Figure 6a). In addition, integration of the protons of the quinoxaline and the phenylenedioxy rings eliminated the possibility of aromatic substitution (e.g., hydroxylation). The four protons of the phenylenedioxy ring appeared as two multiplets centered at 6.9 and 7.1 ppm, a characteristic of paradisubstitution. The locations of the quinoxaline protons were also determined on the basis of their characteristic chemical shifts and splitting patterns. In this manner the low-field singlet at 8.6 ppm was assigned to H_3 since it was deshielded by the adjacent heterocyclic nitrogen. The doublet centered at 8.0 ppm was assigned to H_5 on the basis of its coupling of meta magnitude (J = 2.2 Hz) to H_7. The H_7 signal appeared as a doublet of doublets by virtue of its coupling to two protons, namely H_8 (giving rise to a doublet with J = 9 Hz), and its meta location to H_5, giving rise to the small splittings (J = 2.2 Hz) for each of the doublet lines. The remaining doublet centered at 7.6 ppm was assigned to H_8 due to its coupling to adjacent H_7 (J = 9 Hz). The methyl and methine groups of the 2-propanoic acid moiety appeared as a doublet and

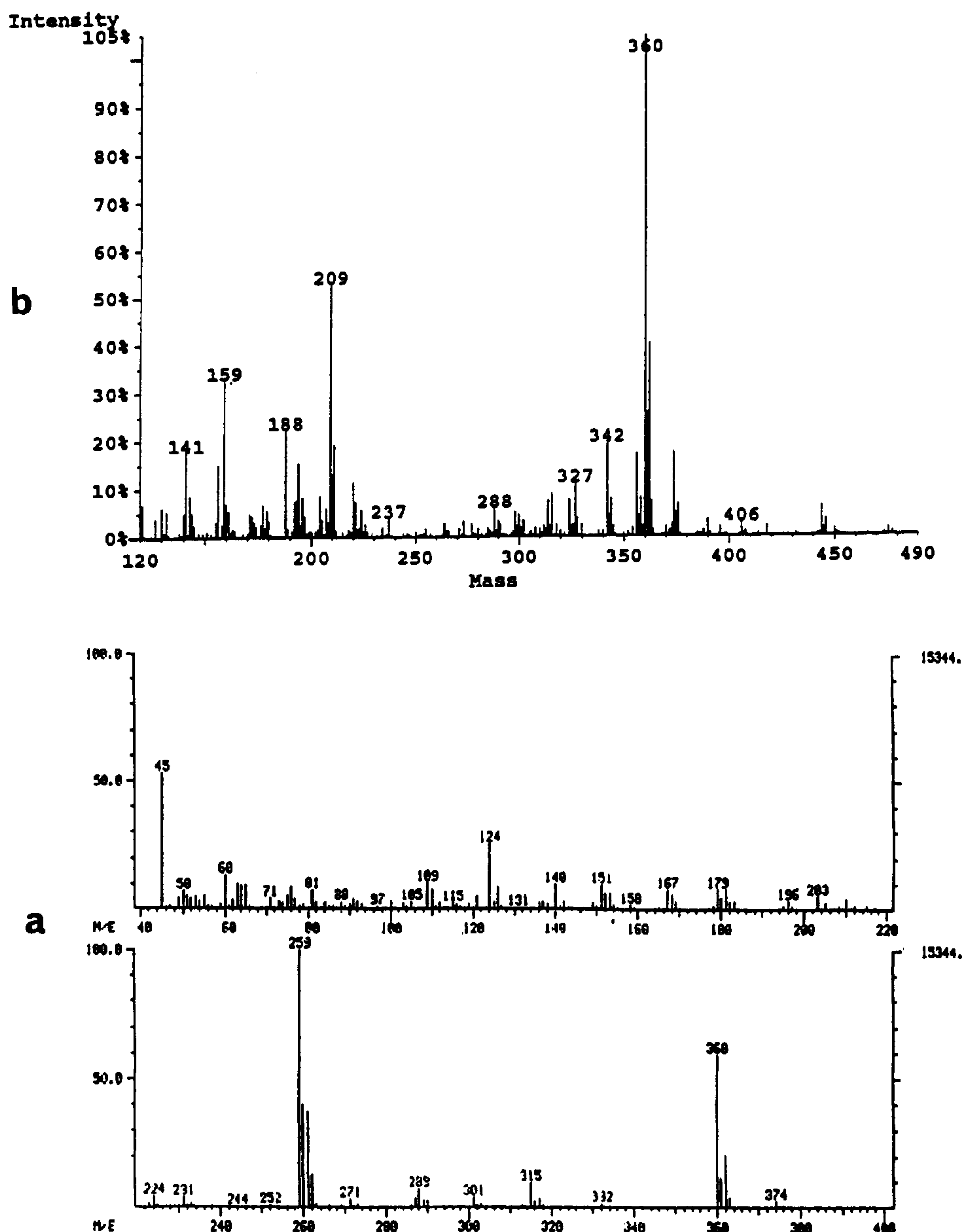

Figure 7. Mass spectra of the peak 1 urinary metabolite obtained under EI (a) and negative ion CI (b) conditions.

a broad quartet centered at 1.55 and 4.8 ppm, respectively. On the basis of MS and NMR results, peak 2 is identified as (*R*)-2-[4-[(6-chloro-2-quinoxalinyl)oxy]phenoxy]propanoic acid (quizalofop).

Identification of Peak 1 Urinary Metabolite. Reversed-phase HPLC indicated that this metabolite is more polar than quizalofop. Both EI and CI mass spectra of the peak 1 urinary metabolite displayed the molecular ion peak at m/z 360, suggesting that peak 1 is a hydroxy derivative of peak 2 (Figure 7). Due to a relatively low concentration of this metabolite in urine, there was an insufficient quantity for NMR study. This metabolite was identified as 3-hydroxyquizalofop by HPLC cochromatography. As shown in Figure 8, a single peak with a retention time of 16.3 min was observed when peak 1 and synthetic 3-hydroxyquizalofop were chromatographed individually or cochromatographed as a mixture. The synthetic standard was prepared as described below.

Synthesis of 3-Hydroxyquizalofop. An authentic sample of 3-hydroxyquizalofop was synthesized in three steps starting with quizalofop-P-tefuryl as shown in Figure 9. Oxidation of quizalofop-P-tefuryl with $KHSO_5$ occurred at the least sterically hindered 4-position of the quinoxaline ring to give the *N*-oxide. The NMR spectrum of the product exhibited an upfield shift of the H_3 proton (singlet) from 8.65 ppm in quizalofop-P-tefuryl to 8.19 ppm, while the H_5 doublet ($J_{5,7}$ = 2.2 Hz) of quizalofop-P-tefuryl was shifted downfield from 8.03 to 8.48 ppm. This observation is consistent with NMR shielding effects observed for other quinoxaline *N*-oxides (Loriga et al., 1990; Zamet et al., 1974) and pyridine *N*-oxides (Ochiai, 1967). The band in the infrared spectrum attributed to the N–O stretching vibration was found at 1355 cm^{-1}, in agreement with assignments to other quinoxaline *N*-oxides (Khan et al., 1972). The mass spectrum of the *N*-oxide displayed the molecular ion at m/z 444.

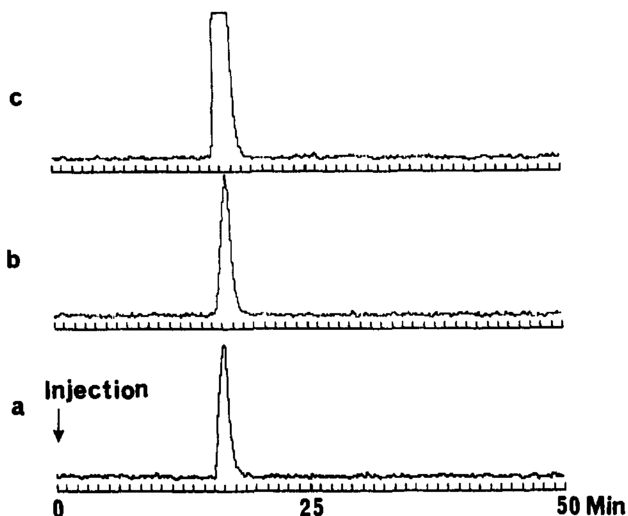

Figure 8. HPLC chromatogram (UV 236 nm) of the peak 1 urinary metabolite (a), synthetic standard of 3-hydroxyquizalofop (b), and cochromatography of (a) and (b) (c).

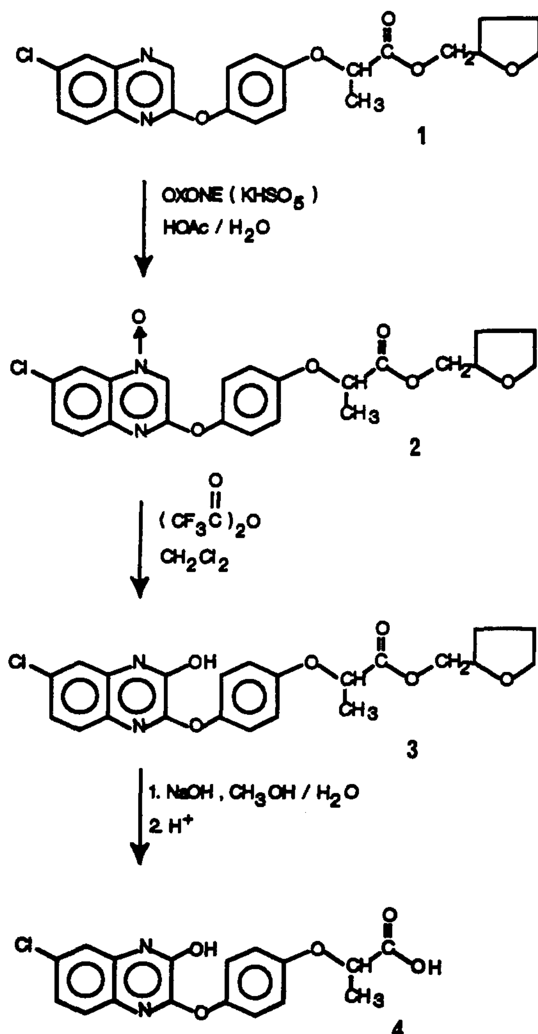

Figure 9. Synthesis of 3-hydroxyquizalofop.

The N-oxide (2) was converted to the 3-hydroxyquinoxaline ester (3) using trifluoroacetic anhydride in methylene chloride at 5 °C (Daeniker and Druey, 1958). The infrared spectrum of the product showed a very strong carbonyl absorption at 1685 cm^{-1} in addition to the ester carbonyl at 1740 cm^{-1}. The former is attributed to the amide carbonyl of the tautomeric form of the hydroxyquizalofop ester (3). The NMR spectrum (DMSO-d_6) of the product showed an NH (or OH) proton at 12.5 ppm and the absence of a quinoxaline H_3 singlet. The mass spectrum of the product showed the molecular ion at 444 amu, the same as its N-oxide precursor.

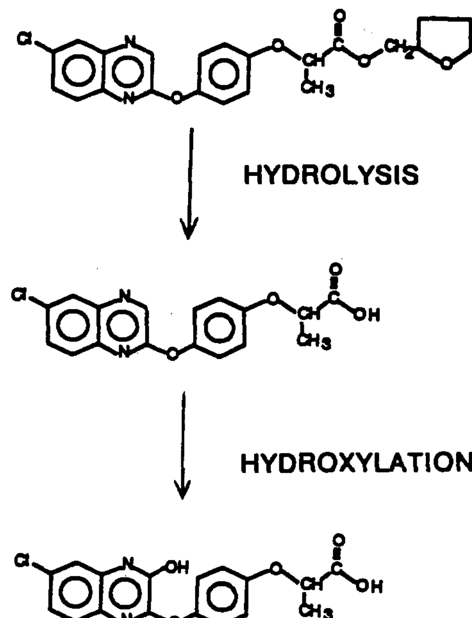

Figure 10. Proposed pathway for formation of urinary metabolites of quizalofop-P-tefuryl by goats.

Saponification of the 3-hydroxyquizalofop-tetrahydrofurfuryl ester (3) in 1 equiv of NaOH in 15% methanol–water gave the desired 3-hydroxyquizalofop. ^1H NMR confirmed the absence of the tetrahydrofurfuryl moiety (Figure 6b), and the infrared spectrum showed a broad band at 2500–3600 cm^{-1} and a strong absorption at 1760 cm^{-1} for the carboxyl group. The EIMS spectrum displayed the molecular ion at m/z 360 identical to that of peak 1 (Figure 7).

Conclusions. Oral administration of quizalofop-P-tefuryl to a lactating goat resulted in a low level of residues in edible tissues and in milk. The metabolism of quizalofop-P-tefuryl does not appear to be complex. Only two metabolites, quizalofop and a hydroxy derivative of quizalofop formed by ester hydrolysis and hydroxylation, were observed in the radiochromatogram of urine. Although quizalofop and hydroxyquizalofop were proposed to be soil and animal metabolites of the ethyl ester of quizalofop, this paper provides the only definitive synthesis of 3-hydroxyquizalofop and characterization of these interesting metabolites. The large ratio of quizalofop to hydroxyquizalofop and the absence of 3-hydroxyquizalofop-P-tefuryl suggest that the pathway shown in Figure 10 is important for metabolism of quizalofop-P-tefuryl in goats.

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