Prazepam Metabolism in the Rat

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Abstract □ Groups of rats were treated by gavage with ^{14}C-labeled prazepam (10 mg./kg.), and the fate of the isotope was determined by measuring the radioactivity in the blood plasma, urine, feces, and selected tissues. The half-life of the drug and its metabolites in the plasma was found to be 2.5 hr. Twenty-four hours after drug administration, 17.3% of the drug radioactivity was excreted in the urine, 33.6% was excreted in the feces, and 35.1% was present in the GI tract. Fractionation of the 24-hr. urine collection showed its radioactivity to consist of 14.7% unconjugated compounds, 14.7% glucuronides, 52.0% sulfates, and 18.6% unclassified polar compounds. Unchanged prazepam was identified in the unconjugated fraction along with oxazepam and desalkylprazepam. The glucuronides identified were conjugates of 4'-hydroxydesalkylprazepam and 4'-hydroxyoxazepam. The sulfate fraction included 4'-hydroxydesalkylprazepam sulfate and 4'-hydroxyoxazepam sulfate.

Keyphrases □ Prazepam, radiolabeled—absorption, excretion, and tissue distribution in rats, identification of metabolites □ Metabolism, radiolabeled prazepam—absorption, excretion, and tissue distribution in rats, identification of metabolites □ Absorption—radiolabeled prazepam, rats □ Excretion—radiolabeled prazepam, rats

Consistent with the pharmacological activity of prazepam in animals (1, 2), the tranquilizer is effective in treating a variety of anxiety states in man (3–10). Earlier reports dealt with the metabolism of prazepam in man (11–13) and the dog (14, 15) and with the biotransformation of prazepam by the 9000×*g* fractions prepared from human, canine, and rodent livers (13, 16). The present report describes prazepam metabolism in the rat; it covers drug absorption, excretion, and tissue distribution and the identification of drug metabolites excreted in the urine.

EXPERIMENTAL

Reference Compounds—Ring-labeled prazepam [7-chloro-1-(cyclopropylmethyl) - 1,3-dihydro - 5 - phenyl - 2*H* - 1,4 - benzodiazepin-2-one-5-^{14}C] was synthesized with a specific activity of 1.31 mc./g.; its chemical purity and radiochemical purity were >99% (17). Also available were authentic samples of desalkylprazepam, 3-hydroxyprazepam, oxazepam, 4'-hydroxydesalkylprazepam, 4'-hydroxyoxazepam, 2-amino-5-chlorobenzophenone, and 4'-hydroxy-2-amino-5-chlorobenzophenone.

Radioactivity Counting—Quantitative assays for ^{14}C were performed using a liquid scintillation spectrometer[1]. The external standardization method was employed for quench corrections.

Animals and Dosing—Male Wistar rats[2], 280 g. mean weight, were treated by gavage with a solution of ^{14}C-prazepam in polyethylene glycol 400. The dose was 10 mg./kg. body weight. The animals were housed in individual glass metabolic cages without food or water during the experiments. Four rats were used to determine the half-life of plasma radioactivity, and six animals were employed for the tissue distribution, excretion, and biotransformation studies.

Plasma Half-Life—Blood samples were withdrawn by heart puncture at the following intervals after dosing: 0.5, 1, 2, 4, 6, and 24 hr. The heparin-treated samples were centrifuged in a desktop clinical centrifuge for 20 min., and the separated plasma preparations were assayed for ^{14}C by scintillation spectrometry.

Distribution of Drug Radioactivity in Tissues—Twenty-four hours after drug treatment, the rats were killed and selected tissues were excised. The fresh tissues were pooled by type, homogenized in a blender[3] with 75% aqueous dioxane, and filtered. The residues were extracted twice in the same manner. Aliquots (1.0 ml.) of the appropriately combined extracts were counted by scintillation spectrometry.

Fecal and Urinary Excretion—The fecal collections were washed from the cages with water and 75% dioxane. The mixtures were kept at 40° overnight and filtered. The residues were reextracted three times with 75% dioxane. Then 1.0-ml. aliquots of the combined filtrates (650 ml.) were counted by scintillation spectrometry. After the urine collections were combined with the vessel rinsings and diluted to 80 ml., aliquots (0.5 ml.) were counted for radioactivity.

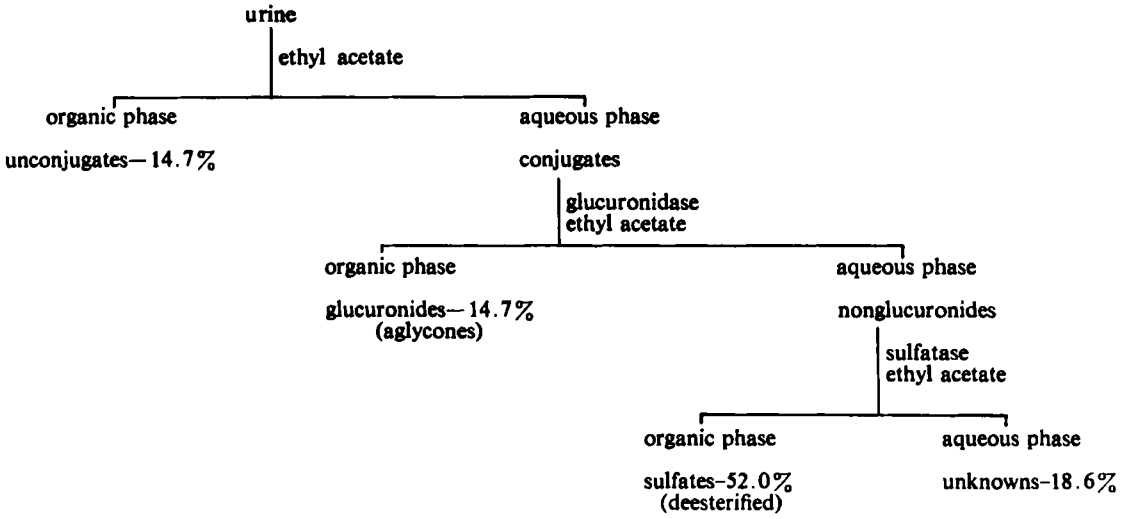
Fractionation of Urinary Drug Metabolites—The fractionation scheme is outlined in Scheme I. It involved: (*a*) extraction of unconjugated urinary metabolites, (*b*) enzymatic hydrolysis of the glucuronide metabolites followed by extraction of the aglycones, and (*c*) enzymatic hydrolysis of the sulfate metabolites followed by extraction of the liberated compounds. The distribution of radioactivity among these fractions was determined by scintillation spectrometry. To obtain the unconjugated compounds, the pH of the entire urine collection (80 ml.) was adjusted to 7.0 and extracted with five 50-ml. portions of ethyl acetate. The combined ethyl acetate extracts were then evaporated to approximately 1 ml. for TLC.

After extracting the unconjugated metabolites, the urine was brought to pH 5.0–5.5 and incubated for 48 hr. at 37° with 240,000 units of β-glucuronidase. Then the pH was adjusted to 7.0 and the solution was extracted five times with 40-ml. portions of ethyl acetate to collect the aglycones. The combined organic phase was evaporated to about 2 ml. for TLC. Before liberating the free phenols from their sulfate conjugates, the ethyl acetate dissolved in the extracted urine was removed by aeration. Then the pH of the pool was adjusted to 6.8 with 1 *N* NaOH and treated with 240,000 units of β-glucuronidase-aryl sulfatase. After incubating for 48 hr. at 37°, the solution was extracted five times with 100-ml. portions of ethyl acetate. The combined extracts were evaporated to approximately 4 ml. for TLC.

Chromatography—Five solvent systems were used for TLC on glass plates coated with silica gel G. The solvents were prepared by volume as follows: 206, benzene–ethyl acetate (5:1); 301, heptane–chloroform–ethanol (1:3:1); 306, chloroform–ethanol–acetone (8:1:1); 307, chloroform–acetone (9:1); and 309, chloroform–acetic acid–methanol (18:1:1). All chromatograms were scanned with a radiochromatogram scanner[4] to locate radioactive bands, and the areas under the peaks were quantified with a planimeter. The cochromatographic technique for the direct comparison of known and unknown compounds was described previously (15).

Hydrolysis of Drug Metabolites and Testing of Split Products for Primary Amine and Phenol Groups—The metabolite under investigation was scraped from TLC plates into a 15-ml. centrifuge tube and extracted with 5 ml. of ethyl acetate by shaking the tube for 30 min. Following evaporation to dryness, the eluted material was hydrolyzed in 1 ml. of 6 *N* HCl for 1 hr. at 100° (18). The hydrolysate was kept ice cold during partial neutralization by the addition of 44 mg. of sodium hydroxide (48 mg. required for neutralization). The acidic solution was extracted with an equal volume of ethyl acetate to collect the 2-amino-5-chlorobenzophenones. All of the ^{14}C was recovered in the ethyl acetate. The extract was concentrated to 100 μl. for chromatography. After TLC, the Bratton–Marshall

[1] Packard Tri-Carb, model 3324.
[2] Marland Farms.
[3] Waring.
[4] Packard model 7201.



Scheme I—Plan for fractionating and identifying prazepam metabolites in rat urine. The unconjugated metabolite fraction, aglycone fraction, and desulfated fraction were submitted to TLC in three solvents. The percentages refer to urinary radioactivity.

test for primary aromatic amines (19) and the ferric ferrocyanide test for phenols (20) were run directly on the chromatograms.

RESULTS

Plasma Half-Life, Tissue Distribution, and Excretion of Prazepam Radioactivity—The mean values for plasma ^{14}C following ^{14}C-prazepam administration are presented in Fig. 1 in terms of prazepam equivalents per milliliter. The data show that the tranquilizer was absorbed rapidly after oral administration to the rat and that the peak plasma level of radioactivity was attained within 30 min. Figure 1, plotted by the method of least squares, indicates that the half-life of plasma ^{14}C was 2.5 hr.

Twenty-four hours after drug treatment, the tissues contained 44.3% of the isotope (Table I). There was no unusual accumulation of radioactivity in any of the tissues. The fecal excretion (33.6% of the dose) was almost twice the urinary excretion (17.3%), and the total recovery of drug radioactivity was 95.2%.

Fractionation of Labeled Urinary Compounds—Scheme I shows that the sulfates comprised more than half of the urinary drug metabolites. The other three fractions (unconjugates, glucuronides, and unknown polar metabolites) contained the balance in comparable quantities.

Chromatography—Table II lists the R_f values of all of the reference compounds in five solvents, and it is evident that their use permitted the separation of each listed compound from any other. Solvents 301, 306, and 309 were especially valuable for the identification of oxazepam, 4′-hydroxyoxazepam, and 4′-hydroxydesalkylprazepam. Solvents 206 and 307 gave excellent resolutions of 2-amino-5-chlorobenzophenonone, 2-cyclopropylmethylamino-5-chlorobenzophenone, and 4′-hydroxy-2-amino-5-chlorobenzophenone.

Identification of Labeled Unconjugated Compounds—As indicated in Scheme I, 14.7% of the excreted radioactivity was in the form of unconjugated compounds. TLC in Solvent 306 revealed the presence of five radioactive areas. Unchanged prazepam, identified by TLC and its hydrolytic conversion to 2-cyclopropylmethylamino-5-chlorobenzophenone, accounted for 5% of the ^{14}C in the unconjugated fraction (Table III). With the same techniques the only metabolites identified were oxazepam and desalkylprazepam, which accounted for 55 and 4%, respectively, of the radioactivity of the unconjugated fraction. Thus, prazepam, oxazepam, and desalkylprazepam accounted for 0.7, 8.1, and 0.6%, respectively, of the total urinary radioactivity. Unknown metabolites represented 36% of the radioactivity of the unconjugated fraction.

Identification of Labeled Glucuronides—This fraction contained 14.7% of the urinary radioactivity (Scheme I). Chromatography of 100-μl. aliquots in Solvent 306 revealed the presence of five radioactive peaks. The major peak, comprising 61% of the radioactivity of this fraction, was scraped from several plates and eluted with ethyl acetate. Rechromatography in Solvent 309 gave rise to three peaks. Two of these peaks were identified tentatively as oxazepam and 4′-hydroxydesalkylprazepam based upon their chromatographic behavior when they were cochromatographed with authentic reference compounds in Solvents 301, 306, and 309 (Table II). When the aglycone that migrated as oxazepam was hydrolyzed as already described, it yielded a labeled split product, which traveled with authentic 2-methylamino-5-chlorobenzophenone in cochromatographic tests conducted in several solvent systems. Additionally, the labeled hydrolysis product gave a positive Bratton–Marshall test and a negative phenol test. Hydrolysis of the aglycone that behaved chromatographically as 4′-hydroxydesalkylprazepam gave a product that migrated with synthetic 4′-hydroxy-2-amino-5-chlorobenzophenone in all solvent systems. Furthermore, this labeled hydrolysis product responded positively to Bratton–Marshall and phenol tests.

To collect the third aglycone, the R_f 0.45 zone was scraped from a series of plates developed in Solvent 306 and the radioactive material was extracted from the gel with ethyl acetate. Upon TLC in Solvents 301, 306, and 309, the extracted compound gave the

Table I—Tissue Distribution and Excretion of ^{14}C after Oral Administration of Ring-Labeled Prazepam to Rats (10 mg./kg.)

Specimen	Percent of ^{14}C Dose Found after 24 hr.
Brain	0.03
Cadaver	6.98
GI tract	35.10
Heart	0.01
Kidney	0.27
Liver	1.24
Lung	0.03
Spleen	0.65
Feces	33.6
Urine	17.3
Total recovery	95.2

Table II—R_f Values of Reference Compounds

Compound	R_f in Solvent 206	301	306	307	309
Prazepam	0.45	—	0.88	0.60	—
Desalkylprazepam	0.11	—	0.72	0.30	—
Oxazepam	0.04	0.70	0.55	0.15	0.65
4′-Hydroxyoxazepam	—	0.55	0.43	—	0.25
4′-Hydroxydesalkylprazepam	—	0.68	0.50	—	0.20
2-Amino-5-chlorobenzophenone	0.77	—	0.90	0.85	—
2-Cyclopropylmethylamino-5-chlorobenzophenone	0.95	—	0.95	0.97	—
4′-Hydroxy-2-amino-5-chlorobenzophenone	0.44	—	0.80	0.55	—

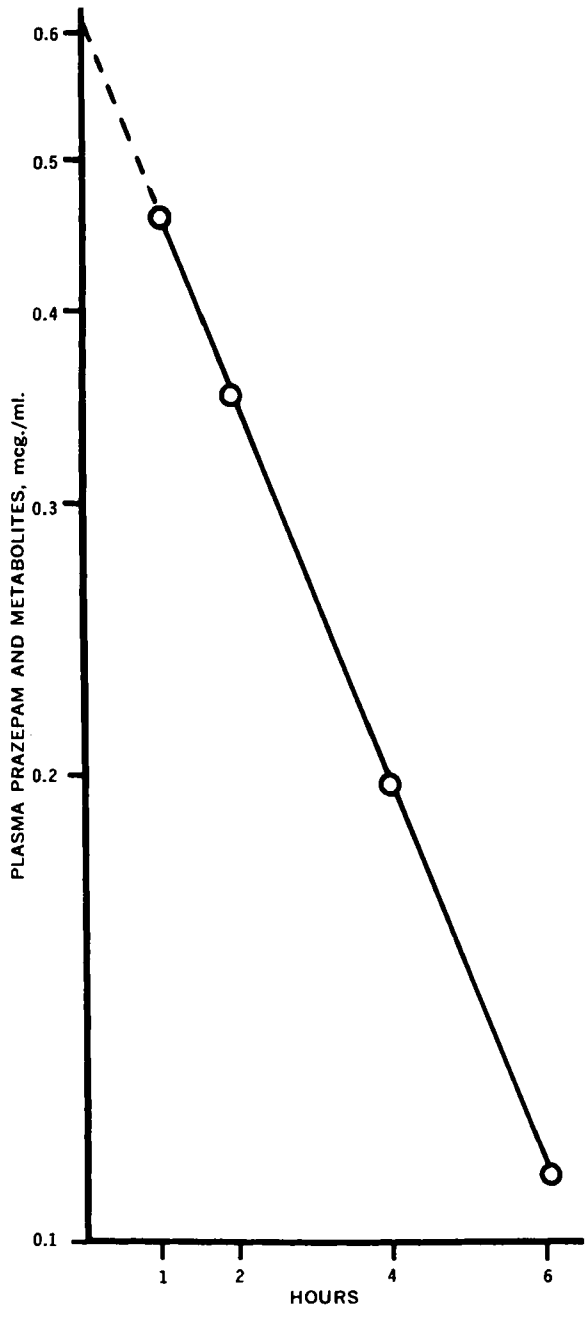


Figure 1—*Concentrations of prazepam and metabolites in the blood plasma of rats.*

same R_f values as 4'-hydroxyoxazepam, and cochromatography did not resolve the urinary and synthetic preparations. Hydrolysis of the urinary aglycone yielded a phenolic primary aromatic amine, which was identified as 4'-hydroxy-2-amino-5-chlorobenzophenone by the test procedures already described.

As shown in Table III, the radiolabeled urinary glucuronide fraction consisted of 39% oxazepam glucuronide, 17% 4'-hydroxyoxazepam glucuronide, 22% 4'-hydroxydesalkylprazepam glucuronide, and 22% unknown glucuronides.

Identification of Labeled Sulfates—It can be seen from Scheme I that the sulfate fraction accounted for 52% of the urinary radioactivity. Chromatography of 100-μl. aliquots in Solvent 306 showed five radioactive peaks. The major peak was scraped from several plates and eluted with ethyl acetate. Cochromatography of this unknown with 4'-hydroxydesalkylprazepam in Solvents 301, 306, and 309 revealed identical chromatographic behavior between the unknown and reference compound. Hydrolysis of the main sulfate metabolite followed by cochromatography with 4'-hydroxy-2-amino-5-chlorobenzophenone in three solvent systems also showed

Table III—Qualitative and Quantitative Assay of Urine Collected from a Group of Six Rats 24 hr. after ^{14}C-Prazepam Administration

Identification	Percent of Fraction[a]	Percent of Total Urinary Radioactivity	
Unconjugates			
Prazepam	5	0.7	
Desalkylprazepam	4	0.6	
Oxazepam	55	8.1	
Unknowns	36	5.3	
			14.7
Glucuronides			
Oxazepam	39	5.8	
4'-Hydroxyoxazepam	17	2.5	
4'-Hydroxydesalkylprazepam	22	3.2	
Unknowns	22	3.2	
			14.7
Sulfates			
4'-Hydroxyoxazepam	7	3.6	
4'-Hydroxydesalkylprazepam	65	33.8	
Unknowns	28	14.6	
			52.0
Unclassified polar compounds			
Unknowns	100	18.6	
			18.6
			100.0

[a] Based upon data obtained with Solvent 306 and resolution of oxazepam from 4'-hydroxydesalkylprazepam with Solvent 309.

agreement between the hydrolyzed metabolite and authentic 4'-hydroxy-2-amino-5-chlorobenzophenone. This metabolite gave positive phenol and Bratton–Marshall tests.

A peak with an R_f value 0.45 was scraped from several plates developed in Solvent 306 and was eluted with ethyl acetate. This metabolite was cochromatographed with 4'-hydroxyoxazepam in Solvents 301, 306, and 309. Agreement was observed between the unknown metabolite and authentic 4'-hydroxyoxazepam in all cases. Hydrolysis of this metabolite followed by cochromatography with 4'-hydroxy-2-amino-5-chlorobenzophenone in three solvent systems showed agreement between the hydrolyzed metabolite and the reference compound. Spraying with the phenol reagent or the Bratton–Marshall reagent gave positive tests in both instances.

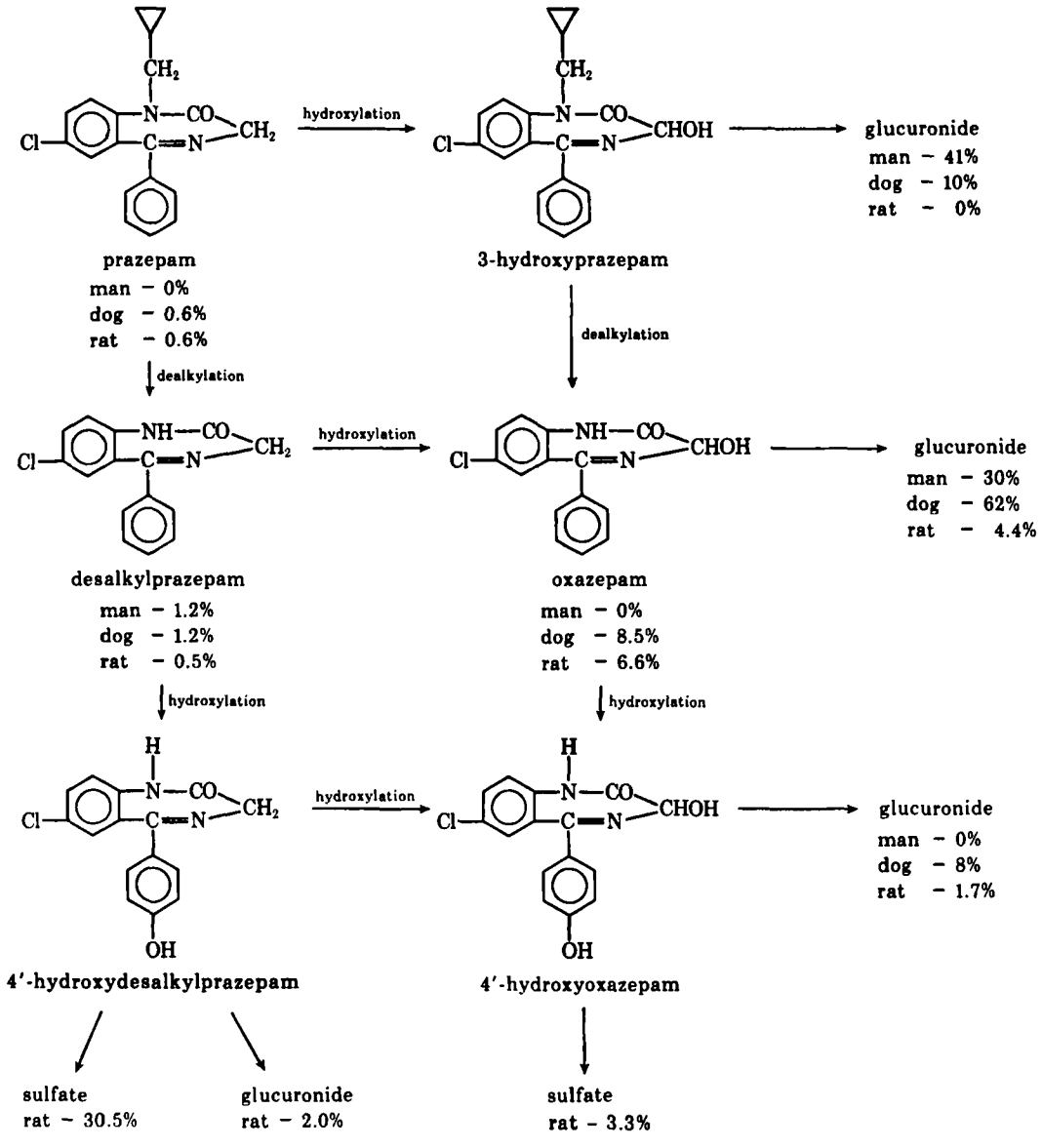
Table III summarizes these findings. 4'-Hydroxydesalkylprazepam sulfate accounted for 65% of the radioactivity of this major urinary fraction, whereas 4'-hydroxyoxazepam sulfate represented 7% of this fraction. Expressed in terms of the total urinary radioactivity, 4'-hydroxydesalkylprazepam sulfate accounted for 33.8% and 4'-hydroxyoxazepam sulfate represented 3.6%. Unknown metabolites were present to the extent of 14.6% of the urinary ^{14}C.

DISCUSSION

Orally administered prazepam was absorbed rapidly by the rat and reached plasma levels that were far greater than those found in the dog treated with the same dose (14). While the half-time of prazepam metabolites in blood plasma was not determined accurately for the dog, the mean values for man (13) and rat were found to be very different, 67 and 2.5 hr., respectively. The urinary excretion of prazepam by the rat in 24 hr. (17%) was more similar to man (14%) than to the dog (3%).

Scheme II illustrates pathways of prazepam metabolism and summarizes the urinary excretion of the end-products by rats, dogs, and humans. Clearly, the rat showed the most complex pattern of prazepam biotransformation. Nine end-products in rat urine accounted for only 50% of the isotope present. By contrast, three metabolites represented 71% of the drug radioactivity in human urine (11) and six end-products represented 90% of the drug ^{14}C in dog urine (15).

In humans and dogs, prazepam undergoes aliphatic hydroxylation and dealkylation as phase 1 reactions. There is no evidence that the rat employs more than one initial attack, namely, dealkylation. All of the metabolites identified in rat urine can be derived from desalkylprazepam (Scheme II). This interpretation agrees



Scheme II—Prazepam biotransformation in man, dog, and rat (For clarity, the sequences involving 4'-oxidation of prazepam and 3-hydroxyprazepam were omitted)

with the results of prazepam metabolism *in vitro*. Incubating prazepam with rat liver microsomal enzymes produced desalkylprazepam but no 3-hydroxyprazepam even after pretreating the animals with prazepam (13) and phenobarbital (16).

Prazepam-treated rats and dogs excreted free oxazepam as well as oxazepam glucuronide. Sisenwine *et al.* (21) made the same observation after administering a high oxazepam dose (40 mg./kg.) to rats. One possibility is that the conjugating system became saturated. However, the absence of unconjugated 4'-hydroxydesalkylprazepam and 4'-hydroxyoxazepam suggests either that oxazepam is a poorer substrate for glucuronyl transferase than these phenolic metabolites or that oxazepam glucuronide is more susceptible to β-glucuronidase than are the other glucuronides.

Prazepam biotransformation in the rat is further distinguished by aromatic hydroxylation and by conjugation with sulfate, reactions that have not yet been observed in the other species. While it is possible that prazepam is hydroxylated directly like diazepam (22), this conversion has no present experimental support because 4'-hydroxyprazepam was detected neither *in vivo* nor *in vitro* (13, 16). Diazepam also undergoes no aromatic hydroxylation by rat liver microsomes (23), although 4'-hydroxydiazepam was found in rat urine (22). It appears that the ability of rat liver microsomes to oxidize phenyl groups is inhibited by the benzodiazepine nucleus. Marcucci *et al.* (24) showed that diazepam inhibits the oxidative dealkylation of 3-hydroxydiazepam to oxazepam *in vitro*. A review of the metabolism of benzodiazepines *in vitro* (25) illustrates the emphasis placed upon the enzymology of the liver and leads one to consider that the aromatic hydroxylations observed *in vivo* but not *in vitro* may involve extrahepatic enzymes.

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Structure Side-Effect Sorting of Drugs I: Extrapyramidal Syndrome

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Abstract □ A computer program using PL/I language was developed to sort the side effects of 540 clinically useful drugs. The common structural features of the drugs that produce the extrapyramidal syndrome are: (*a*) the drug contains at least one tertiary amino group separated by three carbon atoms from a coplanar hydrophobic region, and (*b*) the coplanar hydrophobic region can be a phenothiazine ring, its isosteres, or two benzene rings held close together (*e.g.*, trimethobenzamide and haloperidol). Other tranquilizers and anticonvulsants such as diazepam and diphenylhydantoin are shown to have entirely different structural features.

Keyphrases □ Side effects, computer sorting of 540 drugs—extrapyramidal syndrome related to structure □ Computer sorting of side effects of 540 drugs—extrapyramidal syndrome related to structure □ Structure-activity relationships—features related to extrapyramidal side effects, result of computer sorting of 540 drugs □ Extrapyramidal syndrome—related to structural features, result of computer sorting of side effects of 540 drugs □ Drug sorting by side effects—structure-activity relationships

In recent years, numerous publications on chemical structure-pharmacological activity have appeared in various journals (1–13). However, due to several reasons, little systematic work has been done in sorting and correlating undesirable side effects of various drugs with their chemical structures. One reason is that side effects are usually more variable and more difficult to measure than the major pharmacological effect. In addition, when several drugs are concurrently administered to a patient, it is not easy to pinpoint the agent causing the most undesirable side effect or to detect the presence of drug interactions.

Many potentially useful drugs are not used primarily because of the severity of their side effects, not because of the lack of efficacy. On the other hand, there are many instances of an annoying side effect promoted later to be an appreciated therapeutic effect, such as the development of oral antidiabetic drugs from the observation of hypoglycemia in patients treated with certain sulfonamides. Therefore, it was considered worthwhile to employ a computerized program to sort the side effects of all clinically useful drugs and to correlate these effects with the chemical structure. It is believed that any effect of a drug, desired or undesired, direct or indirect, is determined by its physicochemical properties which are, in turn, governed by its structure.

This report discusses the structural features of the drugs known to cause extrapyramidal syndrome and why other tranquilizers (*e.g.*, diazepam) do not cause this side effect. Extrapyramidal syndrome consists of parkinsonian-like symptoms (*e.g.*, tremors, rigidity, and salivation), akathisia (a psychosis marked by an inability to sit still or to remain seated), and akinesia (loss of the power of voluntary motion).

METHOD

A data bank consisting of 540 clinically useful drugs (14–17) was established, and each side effect is represented by a unique three-digit hexadecimal code. The name of the side effect associated with each code is stored separately in another file, the symptom file. The code is also the key for each record, allowing direct retrieval of the name.

A program was developed[1], using the PL/I language (18, 19), which allows the data bank to be sorted by individual side effect

[1] A listing of the program is available upon request.