Synthesis, *in Vivo* Effects, Metabolism, and Excretion of 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole in the Beagle Dog

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Trained normal and hypertensive beagle dogs were administered tritiated 5-(*p*-hydroxyanilino)-1,2,3,4-thiatriazole both orally (30 mg/kg) and intravenously (20 mg/kg). Plasma levels of radioactivity as well as blood pressure and heart rate were measured concomitantly at various times following dosing. The maximum hypotensive effect occurred 2 hr after intravenous dosing and 4-8 hr after oral dosing. This maximum effect did not correlate with maximum plasma levels of parent drug or metabolite, suggesting that a single agent may not be responsible for the hypotensive effect; a secondary mechanism may be involved. Excretion of radioactivity was followed for 5-6 days after dosing. Biliary secretion of parent drug or its metabolites was indicated when 9-17% of intravenously administered drug radioactivity was excreted *via* the feces. Examination of urinary metabolites from each dog showed unchanged parent drug 5.7-20.7% (iv), 18.6-20.2% (oral); *p*-aminophenol 45.9-66.5% (iv), 40.7-45.5% (oral). The urine from one dog was examined for other metabolites, and the following were found: *p*-hydroxyphenylthiourea, 3.2-5.6%; *p*-hydroxyphenylurea, 7.1-10.5%; APAP, 1.5-1.8%; unknown metabolite, 16.2-23.9%.

The compound, 5-(*p*-hydroxyanilino)-1,2,3,4-thiatriazole† (**6**), has been under investigation at Abbott Laboratories as a possible antihypertensive agent. A previous report[1] revealed the fate of the compound when administered to rats. In this report, we investigated blood levels of radioactivity concomitant with blood pressure and heart rate, along with excretion and metabolism data after administration of the drug both orally and intravenously to specially trained, unanesthetized beagle dogs.

Experimental Section

Synthesis of 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole. *p*-Hydroxyacetanilide (100 mg) was tritiated by catalytic exchange at 70° in 0.3 ml of trifluoroacetic anhydride containing 10 Ci of tritiated water and 25 mg of reduced PtO_2. The crude material was filtered; then the filtrate was refluxed in 6 *N* HCl for 1.5 hr. Unlabeled *p*-aminophenol (300 mg) was added, and the acidic solution was extracted with diethyl ether to remove impurities. The aqueous layer was made basic (pH 10) with NaOH, extracted again with ether to remove impurities, then adjusted to pH 8, and extracted exhaustively with ether. The pH 8 ether extract was evaporated to dryness, and the black residue of *p*-aminophenol was sublimed at 115-120° (0.1 mm). A nearly colorless solid (180 mg, 4.6 mCi/mg) was obtained.

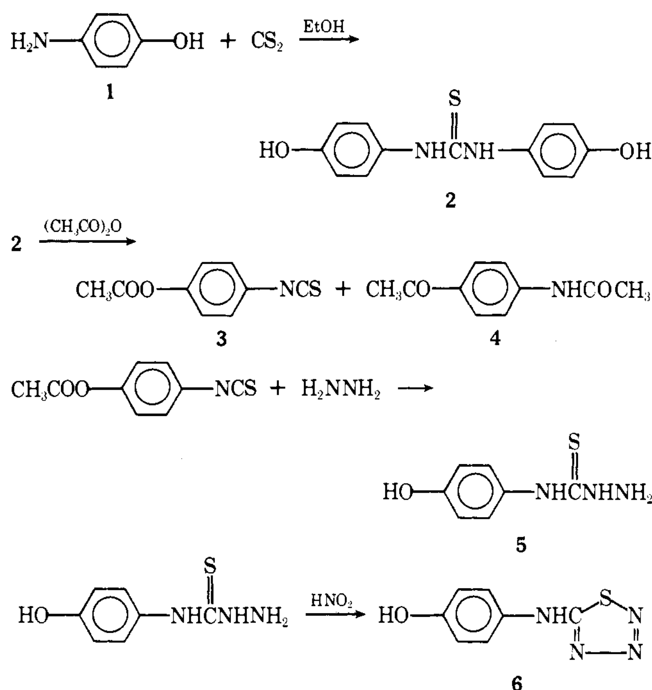
The tritiated *p*-aminophenol (**1**) was diluted with 1.0 g of unlabeled *p*-aminophenol and refluxed with 0.8 ml of CS_2 in 10 ml of absolute ethanol in order to prepare tritiated 1,3-bis(*p*-hydroxyphenyl)thiourea (**2**) according to the method of Kalckhoff.[2] The product was recrystallized from hot ethanol.

Using the method described by Kalckhoff,[2] tritiated *p*-acetoxyphenyl isothiocyanate (**3**) was prepared from the tritiated thiourea **2** and acetic anhydride. The isothiocyanate was separated from the side product, *p*-acetoxyacetanilide (**4**), by extraction of the former into hot hexane. The isothiocyanate was then recrystallized from hexane.

The procedure of Lieber[3] was used to prepare tritiated *p*-hydroxyphenylthiosemicarbazide (**5**) from the reaction of tritiated *p*-acetoxyphenyl isothiocyanate and hydrazine (Scheme I).

The tritiated 4-hydroxyphenyl thiosemicarbazide was diluted with unlabeled 4-hydroxyphenyl thiosemicarbazide to give 6.4 mmol (1.18 g) of material. This was stirred in 60% aqueous acetic acid and cooled in an ice bath. An aqueous solution of $NaNO_2$ (10 mmol, 690 mg, 5 ml) was slowly added with stirring over a period of 5 min. The product, 5-(*p*-hydroxyanilino)-1,2,3,4-thiatriazole (**6**), was filtered after 30 min and washed with water. The crude product was dissolved in warm acetone and decolorized with Darco G-60, and the clear filtrate was treated with water to turbidity. Upon chilling, colorless crystals were formed, which were filtered and air-dried. This crystalline crop was diluted with unlabeled 5-(*p*-hydroxyanilino)-1,2,3,4-thiatriazole and recrystallized from acetone-water to constant specific activity. The final specific activity was 1.0 μCi/mg. Thin-layer chromatography using E. Merck silica gel F-254 plates (250 μ) in four different solvent systems (systems 1-4) indicated that the compound was at least 99% radiochemically pure and that it was identical with authentic material. Both the labeled and unlabeled compounds decomposed at 160° (uncorrected).

Scheme I. Steps in the Synthesis of 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole



The radioactive material was diluted with a clinically approved lot of unlabeled drug, lot no. 811-308, as required for the experiments.

Animals. Three beagle dogs were used in this study. Two animals (no. 6429 and 7756) were normotensive females, and one (no. 1455) was a renal hypertensive male. Hypertension in this latter dog had been produced by bilateral reduction in the caliber of the renal arteries in a manner similar to that described by Goldblatt and coworkers.[4] Earlier studies had shown that there were no sex differences in the behavior of this drug both pharmacologically and metabolically. The dogs were fasted overnight prior to experimentation; they were fed Ideal dog food 2.5 hr after they received the dose and once daily thereafter; water was allowed *ad libitum*.

Polygraphic Measurements. Each dog had been trained to lie quietly on an animal table for measurements of arterial blood pressure, electrocardiogram, and respiration rate. Pulsatile arterial blood pressure was determined in these trained dogs by direct needle puncture of a femoral artery and recorded *via* a pressure transducer on a multichannel polygraph. The control arterial blood pressures were obtained from these dogs at various times during the day for several days prior to administration of drug.

Dose Schedule. In part I of this study, the dogs were adminis-

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Table I. Plasma Levels of Radioactivity, Mean Arterial Blood Pressure (MABP), and Heart Rate after Intravenous Administration of Tritiated 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole to Beagle Dogs[a]

Time after dosing	Radioactivity in plasma expressed as μg/ml of drug			% decrease in MABP			Heart rate, beats/min		
	No. 6429	No. 7756	No. 1455	No. 6429	No. 7756	No. 1455	No. 6429	No. 7756	No. 1455
1 min				2.2	7.1	−13.0	102	102	108
2 min						22.7			210
5 min				−0.2	−4.4	12.7	120	126	144
10 min					11.0	15.9		126	144
15 min	45.5	43.7	48.3	12.3	18.7	14.8	102	132	146
30 min	36.5	35.5	48.2	11.4	17.2	9.5	96	120	120
1 hr	26.4	23.5	35.8	8.1	24.9	10.6	78	114	120
2 hr	14.0	13.8	21.3	20.6	28.8	30.6	120	102	132
4 hr	9.61	8.84	13.4	20.6	18.7	4.3	84	120	126
6 hr	9.83	9.44	12.3	12.3	18.7	29.0	114	96	120
8 hr	9.27	9.93	12.9	14.8	22.6	30.6	96	96	114
25 hr	10.5	10.0	13.3	14.8	13.3	25.3	96	90	78
49 hr	9.55	10.2	13.1	6.4	3.2	1.7	108	84	66
72 hr	9.54	10.4		2.2	5.6		96	96	

[a]Dose: 20 mg/kg solubilized in polyethylene glycol 400–saline (2:1). Dogs no. 6429 and 7756, normal females; dog no. 1455, renally hypertensive male.

Table II. Plasma Levels of Radioactivity, Mean Arterial Blood Pressure (MABP), and Heart Rate after Oral Administration of Tritiated 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole to Beagle Dogs[a]

Time after dosing, hr	Radioactivity in plasma expressed as μg/ml of drug			% decrease in MABP			Heart rate, beats/min		
	No. 6429	No. 7756	No. 1455	No. 6429	No. 7756	No. 1455	No. 6429	No. 7756	No. 1455
1	1.12	0.95	1.50	20.1	11.3	10.3	90	90	102
2	1.48	1.76	2.14	14.2	7.4	14.5	90	84	72
4	6.42	4.32	5.70	10.0	22.8	7.7	96	78	108
6	6.16	6.20	8.52	18.4	17.4	22.4	108	102	108
8	5.60	6.80	8.26	20.1	19.0	18.2	108	90	96
24	5.81	9.82	7.80	5.8	−0.2	17.2	96	114	90
48	8.60	10.2	7.60	−0.8	2.0	2.4	108	102	108
72	8.16	10.3		−0.8	5.9		102	90	

[a]Dose: 30 mg/kg encapsulated in bolus of meat. Dogs no. 6429 and 7756, normal females; dog no. 1455, renally hypertensive male.

tered the drug solubilized in polyethylene glycol 400–saline (2:1) intravenously at a dosage of 20 mg/kg. In part II, the same dogs (after a 7-week rest period) were fed the encapsulated drug in a bolus of meat. A dosage of 30 mg/kg was used. In both parts of the experiment, blood pressure, heart rate, respiration rate, and plasma drug level were determined simultaneously.

Assay Procedure. Radioactivity was used as an indicator of blood levels and excretion rate of drug. Blood samples were withdrawn into heparinized syringes at indicated times and centrifuged immediately. The plasma samples were assayed for radioactivity by Schöniger combustion; urines, cagewashes, and feces were collected at 24-hr intervals. Urinary tritiated water was distilled from each sample by lyophilization. All radioactive samples, after processing as described earlier,[1] were counted in a liquid scintillation counter at conditions suitable for measurement of tritium and corrected for quenching by the internal standard technique.

Enzymic Hydrolysis of Conjugates. The urines were treated as reported earlier.[1] Plasma samples (1 ml) were placed in glass-stoppered 16 × 150 mm test tubes with 1 ml of sodium acetate (0.1 *M*, pH 5.0) buffer and 0.1 ml of Glusulase containing 15,870 Fishman units of β-glucuronidase[5] and 5240 units of sulfatase activity. The tubes were gently agitated at 37° for 20 hr.

Examination of Plasma and Urine for Metabolites. After treatment of the plasma or 0–72-hr urine samples with enzymes, the incubation mixtures were lyophilized and the residues were leached with an amount of 90% methanol (10% water) equal to half the volume of fluid (plasma or urine) in the sample. The methanolic solutions were streaked onto Analtech thin-layer plates and developed in several solvent systems as described previously.[1] For quantification purposes, solvent system 8 (chloroform–acetic acid–water, lower phase, 2:2:1 v/v)[1] was used. Solutions of authentic compounds were spotted on the plates to serve as markers. The developed plates were sequentially scraped in 5-mm sections into liquid scintillation vials containing 1 ml of *N*,*N*-dimethylformamide. The vials were warmed at 50° for 1 hr, then 10 ml of Instagel was added to each vial, and the sample was counted by liquid scintillation. Since all of the samples had essentially the same composition, no correction was made for quenching. The counts per minute thus obtained (corrected for background) were plotted against fraction number, and since each scraped section represented a distance of 5 mm, the locations of radioactive spots (along the abscissa) could be aligned with the locations of authentic samples on the thin-layer plate.

Thin-Layer Chromatography. Analtech silica gel GF plates, 5 × 20 cm, 250 μ, were used with the solvent systems described previously.[1] The R_f values obtained using these plates were not identical with those obtained earlier, but authentic compounds were used with each plate to verify the locations of the various metabolites.

Isotopic dilution experiments were performed as described earlier[1] using *N*-acetyl-*p*-aminophenol (APAP), *p*-hydroxyphenylthiourea, and *p*-hydroxyphenylurea.

Results and Discussion

Blood Studies. Plasma levels of radioactivity following intravenous administration of solubilized tritiated drug (20 mg/kg) along with concomitant heart rates and blood pressure variations from the mean appear on Table I. Similar data following oral administration of drug to the same three dogs are presented on Table II.

In a separate experiment, a normal female dog was administered a 20 mg/kg intravenous dose of tritiated drug, and blood samples were drawn at 5, 15, 30, 60, and 120 min after dosing. Aqueous methanolic extracts of lyophilized plasma samples were examined by thin-layer chromatography, and the results are summarized on Table III. A semilogarithmic plot of the amount of free parent drug *vs.* time indicated that the half-life of the unconjugated parent drug in blood was approximately 30 min.

The constituents found in the blood plasma of a normal female beagle dog at various times following both intravenous and oral doses of tritiated **6** were examined by thin-

Table III. Relative Amounts of Parent Drug and Metabolites Found in Blood Plasma of a Beagle Dog Administered Tritiated 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole[a]

Time after admin, min	% total metabolites[b]	% parent drug
5	49	50
15	73	27
30	85	15
60	92	7
120	96	4

[a]Dose: 20 mg/kg iv. [b]Includes conjugates of parent drug.

layer chromatography of β-glucuronidase and ethereal sulfatase treated plasma samples.

The intravenous administration studies indicated that within 15 min of administration of drug, there was a noticeable drop in blood pressure; the maximal drop occurred about 2 hr after administration of the drug (Table I). An examination of the radioactive constituents in blood plasma indicated that the free and conjugated parent compounds were the predominant species in plasma at 15 min following an intravenous dose. At 2 hr, the point of maximal effect on blood pressure, the relative amount of metabolite (R_f 0.46) increased. A minor (2.6%) peak for *p*-aminophenol (R_f 0.16) was seen at this time point. At 4 hr, the metabolite at R_f 0.46 accounted for 78.4% of the plasma radioactivity.

After oral administration of the drug, a drop in blood pressure can be seen at 1 hr; the maximum drop in blood pressure occurred between 4 and 8 hr (Table II). The difference in time of maximal effect may be due to differences in rate of absorption of the parent drug. In contrast to the results obtained when the drug was administered intravenously, the R_f 0.46 metabolite accounted for a major portion of the plasma radioactivity from 1 to 4 hr. It appeared that the parent drug was still being absorbed at 3 and 4 hr after an oral dose, since a substantial amount of parent drug (free and conjugated) was still observed in the plasma at these times. *p*-Aminophenol was not observed in the plasma at 1 hr but, as in the case of intravenously administered drug, was observed at 2 and 4 hr. The site of conversion of parent drug to metabolite does not appear to be the stomach or small intestine, since the parent drug or its conjugate was still observed in the plasma long after an oral dose. It is likely that the conversion of parent drug to metabolites occurs in the liver.

It is possible that the parent drug itself is active as a hypotensive agent, since a hypotensive effect can be observed immediately following an intravenous dose. However, while there is a maximal effect on blood pressure at 2 hr following an intravenous dose and at 4–8 hr following an oral dose, examination of plasma did not indicate a maximum concentration of the parent drug at these times, nor is there the highest level of metabolite. Moreover, by the plasma radioactivity measurements, the total amount of parent drug plus metabolite was not at the highest level 2 hr after an intravenous dose. After an oral dose, there may or may not be a correlation between maximum plasma radioactivity and maximal effect (Table II). These results lead us to speculate that the hypotensive effect may be due to (a) an active metabolite which has a low plasma but high tissue level; (b) an unknown secondary mechanism; or (c) the combination of both effects.

The half-life of the parent drug in blood appears to be on the order of 30 min (Table III). No half-life of the metabolites can be obtained from the data at hand, but since most of the radioactivity excreted *via* urine appears in the initial urine samples, the biological half-lives of the metabolites are probably on the order of a few hours. Thus, after an intravenous dose, little or no parent drug or metabolite would be expected to be present in the plasma at 25 hr. Yet, because a definite hypotensive effect can be seen at 25 hr following an intravenous dose, the operation of a secondary mechanism appears to be indicated.

The plateau observed in blood levels of radioactivity starting at about 6 hr following administration of drug (Tables I and II) may be caused by (a) enterohepatic circulation of a small amount of parent drug or metabolite or (b) slow leaching of small amounts of drug radioactivity from a tissue depot.

Table IV. Recovery of Radioactivity after Administration of Tritiated 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole Orally and Intravenously to Beagle Dogs[a]

Dog no. and route	% recovery of radioactivity		Estd % remaining as tritiated water	Total %
	Urine	Feces		
6429, iv	66.7	8.87	7.55	83.1
7756, iv	63.6	11.4	7.25	82.2
1455, iv	65.9	17.0	4.84	87.7
6429, oral	69.1	25.9	5.15	100.2
7756, oral	46.9	33.4	4.68	85.0
1455, oral	26.7	60.0	3.36	90.1

[a]Duration of experiments: dogs no. 6429 and 7756, 144 hr; dog no. 1455, 120 hr. Dose: 20 mg/kg iv; 30 mg/kg oral.

Table V. Thin-Layer Chromatographic Distribution of Urinary Radioactivity Following Administration of Tritiated 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole to Beagle Dogs[a]

Dog no. and route	% of urinary radioactivity found in region		
	R_f 0.16	R_f 0.46	R_f 0.75
6429, iv	66.5	27.7	5.7
7756, iv	48.6	30.7	20.7
1455, iv	45.9	48.1	5.8
6429, oral	44.9	34.2	19.8
7756, oral	40.7	39.1	20.2
1455, oral	45.5	35.6	18.6

[a]Doses: iv, 20 mg/kg; oral, 30 mg/kg. Samples: Glusulase-treated 0–72-hr urines from each dog. Thin-layer system: Analtech silica gel GF, 250-μ plates developed in the lower phase of $CHCl_3$–HOAc–H_2O (2:2:1, v/v).

Excretion Studies. The excretion of radioactivity *via* urine and feces is summarized on Table IV. Some 9–17% of intravenously administered drug radioactivity was excreted *via* the feces. The elimination of radioactivity *via* the feces probably occurred through biliary secretion of parent drug and/or its metabolites. From this, we may infer that part of the oral dose had been likewise excreted *via* the bile, and we would thus be able to assume that absorption of orally administered drug was actually higher than what can be estimated from the urinary radioactivity by an additional 9–17%.

As indicated by the results on Table IV, individual differences in oral absorption of the drug appear to exist. While the drug appeared to be absorbed extremely well by dog no. 6429, dog no. 1455 appeared to have absorbed the dose rather poorly. Yet, the plasma levels of radioactivity following an oral dose (Table II) are comparable in both animals and do not seem to indicate lower absorption of drug by dog no. 1455. The fact that renal blood flow in dog no. 1455 is impaired may explain the difference in mode of excretion of drug, *i.e.*, a compensatory mechanism may be in operation, shunting more of the xenobiotic substance to be excreted *via* biliary secretion and into feces instead of *via* the impaired renal route. Thus, it ap-

Table VI. Distribution of Metabolites of Tritiated 5-(*p*-Hydroxyanilino)-1,2,3,4-thiatriazole in the Urine of a Female Beagle Dog

Route and dose	% unchanged drug[a]	% *p*-aminophenol[a]	% radioactivity in R_f 0.46 region[a]	% *p*-hydroxyphenylthiourea[b]	% *p*-hydroxyphenylurea[b]	% APAP[b]	% metabolite (calcd)
Iv, 20 mg/kg	20.7	48.6	30.7	5.6	7.1	1.8	16.2
Oral, 30 mg/kg	20.2	40.7	39.1	3.2	10.5	1.5	23.9

[a]By thin-layer chromatography of 0–72-hr urines. [b]By isotopic dilution.

pears that absorption of the drug may have indeed been the same in both dogs or even higher in dog no. 1455.

The per cent of urinary radioactivity which is excreted as tritiated water ranged from 0.26 (day 1) to 41.0% (day 6). This increase was gradual in all cases, starting out at less than 0.5% at day 1 to a high value toward the latter stages of the experiment. This increase in tritiated water may be due to (a) biological exchange of tritium for hydrogen or (b) metabolism of the phenyl ring so as to release the tritium label. The tritium which is liberated by any of these processes is probably in equilibrium with body water and is ultimately excreted by the normal channels.

An estimate of the amount of tritium label remaining in the dogs as tritiated water was made at the end of each experiment, assuming that the body was 70% water and using the radioactivity of tritiated water found in the final urine samples. Total urinary and fecal excretion of radioactivity as well as an estimate of tritiated water still remaining in the dogs is summarized on Table IV. No measure was made on the loss of tritiated water *via* the skin or lungs. In addition, some loss of tritiated water could have occurred by way of the feces. Since the fecal samples were dried before being burnt for radioassay, there was no measure of the tritiated water excreted *via* this route.

Urinary Metabolites. Examination of the urines revealed a high degree of conjugation of parent drug as well as metabolites. Each 0–72-hr urine sample was treated with Glusulase and then subjected to thin-layer chromatography using solvent system 8. By this method, it was possible to obtain three distinct peaks in each case: an R_f 0.75 peak, which corresponded to unchanged parent drug, an R_f 0.46 peak, which corresponded to the mobilities of *N*-acetyl-*p*-aminophenol (APAP), *p*-hydroxyphenylurea, *p*-hydroxyphenylthiourea, and a metabolite of unknown structure, possibly a tetrazole, described earlier;[1] and an R_f 0.16 region, corresponding to *p*-aminophenol. The results from these determinations are summarized on Table V. In order to further elucidate the region of R_f 0.46, isotopic dilution studies were performed in duplicate as previously described,[1] using APAP, *p*-hydroxyphenylthiourea, and *p*-hydroxyphenylurea. The urine of one dog (no. 7756) which had been administered drug both intravenously and orally was used for the isotopic dilution studies.

The amount of unknown metabolite was calculated by subtracting the per cent radioactivity attributable to the three isotopically diluted compounds from the total per cent of radioactivity which migrated to the region of R_f 0.46 (solvent system 8). The results are summarized on Table VI.

The major urinary metabolite in beagle dogs after administration of **6** appears to be *p*-aminophenol; based on thin-layer chromatographic studies in several solvent systems, much of this appears to be conjugated as the *N*-glucuronide. Glusulase treatment of urine appears to free some of the *p*-aminophenol, but attempts to acid hydrolyze the *N*-glucuronide resulted in degradation of other metabolites to *p*-aminophenol. We thus have no reliable estimate of the degree of *p*-aminophenol conjugated as the *N*-glucuronide. *p*-Aminophenol and its conjugates appear to account for 53.7% of the urinary radioactivity after intravenous dosing and 43.7% after oral dosing. Unchanged parent drug **6** averaged 10.7% of the urinary radioactivity after intravenous dosing and 19.5% after oral dosing. The unknown metabolite was estimated to account for 16.2 (intravenous dosing) and 23.9% (oral dosing) of the urinary radioactivity in one dog. *p*-Hydroxyphenylthiourea and what is probably its degradation product, *p*-hydroxyphenylurea, totaled 12.7% after intravenous dosing and 13.7% after oral dosing in one dog. As would be expected, only a trace of APAP was found in dog urine. All of these metabolites appear to be conjugated to a high degree by glucuronide and to a lesser degree by ethereal sulfate.

Fecal Metabolites. The gastrointestinal tracts and contents of two dogs sacrificed 8 hr after oral administration of tritiated **6** were minced, homogenized, and extracted with methanol. The only radioactive compound found in these samples was unchanged parent drug **6**. A check of ethanolic fecal extracts from samples in other studies by thin-layer chromatography revealed a mixture of unchanged parent drug as well as a smear at the origin, probably due to conjugated material. No attempt was made to identify the constituents at the origin.

Summary

Trained beagle dogs were administered 20 mg/kg of tritiated **6** intravenously. After a 7-week rest period, the same dogs were dosed orally with 30 mg/kg of the same drug. Blood pressure, heart rate, and plasma radioactivity were measured simultaneously at various times following the doses; maximum hypotensive effect occurred 2 hr after intravenous dosing and 4–8 hr after oral dosing. This maximum effect did not correlate with maximum plasma levels of parent drug or metabolite. The hypotensive effect may be due to (1) a metabolite which displays low plasma but high tissue level, (2) an unknown secondary mechanism, or (3) a combination of both effects. The observation of a definite hypotensive effect at 25 hr would seem to support a secondary mechanism. Urinary and fecal excretion of radioactivity was monitored for 5–6 days following the doses. Some 9–17% of intravenously administered drug radioactivity was excreted *via* the feces, showing biliary secretion of the drug or its metabolites. Examination of urinary metabolites from the dogs showed unchanged parent drug, *p*-aminophenol, *p*-hydroxyphenylthiourea, *p*-hydroxyphenylurea, *N*-acetyl-*p*-aminophenol, and a metabolite of unknown structure. Fecal metabolites appear to be mainly unchanged parent drug.

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