distilled. The crude product was dissolved in 500 ml of 1:1 C_6H_6–Et_2O, and excess dry HCl was used to prepare the dihydrochloride salt, which was crystallized from 75 ml of EtOH; yield 22 g (79%), mp 158–160°. The pK_a in 66% DMF was 4.5 and 9.1. *Anal.* ($C_{12}H_{15}N_3 \cdot 2HCl$) C, H, N.

2-(2-Aminoethyl)imidazole (3) Dihydrochloride.—2-β-Aminoethyl-1-benzylimidazole dihydrochloride, 5.48 g, was dissolved in 100 ml of liquid NH_3, and to the solution were added with stirring small pieces of sodium until a blue color persisted (1.6–1.9 g). The mixture was stirred for 10 min, after which 2 g of NH_4Cl was added, and the NH_3 was allowed to evaporate completely. The residue was extracted with 50 ml of hot EtOH. Sodium chloride was filtered, and excess dry HCl was passed into the EtOH extract. The product was filtered and washed with EtOH and Et_2O; yield 2.82 g (76%). It was recrystallized from 50 ml of 1:4 H_2O–EtOH; mp 265–266°; pK_a in 66% DMF was 5.4 and 9.3. *Anal.* ($C_5H_9N_3 \cdot 2HCl$) C, H, Cl, N.

2-Cyanomethylimidazole.—To a solution of 8.85 g of 1-benzyl-2-cyanomethylimidazole (**10**) in 100 ml of liquid NH_3 were added sodium pieces with stirring until a blue color persisted (2.6 g). The mixture was stirred for 10 min, after which 6.05 g of NH_4Cl was added, and the NH_3 was evaporated completely. The residue was extracted with hot EtOH, and the crude product (4 g) was obtained by concentrating the extract. The product was recrystallized from H_2O; mp 166.5–167.5°; pK_a in 66% DMF was 4.05 and 13.8. *Anal.* ($C_5H_5N_3$) C, H.

1-Benzyl-2-(2-dimethylaminoethyl)imidazole (22).—2-(2-Aminoethyl)-1-benzylimidazole dihydrochloride (5.0 g) was converted to the free base using 50% NaOH. The amine was extracted with C_6H_6–Et_2O, and the solution was dried over KOH. Removal of the solvents left 3.7 g of amorphous base that was then dissolved in 150 ml of EtOH and 50 ml of 37% formaldehyde. The solution was hydrogenated for 20 hr at 3–4 atm hydrogen pressure using 1.5 g of 5% Pd–C. The catalyst was filtered, and the solvents were distilled *in vacuo*. The crude product was dissolved in CH_2Cl_2, and the solution was extracted with aqueous HCl. The extract was made basic (NaOH), and the product was reextracted into CH_2Cl_2. Concentration left 1.9 g of product as an oil. A dipicrate salt was prepared and recrystallized from Me_2CO, mp 180–185°. *Anal.* ($C_{14}H_{19}N_3 \cdot 2C_6H_3N_3O_7$) C, H, N. The same dimethyl derivative (**22**) was also prepared by methylation of the primary amine (**12**) with formaldehyde–formic acid.

2-(2-Dimethylaminoethyl)imidazole (23) Dihydrochloride.—The benzyl derivative above (**22**), 1.6 g, was dissolved in 50 ml of liquid NH_3, and sodium pieces were added with stirring until a blue color persisted. After 15 min 0.37 g of NH_4Cl was added, and the NH_3 was evaporated completely. The residue was extracted with hot EtOH, excess dry HCl was added, and the solvent was distilled. The crude product was recrystallized from EtOH–Me_2CO; yield 0.6 g, mp 213–216°. *Anal.* ($C_7H_{13}N_3 \cdot 2HCl$) C, H, N.

Acknowledgment.—We wish to thank Dr. W. W. Hargrove and associates for the microanalyses and physical measurements and Mr. E. Lavagnino and associates and Mrs. Barbara Spry for preparing some of the intermediates. We are indebted to Dr. R. G. Jones for stimulating our interest in this problem.

Metabolism of Brompheniramine

R. B. BRUCE, L. B. TURNBULL, J. H. NEWMAN, AND J. E. PITTS

A. H. Robins Company, Inc., Research Laboratories, Richmond, Virginia

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The metabolism of brompheniramine-^{14}C has been investigated in the dog and the human. Six metabolites have been identified and quantitated in dog urine and five of these have also been found in human urine. These account for approximately 50% of the dose in each species. Nine brompheniramine-related compounds have been synthesized as possible metabolites. The following were found to be present in the urine after an oral dose: unchanged brompheniramine, the mono- and didemethylated derivatives, 2-{*p*-bromo-α-[2-(dimethylamino)-ethyl]benzyl}pyridine N′-oxide (not found in the human), β-(*p*-bromophenyl)-2-pyridinepropionic acid, and its glycine conjugate.

Brompheniramine maleate is an antihistamine used extensively for the prevention and control of allergic reactions. Chemically it is 2-{*p*-bromo-α-[2-(amino)-ethyl]benzyl}pyridine maleate.

The metabolism of this drug has not been presented previously and it is the purpose of this report to submit the findings from a study of its metabolism in dogs and humans. Chlorpheniramine, the chloro derivative of pheniramine, is metabolized to the mono- and didemethylated derivatives.[1] Corresponding metabolites have been found to occur from brompheniramine administration and, in addition, other metabolites have been identified and quantitated.

Experimental Section

The experimental part of this study involved two phases: synthesis of metabolites and identification of these metabolites in the urine of dogs and humans given oral doses of brompheniramine maleate.

Preliminary investigation by tlc of the base extractables of urine, from dogs that had received brompheniramine, indicated that unchanged drug and at least two additional related compounds were present. Brompheniramine-^{14}C was then synthesized so that further investigation of these and other metabolites could be carried out. A number of related compounds were also synthesized as possible metabolites.

Metabolism Studies.—Oral doses of 7.5 mg/kg of brompheniramine-^{14}C were administered to mongrel dogs weighing 8.5–10 kg. Urine and feces were collected for 96 hr and stored in the freezer until analyzed.

Normal, male, human subjects were given four oral doses of brompheniramine-^{14}C of 8.0 mg each over a period of 12 hr. Following the first dose and continuing for 48 hr after the final dose, each urine void was collected in separate containers. After that time, pooled 24-hr specimens were collected for 5 days. Feces were collected for 3 days.

Analytical Methods. Isotopes.—Radioactivity in liquid samples was measured using a Packard liquid scintillation spectrometer, Series 314E. The aqueous phosphor consisted of toluene–dioxane–EtOH (4:4:2.4) containing 80 g of naphthalene and 5 g of PPO/l.

Feces were counted after oxidation to CO_2. They were dried in a vacuum oven at 55° and ground in a blender. The dried, ground samples were combusted in a combustion furnace by a modification of the method described by Peets, *et al.*[2] The liberated CO_2 was counted in a phosphor consisting of 4 g of PPO/l. of toluene.

Chemical Analysis.—The chemical method of analysis involved the oxidation of brompheniramine to *p*-bromophenyl 2-pyridyl ketone and its subsequent determination by glpc, using chlor-

(1) E. Peeto, R. Weinstein, and S. Symchlwicy, *Pharmacologist*, **9**, 216 (1967).

(2) E. A. Peets, J. R. Florini, and D. A. Buyske, *Anal. Chem.*, **32**, 1465 (1960).

pheniramine as an internal standard. The method is to be published and is sensitive to less than 2 ng/ml of sample.

Synthesis.[3] **2-{p-Bromo-α-[2-(dimethylamino)-1,2-^{14}C-ethyl]benzyl}pyridine Maleate (I) (Brompheniramine-^{14}C).**—A 500-mg sample (3.0 mCi, 4.00 mmoles) of 1,2-^{14}C-dimethylaminoethanol hydrochloride was dissolved in 6 ml of $SOCl_2$. After 15 min the excess reagent was removed *in vacuo*, and the crystalline residue was dissolved in 8 ml of H_2O which was then made alkaline and extracted three times with 20 ml of ether. The ether solution was dried ($MgSO_4$) and concentrated to 10 ml. This solution was added to 30 ml of liquid NH_3 containing 340 mg (6.18 mmoles) of KNH_2 (generated *in situ*) and 1.385 g (6.18 mmoles) of 2-(p-bromobenzyl)pyridine. After stirring at reflux for 44 hr the NH_3 was evaporated and the residue was partitioned between H_2O-C_6H_6. The benzene layer was extracted with 15 ml of H_2O containing 2.81 ml of 1.0 N HCl. When this was made alkaline and reextracted (C_6H_6), 451 mg of crude base was obtained. This was chromatographed on a small Florisil column and the resulting base was converted to crystalline maleate salt by the addition of an equivalent amount of maleic acid. Two recrystallizations from *i*-PrOH gave 287 mg, sp act. 3.78 μCi/mg (17% of theory), mp 133–134.5°. Ir spectra were identical with spectra of authentic material and the free base gave a single spot on tlc.

2-{p-Bromo-α-[2-(methylamino)ethyl]benzyl}pyridine Oxalate (II).—To 75 ml of refluxing liquid NH_3 containing 2.20 g (40.0 mmoles) of KNH_2 (generated *in situ*) and 5.00 g (20.0 mmoles) of 2-(p-bromobenzyl)pyridine was added all at once 2.60 g (20.0 mmoles) of methylaminoethyl chloride hydrochloride and the reaction mixture was stirred for 3 hr. After removal of the NH_3, the residue was partitioned (C_6H_6-H_2O). The C_6H_6 extract contained 4.95 g of residue which was chromatographed on 10 g of grade III acid-washed alumina. MeOH–Et_2O (1:3) removed the less polar components and the column was finally stripped with 10% Et_2NH-Et_2O which gave 1.07 g of free base (16% yield). From this base there was obtained 825 mg of a crystalline oxalate salt from MeOH. Spectra were consistent with the assigned structure. A sample recrystallized for analysis had mp 192–193.5°. *Anal.* ($C_{17}H_{19}BrN_2O_4$) C, H, N.

2-{p-Bromo-α-[2-(amino)ethyl]benzyl}pyridine Maleate (III).—To 125 ml of refluxing liquid NH_3 containing 2.66 g (48.4 mmoles) of KNH_2 (generated *in situ*) and 6.00 g (24.2 mmoles) of 2-(p-bromobenzyl)pyridine was added in a single portion 2.44 g (21.0 mmoles) of chloroethylamine hydrochloride and the solution was stirred for 3 hr. After evaporation of NH_3 the residue was extracted (C_6H_6) and this solution was back-extracted with H_2O containing 24.0 mmoles of HCl. Alkalinization and C_6H_6 extraction gave 3.24 g of brown gum. This was fractionated on a 90-g column of neutral alumina (grade III). The fractions were monitored with tlc, using 4% MeOH–C_6H_6 on neutral alumina layers. One gram of one-spot free base was obtained (14% yield) which gave 0.952 g of crystalline maleate. A sample was recrystallized from EtOH–Et_2O for analysis. Spectra were consistent with the assigned structure. *Anal.* ($C_{17}H_{19}BrN_2O_4$) C, H, N.

2-{p-Bromo-α-[2-(dimethylamino)ethyl]benzyl}pyridine N′-Oxide Oxalate (IV).—A 7.35-g sample of brompheniramine was dissolved in a solution consisting of 30 ml of 10% H_2O_2 and 33 ml of MeOH. After 16 hr at room temperature, a thin layer (5% MeOH–C_6H_6 on neutral alumina) plate indicated that no starting material remained and a single product had formed. Excess peroxide was spent with PtO_2, the solvent was pumped off, and an equivalent amount of oxalic acid was added. A 95% yield of crystalline oxide oxalate was obtained which, after recrystallizing from EtOH, had mp 163–163.5°. Its spectra were consistent with the assigned structure. *Anal.* ($C_{18}H_{21}BrN_2O_5$) C, H, N.

β-(p-Bromophenyl)-2-pyridinepropionic Acid (V).—To 150 ml of liquid NH_3 containing 3.63 g (0.066 mole) of KNH_2 (formed *in situ*) and 15.0 g (0.0603 mole) of 2-(p-bromobenzyl)pyridine was added 10.69 g (0.092 mole) of sodium chloroacetate. The solution was stirred for 8 hr, NH_3 was allowed to evaporate, and the residue was dissolved in H_2O. After the aqueous solution was extracted (C_6H_6), its pH was adjusted to pH 5.5, and the resulting crystalline fraction was collected by filtration. Recrystallization from MeOH–EtOH gave 14.8 g (80%). Spectra were consistent with its assigned structure. A sample recrystallized from EtOH for analysis gave mp 182–183° dec (sample introduced to bath at 179°). *Anal.* ($C_{14}H_{12}BrNO_2$) C, H, N.

N-{β-(p-Bromophenyl)-β-(2-pyridyl)propionyl}glycine (VI).—CH_2Cl_2 (175 ml) containing 5.0 g (16.4 mmoles) of β-(p-bromophenyl)-β-(2-pyridyl)propionic acid, 1.66 g (16.4 mmoles) of NEt_3, 2.28 g (16.4 mmoles) of ethyl glycinate hydrochloride, and 3.37 g (16.4 mmoles) of dicyclohexylcarbodiimide was stirred at room temperature for 4 hr. A precipitate was removed by filtration from the darkened solution and the filtrate was shaken with an equal volume of dilute NH_4OH. The CH_2Cl_2 was evaporated leaving 6.5 g of residue which was dissolved in 50 ml of dioxane containing 23 ml of 1 N NaOH, and, after standing for 1.5 hr, the now lighter in color solution was neutralized with 23 ml of 1 N HCl. After removal of the dioxane, the product crystallized from aqueous solution and was recrystallized from EtOH (also treated with decolorizing charcoal). Crystalline material (3 g, 51%) was obtained whose spectra were consistent with the assigned structure and a sample recrystallized several times for analysis had mp 158.5–159.5°. *Anal.* ($C_{16}H_{15}BrN_2O_3$) C, H, N.

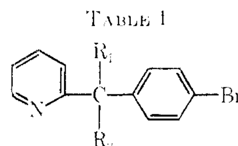
p-Bromophenyl 2-Pyridyl Ketone (VII).—A 20-g (0.080-mole) sample of p-bromphenyl-2-pyrridylmethane was refluxed with 20 g (0.126 mole) of $KMnO_4$ in 1.3 l. of H_2O for 3.5 hr. After cooling the mixture, EtOH was added to spend the excess permanganate. The MnO_2 was removed by filtration, and the filtrate was extracted with a large volume of $CHCl_3$. The extract was concentrated *in vacuo* and the resultant oil crystallized. This product was recrystallized from petroleum ether (bp 30–60°)–MeOH to yield 18.5 g of product which melted at 48–50°, yield 83.3%. *Anal.* ($C_{12}H_8BrNO$) C, H, N.

β-(p-Bromophenyl)-β-hydroxy-2-pyridinepropionic Acid (VIII).—A 3-g sample of N,N-dimethyl-β-(p-bromophenyl)-β-hydroxypropionamide was refluxed 15 min in 100 ml of 2.5 N HCl. The solution was cooled and the pH was adjusted to 5 with NH_4OH. The resulting gummy precipitate was dissolved in hot EtOH and filtered to remove residual salt. The product was crystallized from EtOH to yield 1.4 g of white powder which melted at 146–147° (yield 50%). *Anal.* ($C_{14}H_{12}BrNO_3$) C, H, N.

β-(p-Bromophenyl)-N,N-dimethyl-β-hydroxy-2-pyridinepropionamide (IX).—A mixture of 5.0 g (0.019 mole) of p-bromophenyl 2-pyridyl ketone, 2.46 g (0.028 mole) of N,N-dimethylacetamide, and 645 g (0.028 mole) of $LiNH_2$ (generated *in situ*) in 100 ml of NH_3 and 45 ml of dry Et_2O was stirred for 45 min. NH_3 was allowed to evaporate and the residue was partitioned (C_6H_6–H_2O). The C_6H_6 extract gave the crystalline amide which amounted to 3.4 g after recrystallization (C_6H_6): mp 117–118°, 51% yield. *Anal.* ($C_{16}H_{17}BrN_2O_2$) C, H, N.

Thin Layer Chromatography.—Four systems were found to be satisfactory for the separation of the brompheniramine derivatives: A, *n*-BuOH–AcOH–H_2O (40:11:25) on silica gel G; B, *n*-BuOH–95% EtOH–0.5 N NH_4OH (4:1:1) on silica gel G; C, $CHCl_3$–heptane–Et_2NH (45:45:10) on silica gel G; and D, C_6H_6–MeOH (96:4) on neutral alumina G. Spots were visualized by exposure of plates to I_2 vapor or by spraying with Dragendorff's reagent. Radioactive compounds were detected by exposure of plates to X-ray film either overnight or for several days. The X-ray film was developed in the usual manner. The R_f values of a number of these compounds are shown in Table I.

TABLE I



R_f VALUES OF BROMPHENIRAMINE-RELATED COMPOUNDS

No.	R_1	R_2	Solvent system A	B	C	D
I	H	$CH_2CH_3N(CH_3)_2$	0.63	0.32	0.36	0.75
II	H	$CH_2CH_2NHCH_3$	0.67	0.12	0.13	0.25
III	H	$CH_2CH_2NH_2$	0.75	0.20	0.09	0.15
IV	H	$CH_2CH_2N(CH_3)_2$ (with O ← on N)	0.47	0.29		
V	H	CH_2COOH	0.80	0.42		
VI	H	$CH_2CONHCH_2COOH$	0.65	0.37		
VII		R_1R_2 = =O	0.70	0.86		
VIII	OH	CH_2COOH	0.85	0.77		
IX	OH	$CH_2CON(CH_3)_2$	0.85	0.94		

(3) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Isotope Dilution.—Isotope dilution experiments were carried out by adding nonradioactive compounds to the urine of dogs that had received brompheniramine-^{14}C. The compound of interest was isolated by procedures described below and recrystallized to constant specific activity.

Urine Extraction.—The metabolites in urine were partitioned into two groups: ether-soluble basic metabolites and polar metabolites. The pH of an aliquot of urine was adjusted to 12 with alkali, and the urine was extracted five times with twice its volume of ether. The resulting ether solution was evaporated to yield the ether-soluble amines. The pH of the residual urine was adjusted to 7 and extracted with two equal portions of *n*-BuOH. This yielded 97–100% of the radioactivity present. The BuOH was evaporated to dryness *in vacuo*. The residue was taken up in H_2O and passed through a small Amberlite CG-50 (H^+ form) column. The column was washed with 7 vol of H_2O and finally eluted with 2 *N* NH_4OH which removed all of the radioactivity. The NH_3 solution was evaporated to dryness to give the polar fraction.

Results and Discussion

The results from the analysis of urine samples from the dog and human, for total radioactivity, are shown in Tables II and III, respectively. These results indicate

TABLE II

THE EXCRETION OF RADIOACTIVITY EXPRESSED AS BROMPHENIRAMINE MALEATE BY A DOG THAT RECEIVED AN ORAL DOSE OF 60.3 mg (2.28 μCi) OF BROMPHENIRAMINE-^{14}C MALEATE

	Brompheniramine maleate			
	Urine		Feces	
Time after dosing, hr	mg	% of dose	mg	% of dose
0–54	21.84	36.22	8.07	13.39
54–73	3.98	6.60	3.79	6.28
73–96	2.59	4.30	2.79	4.62
Totals	28.41	47.12	14.65	24.29

TABLE III

EXCRETION OF RADIOACTIVITY EXPRESSED AS BROMPHENIRAMINE MALEATE BY TWO HUMAN SUBJECTS WHO RECEIVED ORAL DOSES OF 32 mg OF BROMPHENIRAMINE-^{14}C MALEATE

	^{14}C as Brompheniramine excreted, mg[a]	
Excreted in	A	B
Urine		
0–24 hr	2.14	3.56
24–48 hr	5.19	5.43
48–72 hr	4.44	4.20
72–96 hr	2.30	2.65
96–120 hr	2.67	1.49
Total	16.74 (52.3)	17.33 (54.2)
Feces (72 hr)	0.44 (1.4)	0.84 (2.6)
Total recd	17.18 (53.7)	18.17 (56.8)

[a] Values in parentheses are per cent of dose.

that approximately 47% of the dose was excreted in the urine and 24% in the feces of the dog. In man, 52–54% was excreted in urine, whereas only 1.4–2.6% was excreted in the feces. The feces from man were collected for only 72 hr while they were collected for 96 hr from the dog.

The preliminary investigations of metabolites were carried out with dog urine, since this had a much higher specific activity than the urine obtained from humans. The ether-soluble amines were chromatographed in systems A–D. This revealed three main drug-related compounds and a fourth minor component was seen with systems A and D. This minor component has not been identified but it amounts to less than 2% of the radioactivity in the urine. The three major components cochromatographed with brompheniramine (I), its primary amine (II), or its secondary amine (III) in all four tlc systems, giving a preliminary identification. The identity of each component was then established by isotope dilution, which also gave the quantity of each present in the urine. These results are shown in Table IV.

TABLE IV

BROMPHENIRAMINE DERIVATIVES AND THE QUANTITIES OF EACH FOUND IN DOG AND HUMAN URINE

		% of dose	
Compd (Salt)	Solvent for recrystn	Dog urine	Human urine
I (maleate)	MeCOEt-EtOAC	2.5	10.5
II (oxalate)	EtOH-Et_2O	2.1	11.5
III (maleate)	EtOAC	14.9	9.9
IV	EtOH	1.2	0
V	EtOH-Et_2O	1.4	4.2
VI	MeCN	3.1	1.6

Tlc of the polar fraction in system A gave four radioactive zones at R_f 0.45, 0.55, 0.65, and 0.80. The four zones were removed from the plate and extracted with methanol, and the extracts were chromatographed on the same plates with synthesized compounds. The R_f 0.80 fraction cochromatographed in systems A and B with β-(*p*-bromophenyl)-2-pyridinepropionic acid (V). The R_f 0.65 fraction cochromatographed in the same two systems with β-(*p*-bromophenyl)-2-pyridinepropionylglycine (VI). The R_f 0.55 fraction cochromatographed in system A with 2-{*p*-bromo-α-[2-(amino)-ethyl]benzyl}pyridine (III) and this zone was probably due to some unextracted remainder of this compound that was not removed by the initial ether extraction. Zone 4, R_f 0.45, consisted of several different compounds very close together. In system B, these compounds were better separated and one of the components cochromatographed with 2-{*p*-bromo-α-[2-(dimethylamino)ethyl]benzyl}pyridine N′-oxide (IV). The R_f values were also identical in system A. In order to confirm the identity of these metabolites and to determine the amounts excreted, isotope dilution experiments were carried out (Table IV).

Similar studies were carried out with urine from humans who had received brompheniramine-^{14}C. Isolation by the procedures described above showed the presence of corresponding metabolites (Table IV). Approximately two-thirds of the radioactivity excreted by humans was separated as ether-soluble amines. The three amines were excreted in approximately equal amounts in human urine. In the dog the primary amine (III) accounted for 76% of the excreted amines. The unidentified amine that occurred in dog urine was also present in human urine. No amine oxide (IV) could be detected in human urine. The polar fraction of human urine contained at least four brompheniramine-related components. Two of these were identified as the propionic acid (V) and its glycine conjugate (VI). The free acid in this case occurred in the larger amount, whereas the reverse was true for the dog.

The remaining three compounds synthesized and listed in Table III could not be identified in either dog or human urine, indicating that hydroxylation of the benzyl α-carbon did not occur to a significant extent.

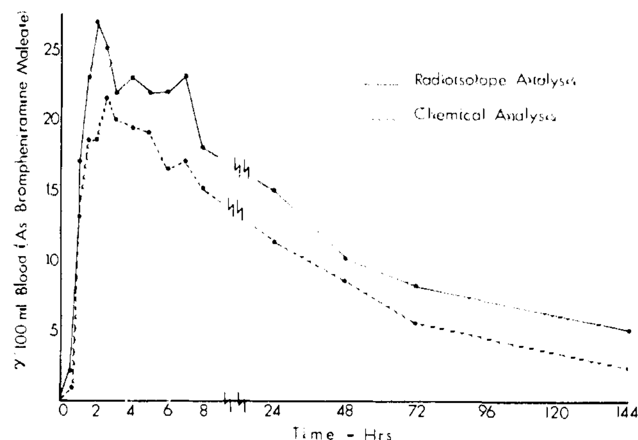


Figure 1.—Blood levels of a dog that received an oral dose of 4.4 mg of brompheniramine-^{14}C

If the ketone VII were formed, $^{14}CO_2$ should appear in the expired air. In order to investigate this possibility, a dog was administered an oral dose of brompheniramine-^{14}C (I) and placed in a cage[4] so that expired CO_2 could be collected and counted for a 24-hr period. No radioactivity could be detected. Since both carbons of the ethyl chain are labeled with ^{14}C, extensive metabolism of this portion of the moelcule does not appear to occur.

Blood levels and excretion were studied in a dog that received an oral dose of 4.4 mg of brompheniramine-^{14}C (I). Samples were analyzed for radioactivity and by the chemical method. These results are shown in Table V and in Figure 1. The larger dose (7 mg/kg) was not administered in this case because it would have necessitated a large dilution of the samples for the chemical method of analysis. The total urinary excre-

(4) R. B. Bruce and J. H. Newman, *Intern. J. Appl. Radiation Isotopes*, in press.

TABLE V

EXCRETION OF BROMPHENIRAMINE MALEATE AND ITS METABOLITES IN THE URINE AND FECES OF A DOG FOLLOWING THE ADMINISTRATION OF 4.4 mg ORALLY

	mg of brompheniramine maleate excreted		
	Urine		Feces
Time after dosing, hr	Chemical method	Radioisotope method	Radioisotope method
0–24	0.492	0.667	0.026
24–48	0.409	0.608	0.011
48–72	0.286	0.388	0.456
72–144	0.445	0.668	0.259

tion in this dog agrees well with that found from the dog receiving the larger dose. In the case of the lower dose, 53% was excreted in the urine and 17% in the feces. The urine value also agrees with those found for humans.

The ratio of the results found for the excretion by the isotope method and chemical method is of interest. The chemical method determines only basic compounds, whereas the isotope method determines any compound that has the radioactive carbon present. Brompheniramine and its metabolites are slowly excreted over a long period and one would expect the ratio of the isotope to the chemical method to increase with time. However, this is not the case. The ratio remains constant for the 144-hr period. This would seem to indicate that the drug is readily absorbed into the tissues and is then slowly released to be metabolized and excreted. The blood levels (Figure 1) confirm this. Following an equilibration period, the curves remain almost parallel for the 144 hr. It is likely that the amine being slowly released by the tissues is not unchanged brompheniramine but one of its basic metabolites (II or III) since the half-life of the total basic compounds in the human is approximately twice that of unchanged brompheniramine (unpublished results).

Synthesis and Biological Activity of Some 1-Substituted 3-Pyrrolidinylureas

GROVER C. HELSLEY, BERNARD V. FRANKO, WILLIAM J. WELSTEAD, AND CARL D. LUNSFORD

Research Laboratories, A. H. Robins Company, Inc., Richmond, Virginia

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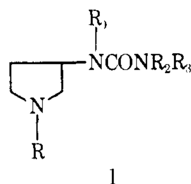
A series of 1-substituted 3-pyrrolidinylureas was synthesized and evaluated for pharmacologic activity. Some of the activities observed were CNS depressant, antiarrhythmic, local anesthetic, and hypoglycemic.

It has been reported that alkyl, aryl, or aralkyl derivatives of urea possess anticonvulsant, hypnotic, sedative, and depressant activity.[1] This paper describes the synthesis and pharmacological properties of a series of 1-substituted 3-pyrrolidinylureas (I).



I

Chemistry.—The general synthetic scheme utilized in preparing the urea derivatives is illustrated in Chart I.

The 3-aminopyrrolidines (II) were prepared by the reaction of the 3-chloropyrrolidines[2] with potassium phthalimide in dimethyl sulfoxide[3] and subsequent treatment of the resulting 3-phthalimidopyrrolidine (Table I) with hydrazine, or by the nucleophilic displacement of the tosylate of a 3-pyrrolidinol. The latter method of preparing 1-substituted 3-aminopyrrolidines has been reported.[4] The properties of the

(1) For references on this activity refer to P. Aeberli, J. Gogerty, and W. J. Houlihan, *J. Med. Chem.*, **10**, 636 (1967).

(2) B. V. Franko and C. D. Lunsford, *ibid.*, **2**, 523 (1960).

(3) G. C. Helsley, U. S. Patent 3,316,276 (April 25, 1967).

(4) W. J. Welstead, Jr., J. P. DaVanzo, G. C. Helsley, C. D. Lunsford, and C. R. Taylor, Jr., *J. Med. Chem.*, **10**, 1015 (1967).