Prazepam Metabolites in Dog Urine

FREDERICK J. DiCARLO and JEAN-PAUL VIAU

Abstract □ Within 24 hr. after receiving a single oral dose (10 mg./kg.) of ^{14}C-labeled prazepam, two dogs excreted small quantities (4.6 and 1.8%) of the radioactivity into the urine. Thin-layer chromatograms showed the presence of at least eight radioactive compounds in these urine collections. Six of the labeled compounds were identified, and accounted for 86% of the ^{14}C in the urine from Dog 1 and 95% of the ^{14}C in the urine from Dog 2. These compounds and their contributions to the urinary radioactivity were: prazepam (1%, Dog 1; 0.2%, Dog 2); desalkylprazepam (2%, Dog 1; 0.4%, Dog 2); 3-hydroxyprazepam glucuronide (9%, Dog 1; 11%, Dog 2); oxazepam (14%, Dog 1; 3%, Dog 2); oxazepam glucuronide (52%, Dog 1; 72%, Dog 2), and 4′-hydroxyoxazepam glucuronide (8%, Dogs 1 and 2).

Keyphrases □ Prazepam-^{14}C metabolites—urinary excretion, dog □ Metabolites, prazepam—isolation, identification □ TLC—separation, identification □ Scintillometry—analysis

The identification of prazepam metabolites was of interest because it appeared that the drug might serve as the precursor to a series of tranquilizers. A previous study (1) demonstrated that prazepam is converted into one established tranquilizer, oxazepam, by the dog. Dealkylation and hydroxylation are involved in transforming prazepam into oxazepam and it was interesting to learn whether one or both oxidative sequences actually occur *in vivo*. Also in question was whether the dog hydroxylates the 5-phenyl group of benzodiazepins as does the rabbit (2). These points were investigated both qualitatively and quantitatively with the aid of ring-labeled prazepam.

EXPERIMENTAL

Reference Compounds—*N*-Phthalimidoacetyl-5-chloro-2-cyclopropylmethylamino-benzophenone-(carbonyl-^{14}C) was treated with hydrazine to form *N*-glycyl-5-chloro-2-cyclopropylmethylamino-benzophenone-(carbonyl-^{14}C) which cyclized spontaneously to yield 7-chloro-1-(cyclopropylmethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-one-5-^{14}C (3). The product, better known as prazepam, showed chemical and radiochemical purity in excess of 99%. Its specific activity was 1.31 mc./g.

^{14}C-2-Cyclopropylmethylamino-5-chlorobenzophenone (CACB) was prepared by hydrolyzing 1 mg. of ^{14}C-prazepam in 0.5 ml. of 6 *N* HCl for 1 hr. in a boiling water bath (4). For chromatography, 5 ml. of water was added to the reaction mixture, the solution was neutralized partially with NaOH, and the product was extracted with ethyl acetate. Upon chromatography in a variety of solvents, the reaction product yielded a single radioactive spot which was yellow and did not react as a primary aromatic amine (5).

Other available reference compounds were desalkylprazepam, 3-hydroxyprazepam, oxazepam, 2-amino-5-chlorobenzophenone (ACB), and 4′-hydroxy-2-amino-5-chlorobenzophenone (4′-hydroxy ACB). The chemical purity of these preparations was >95%.

Protocol—Two male mongrel dogs of beagle conformity were used. Their weights were 8.6 and 10.5 kg. Each animal was fed a capsule containing ^{14}C-prazepam equivalent to 10 mg./kg. body weight and placed into a separate metabolic cage. Urine was collected at 24-hr. intervals for 3 days and counted by scintillation spectrometry.

The 0–24-hr. urine collections were used to identify drug metabolites as outlined in Fig. 1. The plan was based upon: (*a*) hydrolysis of the urinary drug metabolites to ACB and its derivatives, (*b*) extraction of unconjugated urinary metabolites, and (*c*) enzymatic hydrolysis of the conjugated metabolites followed by extraction of the aglycones.

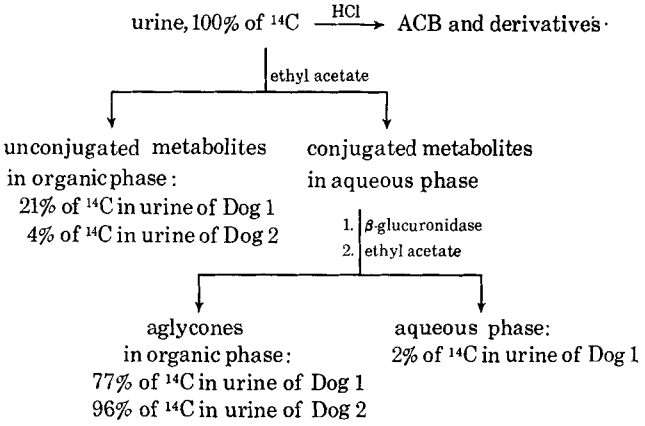


Figure 1—*Plan for identifying prazepam metabolites in dog urine. The urine, unconjugated metabolite fraction, aglycone fraction, and hydrolysate were submitted to TLC in four solvents.*

Hydrolysis of Drug Metabolites—Walkenstein *et al.* (4) described a method of quantitatively hydrolyzing diazepam, oxazepam and their analogs to their corresponding 2-amino-5-chlorobenzophenones. This procedure was used for the identification of prazepam metabolites. A 10-ml. portion of the dog urine was hydrolyzed by heating with an equal volume of concentrated HCl for 1 hr. at 100°. The hydrolysate was kept ice cold during partial neutralization by the addition of 4.4 g. of NaOH (4.8 g. required for neutralization). The acidic solution was extracted with three 5-ml. portions of ethyl acetate. All of the urinary ^{14}C was recovered in the ethyl acetate. The extracts were combined and concentrated to about 1 ml. for chromatography.

Extraction of Unconjugated Metabolites—A 50-ml. portion of the urine was adjusted to pH 7.0 and extracted with five 20-ml. portions of ethyl acetate. The combined ethyl acetate extracts were evaporated to about 1.5 ml.

Extraction of Aglycones of Conjugated Metabolites—After extracting the unconjugated metabolites, the urine was brought to pH 5.0–5.5 and incubated overnight at 37° with 50,000 units of β-glucuronidase. Then the pH was adjusted to 7.0 and the solution was extracted five times with 20-ml. portions of ethyl acetate. The combined organic phase was evaporated to about 2 ml.

Thin-Layer Chromatography—Submitted to chromatography were the reference compounds; untreated urines; hydrolyzed urines; extracts of unconjugated metabolites; extracts of the aglycones of conjugated metabolites; hydrolysates of authentic prazepam, oxazepam, 3-hydroxyprazepam, and desalkylprazepam; and hydrolysates of fractions eluted from chromatograms. All of the chromatograms were developed on glass plates coated with silica gel G. The solvent systems employed were 206: benzene–ethyl acetate (5:1), 304: chloroform–acetic acid–methanol (15:1:4), 306: chloroform–ethanol–acetone (8:1:1), and 307: chloroform–acetone (9:1).

Rechromatography—Rechromatography was conducted in order to confirm R_f data, to obtain R_f values in other solvents, and to check the purity of fractions. The technique for collecting a given radioactive fraction from TLC plates simply involved scraping the area from several plates, eluting the fraction with ethyl acetate, and concentrating the eluate.

Cochromatography—Cochromatography refers to spotting a mixture of an unknown and a reference compound and developing

Table I—TLC of Reference Compounds

Compound	R_f Values—Solvent 206	Solvent 304	Solvent 306	Solvent 307
Prazepam	0.45	0.97	0.88	0.60
Oxazepam	0.04	0.88	0.55	0.15
3-Hydroxyprazepam	0.35	0.96	0.78	0.52
Desalkylprazepam	0.11	0.95	0.72	0.30
ACB[a]	0.77	0.95	0.90	0.85
CACB[b]	0.95	0.97	0.95	0.97
4′-Hydroxy ACB	0.44	0.97	0.80	0.55

[a] 2-Amino-5-chlorobenzophenone. [b] 2-Cyclopropylmethylamino-5-chlorobenzophenone.

the chromatogram. This procedure was employed to detect any minor difference between the migration of the unknown and known compounds.

Detection Methods Applied to Chromatograms—The radioactive bands on the chromatograms were scanned with a Packard model 7201 radiochromatogram scanner to determine their R_f values. Chromatograms of the hydrolysis products, with the benzophenones (ACB or CACB) as the major components, showed distinct yellow spots for these compounds. ACB, a primary aromatic amine, was detected at low levels by running the Bratton-Marshall assay (5) directly on chromatograms. This was done by spraying chromatograms successively with 4 *N* HCl, 0.5% sodium nitrite, 0.5% ammonium sulfamate, and finally 0.1% *N*-(1-naphthyl)-ethylenediamine dihydrochloride. Prazepam, desalkylprazepam, and 3-hydroxyprazepam were sometimes located on chromatograms by enclosing the plates in a cylinder with crystalline iodine. The iodine vapor caused the compounds to become yellow. Some plates were sprayed with a phenol reagent to detect 4′-hydroxy ACB. The reagent was freshly prepared by dissolving 1.0 g. of ferric chloride and 50 mg. of potassium ferricyanide in 10 ml. of water (6).

Quantitative Methods—Scintillation spectrometry was used to determine the absolute levels of radioactivity in the various fractions. For this purpose, a dioxane cocktail was employed in conjunction with a Packard Tri-Carb model 3324 liquid scintillation spectrometer equipped with automatic external standardization. The relative quantities of the compounds resolved chromatographically were determined by using a planimeter to measure the areas under the peaks of radioscans.

RESULTS

In 24 hr., Dog 1 excreted 4.6% of the administered radioactivity into the urine and Dog 2 excreted only 1.8%. The urinary recovery values for 72 hr. were 9.2% from Dog 1 and 8.3% from Dog 2. Figure 1 shows that the distribution of radioactivity between unconjugated and conjugated metabolites also differed considerably for the 24-hr. urine collections from the two dogs. Nevertheless, there was a preponderance of conjugated labeled compounds (77 and 96%) in these specimens.

All of the benzodiazepin and benzophenone reference compounds were separable from one another by TLC (Table I). Table II illustrates the resolutions obtained by applying the same technique to the urine from Dog 1, to the same urine after hydrolysis, to extracts of the unconjugated metabolites, and to extracts of the aglycones of the labeled glucuronides. Table III shows the translation of these data into terms of specific compounds based upon the identifications described below.

Identification of Prazepam—It was known that prazepam, if present, would be in the unconjugated fraction. This fraction was submitted to chromatography in three solvents. Chromatograms developed in Solvents 206 and 307 showed 5 to 6% of the unconjugated radioactivity to be located at R_f values corresponding to prazepam (Table II). Chromatograms produced in Solvent 306 gave a higher ^{14}C value (13%) for the prazepam area and suggested that desalkylprazepam might also be present. After extracting the suspected prazepam from thin-layer chromatograms, rechromatography in different solvents yielded single radioactive bands at R_f values corresponding to prazepam. In addition, exposure of the chromatograms to iodine vapor produced yellow bands only where there was radioactivity. When the eluates of the suspected prazepam were hydrolyzed and chromatographed in four solvents, a single radioactive product was formed. This product corresponded to 2-cyclopropylmethylamino-5-chlorobenzophenone (CACB) upon chromatography in all solvents and was so identified. The identification of prazepam was based upon all of these facts (radioactivity, quantitative agreement between the quantities estimated to be present on different chromatograms, reaction with iodine, R_f values in four solvents, and conversion to tagged CACB).

Identification of Desalkylprazepam—This compound was also sought in the unconjugated fraction. Again, there was a problem with one of the solvents, this time because 72% of all of the ^{14}C in this fraction centered at R_f 0.05 and obscured the metabolite with an R_f of 0.11 (Solvent 206). However, well-resolved spots were observed at appropriate places on chromatograms developed in the other two solvents and the quantities of ^{14}C corresponded satisfactorily: 13 and 10% of the ^{14}C of the unconjugated fraction in Solvents 306 and 307, respectively (Table II). Eluates of the spots showed single radioactive bands upon rechromatography in the various solvents, and the R_f values corresponded to desalkylprazepam. Cochromatography of the metabolite with synthetic desalkylprazepam showed the presence of ^{14}C and of the iodine-reacting material at the same R_f in each solvent. Further confirmation of the identity of the metabolite came from its hydrolysis to ACB. The hydrolysis product was radioactive, yielded the same R_f values as ACB, and was inseparable from authentic ACB by cochromatography.

Identification of Oxazepam—The presence of free oxazepam was indicated by chromatography of the urine in Solvents 304 and 306 and by chromatography of the unconjugated fraction in Solvents 206, 306, and 307 (Table II). In addition, the quantities of the metabolite agreed fairly well, considering that five different experimental situations were involved. The methods used to identify oxazepam unequivocally were described earlier in detail (1).

Table II—TLC of Urine of Dog 1 and Its Major Fractions

Sample	Solvent	R_f and Amount
Urine	206	0.0 (100%)
Urine	304	0.12 (75%), 0.30 (13%), 0.89 (12%)
Urine	306	0.0 (86.5%), 0.40 (13.5%)
Urine	307	0.05 (100%)
Hydrolysate	206	0.0 (19%), 0.22 (5%), 0.35 (8%), 0.78 (62%), 0.95 (5%)
Hydrolysate	206[a]	0.0 (28%), 0.35 (7%), 0.49 (6%), 0.78 (59%)
Hydrolysate	304	0.25 (2%), 0.95 (98%)
Hydrolysate	306	0.03 (13%), 0.40 (10%), 0.58 (7%), 0.95 (70%)
Hydrolysate	307	0.03 (27%), 0.58 (13%), 0.88 (60%)
Unconjugated	206	0.05 (72%), 0.20 (11%), 0.40 (6%), 0.80 (11%)
Unconjugated	306	0.05 (12%), 0.49 (61%), 0.80 (13%), 0.92 (14%)
Unconjugated	307	0.10 (38%), 0.20 (47%), 0.35 (10%), 0.67 (5%), 0.88 (10%)
Aglycones	206	0.07 (100%)
Aglycones	304	0.89 (100%)
Aglycones	306	0.0 (9%), 0.22 (10%), 0.50 (68%), 0.75 (13%)
Aglycones	307	0.10 (91%), 0.25 (9%)

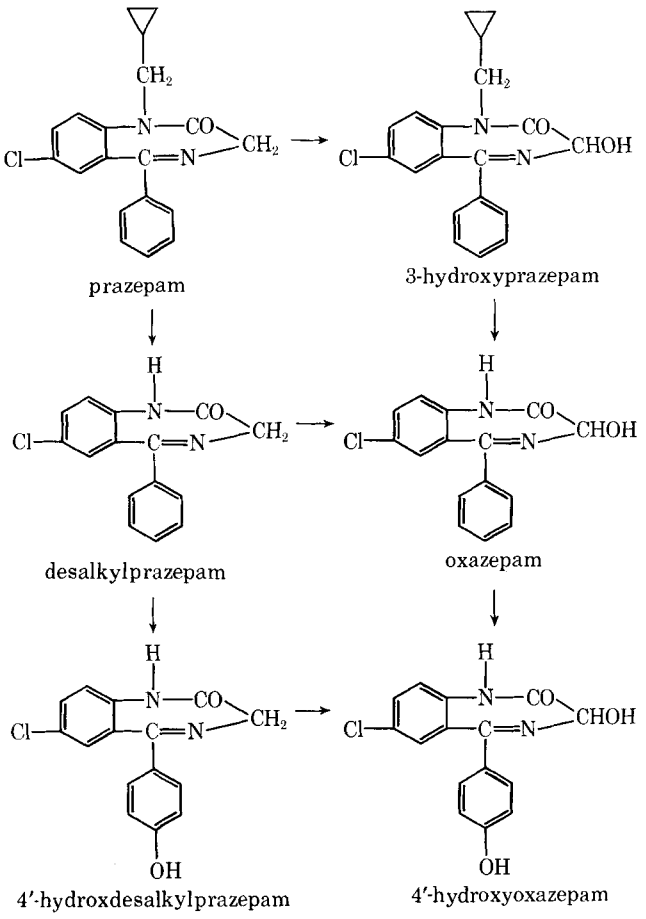
[a] Sample hydrolyzed for 18 hr. rather than the usual 1 hr.

Table III—Identification and Estimation of Metabolites in Urine of Dog 1

Compound	Urine or Fraction	Solvent	Urine, %
Prazepam	Unconjugated	206	1
Prazepam	Unconjugated	307	1
Oxazepam	Urine	304	12
Oxazepam	Urine	306	14
Oxazepam	Unconjugated	206	15
Oxazepam	Unconjugated	306	13
Oxazepam	Unconjugated	307	10
Desalkylprazepam	Unconjugated	306	3
Desalkylprazepam	Unconjugated	307	2
Oxazepam glucuronide	Aglycone	206	77
Oxazepam glucuronide	Aglycone	304	77
Oxazepam glucuronide	Aglycone	306	52[c]
Oxazepam glucuronide	Aglycone	307	70
3-Hydroxyprazepam glucuronide[a]	Aglycone	306	10
3-Hydroxyprazepam glucuronide[a]	Aglycone	307	7
4′-Hydroxyoxazepam[b]	Hydrolysate	307	13[d]

[a] N_1-Cyclopropylmethyloxazepam glucuronide. Confirmed by 4% CACB in hydrolysate, Solvent 206. [b] No model compound available; based upon detection of hydrolysis product. 4′-Hydroxyoxazepam may be the R_f 0.22 spot in Solvent 306, aglycone fraction; 8% of urinary ^{14}C. [c] Most probable value because sample was resolved into four radioactive areas whereas Solvents 206 and 304 gave one spot and Solvent 307 gave two. [d] Further chromatography in Solvents 307, 206, and 306 showed about 60% of this material to be 4′-hydroxyoxazepam.

Identification of Oxazepam Glucuronide—After treating the ethyl acetate-extracted urine with β-glucuronidase, it was possible to extract practically all of the remaining labeled material from the urine of Dog 1 into ethyl acetate (Fig. 1). Chromatograms developed in four solvents showed spots corresponding to oxazepam. The oxazepam contribution to the conjugated fraction was 68% as indicated by chromatography in Solvent 306 (Table II). The higher estimates (91 to 100%) obtained from the other solvents obviously included other aglycones.



Scheme I—Oxidative metabolism of prazepam in dogs. (The sequences involving 4′-oxidation of prazepam and of N_1-cyclopropylmethyloxazepam were omitted for clarity.)

Table IV—Prazepam and Its Metabolites in Dog Urine

Compound	—^{14}C in Urine, %— Dog 1	Dog 2
Prazepam	1	0.2
Desalkylprazepam	2	0.4
3-Hydroxyprazepam glucuronide	9	11
Oxazepam	14	3
Oxazepam glucuronide	52	72
4′-Hydroxyoxazepam glucuronide	8	8
Total	86	95

Identification of 3-Hydroxyprazepam Glucuronide—Chromatography following treatment with β-glucuronidase also suggested the presence of 3-hydroxyprazepam. The material separated from oxazepam by Solvent 306 was identified as 3-hydroxyprazepam on the basis of rechromatography data, cochromatography experiments with authentic material, and conversion to CACB by acid hydrolysis.

Identification of 4′-Hydroxyoxazepam Glucuronide—As expected from the results presented above, the direct hydrolysis of the dog urine yielded radioactive bands corresponding to ACB and CACB (Table II). Other radioactive compounds were also present. The application of spray reagents to the chromatograms showed that the radioactive band at R_f 0.58 in Solvent 307 gave positive tests for a primary aromatic amino group and for a phenolic group. Therefore, it was considered possible that the compound was 4′-hydroxy ACB which could be formed by the hydrolysis of 4′-hydroxyoxazepam or its glucuronide. Since the aglycone, 4′-hydroxyoxazepam, was not available, the authors tried to identify this metabolite through its possible hydrolysis product, 4′-hydroxy ACB, by a chromatographic application of the isotope dilution technique. To this end, radioactive material eluted from R_f 0.58 of TLC plates developed in Solvent 307 was mixed with authentic 4′-hydroxy ACB and submitted to chromatography in Solvent 307. Three radioactive bands showed up in the radioscan. The major band (R_f 0.55) corresponded exactly to the yellow area occupied by 4′-hydroxy ACB. This band was collected and eluted for chromatography in Solvent 206. The radioscan showed a single peak at the same R_f (0.49) as the yellow color. The collection and elution process was repeated for chromatography in Solvent 306. Again, a single radioactive band coincided with the yellow 4′-hydroxy ACB (R_f 0.80).

The urine of both dogs contained the same six compounds and they accounted for 86 to 95% of the radioactivity (Table IV). Although oxazepam glucuronide was the main component of both specimens, its contribution to the total radioactivity varied considerably in the two urine collections. The sums of free and conjugated oxazepam were in closer agreement. The data for the glucuronides of 3-hydroxyprazepam and 4′-hydroxyoxazepam corresponded closely. In both instances, the smallest contributions were made by prazepam and desalkylprazepam.

DISCUSSION

Three oxidative reactions characterize prazepam metabolism in the dog. They are the Phase 1 reactions: (*a*) dealkylation, probably releasing cyclopropylformaldehyde, (*b*) oxidation of the methylene at C-3 to a secondary alcohol function, and (*c*) oxidation of the phenyl group at C-5 to a phenol. Reactions 1 and 2 occur directly with prazepam, as is evident from the identification of 3-hydroxyprazepam and desalkylprazepam (Scheme I). Which of the reactions proceeds faster remains a moot question for prazepam, although the evidence indicates that diazepam is dealkylated more rapidly than it is hydroxylated *in vivo* (7–9) and *in vitro* (10). Reactions 1 and 2 are also involved in the subsequent metabolism. Thus, there are two independent but competitive routes from prazepam to oxazepam. At this time, there is no evidence for the direct hydroxylation of prazepam in the 4′-position; *i.e.*, it is not known whether prazepam simultaneously undergoes Reactions 1, 2,

and 3. Nevertheless, the authors consider that Reaction 3 is properly classified as a Phase 1 conversion (11). Although 4′-hydroxydesalkylprazepam has not been identified, this compound, as well as oxazepam, may be a precursor to 4′-hydroxyoxazepam. Other routes to 4′-hydroxyoxazepam are also possible as stated in the legend of Scheme I.

Another of the unidentified metabolites may be 2′-hydroxyoxazepam. It seems that aromatic hydroxylation in the *ortho* and *para* positions is catalyzed by different enzymes (12) and that the dog generally produces more of the *ortho* isomer (13, 14). The authors' identification of the *para* hydroxy compound (4′-hydroxyoxazepam) in dog urine implies steric hindrance of the *ortho* (2′) position. On the other hand, it is quite possible that some 2′-hydroxy ACB was present with the 4′-hydroxy ACB. Since the 2′-hydroxy compound is not available for study, the possibility cannot be excluded that the four solvent systems did not resolve 2′- and 4′-hydroxy ACB.

In the dog, a single Phase 2 reaction was observed, namely, conjugation with glucuronic acid. As far as could be determined, all of the 3-hydroxyprazepam was conjugated. Thus, a competitive situation would exist if 3-hydroxyprazepam were also converted to oxazepam, as seems likely. The data show that most of the oxazepam was conjugated. The presence of some free oxazepam is interesting and suggests intermediate ranking of the dog among species capable of forming *O*-glucuronides. Although conclusive evidence is lacking, it is surmised that 4′-hydroxyoxazepam was also excreted mainly as a glucuronide.

Unlike diazepam (7, 8) and oxazepam (4), some unaltered prazepam was excreted into the urine by dogs. Thus, dogs treated with prazepam circulate at least three compounds with tranquilizer activity, namely prazepam (15–18), oxazepam, and desalkylprazepam (19).

CONCLUSIONS

The radioactivity from ^{14}C-prazepam administered to dogs was excreted slowly into the urine. Most of the drug was transformed, apparently by oxidative enzymes of the liver microsomes. The major drug metabolite was oxazepam glucuronide. Other glucuronides were formed from 3-hydroxyprazepam and 4′-hydroxyoxazepam. The urine collections also contained unaltered prazepam, desalkylprazepam, and unconjugated oxazepam. Prazepam is considered to serve as the precursor to a series of metabolites with tranquilizer activity.

REFERENCES

(1) F. J. DiCarlo, M. C. Crew, M. D. Melgar, and L. J. Haynes, *J. Pharm. Sci.*, **58**, 960(1969).

(2) G. Jommi, P. Manitto, and M. A. Silanos, *Arch. Biochem. Biophys.*, **108**, 568(1964).

(3) E. J. Merrill, *J. Labelled Compds.*, to be published.

(4) S. S. Walkenstein, R. Wiser, C. H. Gudmundsen, H. B. Kimmel, and R. A. Corradino, *J. Pharm. Sci.*, **53**, 1181(1964).

(5) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537(1939).

(6) H. Ganshirt, "Thin Layer Chromatography," E. Stahl, Ed., Springer-Verlag, Berlin, West Germany, 1965, p. 312.

(7) M. A. Schwartz, B. A. Koechlin, E. Postma, S. Palmer, and G. Krol, *J. Pharmacol. Exp. Ther.*, **149**, 424(1965).

(8) H. W. Ruelius, J. M. Lee, and H. E. Alburn, *Arch. Biochem. Biophys.*, **111**, 376(1965).

(9) J. A. F. DeSilva, B. A. Koechlin, and G. Bader, *J. Pharm. Sci.*, **55**, 692(1966).

(10) J. Kvetina, F. Marucci, and R. Fanelli, *J. Pharm. Pharmacol.*, **20**, 807(1968).

(11) R. T. Williams, *Federation Proc.*, **26**, 1029(1967).

(12) J. R. Gillette, *Advan. Pharmacol.*, **4**, 219(1966).

(13) D. V. Parke and R. T. Williams, *Biochem. J.*, **63**, 12P (1956).

(14) D. V. Parke, *ibid.*, **77**, 493(1960).

(15) E. Dunlop and J. Weisberg, *J. Psychopharmacol.*, **1**, 75 (1966).

(16) E. Dunlop and J. Weisberg, *Psychosomatics*, **9**, 235(1968).

(17) J. W. Shaffer, M. L Yeganeh, N. H. Foxwell, and A. A. Kurland, *J. Clin. Pharmacol.*, **8**, 392(1968).

(18) E. Kingstone, A. Villeneuve, and I. Kossatz, *Current Ther. Res.*, **8**, 159(1966).

(19) L. O. Randall, C. L. Scheckel, and R. F. Banziger, *ibid.*, **7**, 590(1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received July 28, 1969, from the *Department of Biochemistry, Warner-Lambert Research Institute, Morris Plains, NJ 07950*

Accepted for publication September 29, 1969.

The authors thank Mr. Edward J. Merrill for the synthesis of ^{14}C-prazepam.

Gastric Absorption and Distribution of Acetylsalicylic Acid and Other Acidic Compounds in the Rat

CLARENCE H. MORRIS, JOHN E. CHRISTIAN, TOM S. MIYA, and WARREN G. HANSEN

Abstract □ A comparison was made of the gastric absorption and distribution of sodium acetylsalicylate-7-^{14}C with the absorption and distribution of sodium salts of other weakly acidic compounds. Each of the other compounds observed had an absorption pattern which was characteristic for the compound. Only sodium acetylsalicylate caused gastric lesions in the rat. The observations do not rule out the possibility that absorption characteristics of acetylsalicylic acid and its salts may be associated with their ability to cause gastric ulcers.

Keyphrases □ Acetylsalicylate-7-^{14}C, Na—absorption, distribution □ Acidic compounds—acetylsalicylate-7-^{14}C, Na—absorption, distribution comparison □ Gastric lesion production—acetylsalicylate-7-^{14}C, Na, acidic compounds □ TLC—analysis □ Autoradiography—analysis

It has been known for more than 50 years that oral administration of acetylsalicylic acid is followed by erosion of the gastric mucosa and bleeding from the site of the lesion (1). These aspirin-induced lesions have been observed in humans (1), dogs (2), cats (3), guinea pigs (4), and albino rats (5). A number of hypotheses have been suggested to explain the occurrence of these lesions. Davenport (6) and Martin (7) have suggested chemical models based upon the interaction of the compound with cellular constituents following its absorption