^{14}C-methylhistamine to mice pretreated with aminoguanidine or 1-isobutyl-2-isonicotinylhydrazine (IBINH), a monoamine oxidase inhibitor. Urinary ^{14}C-methylimidazoleacetic acid was depressed in animals treated with IBINH and was at normal levels in animals given aminoguanidine. These authors concluded that methylhistamine and histamine are oxidized by different enzymes in mice.

TABLE 1. EFFECT OF DRUGS ON THE METABOLISM OF ^{14}C-HISTAMINE *in vivo*

Drug	Dose (mg/kg)	^{14}C-Histamine remaining Control (% of injected dose ± S.E.M.)	^{14}C-Histamine remaining Drug-treated (% of injected dose ± S.E.M.)	^{14}C-Methylhistamine found Control (% of injected dose ± S.E.M.)	^{14}C-Methylhistamine found Drug-treated (% of injected dose ± S.E.M.)
Chlorpromazine	40	24·1 (± 2·9)	32·7 (± 2·3)*	15·3 (± 0·9)	7·8 (± 0·9)†
Serotonin	10	24·1 (± 2·9)	39·4 (± 2·5)†	15·3 (± 0·9)	8·1 (± 1·8)†
Bufotenine	20	14·0 (± 4·2)	37·5 (± 7·8)*	17·5 (± 4·1)	2·7 (± 2·7)†
Aminoguanidine	10	19·3 (± 3·2)	40·0 (± 3·9)†	23·6 (± 0·6)	36·9 (± 4·3)*
β-Phenylisopropyl-hydrazine	25	20·6 (± 3·1)	25·6 (± 5·0)	10·4 (± 1·4)	17·2 (± 3·0)*
Imipramine	40	20·6 (± 3·1)	26·8 (± 6·0)	10·4 (± 1·4)	9·8 (± 1·1)
Compound 48-80	2	21·4 (± 4·3)	28·0 (± 7·9)	22·0 (± 2·7)	22·3 (± 5·6)
Reserpine	5	21·4 (± 4·3)	23·4 (± 4·7)	22·0 (± 2·7)	19·6 (± 4·5)
Pyribenzamine	5	21·4 (± 4·3)	23·4 (± 4·7)	22·0 (± 2·7)	19·6 (± 4·5)
5-Methoxytryptamine	25	20·6 (± 3·1)	27·0 (± 7·0)	10·4 (± 1·4)	6·3 (± 2·3)

Mice were given drugs followed by 10 μc ^{14}C-histamine. After 10 min the mice were killed and assayed for ^{14}C-histamine remaining and ^{14}C-methylhistamine formed.

* $p > 0.05$.

† $p > 0.01$.

Kapeller-Adler and MacFarlane[5] have reported the purification of a single enzyme from hog kidney which is active in oxidizing both histamine and methylhistamine.

The histamine liberator Compound 48-80, reserpine, imipramine, the antihistaminic pyribenzamine, and 5-methoxytryptamine had no effect on histamine metabolism in the intact mouse.

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Interaction of plasma protein with related 1,3-propanediol dicarbamates

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ALTHOUGH many drugs are known to bind to plasma protein,[1-5] relatively few studies have been reported comparing the protein-binding properties of a series of chemically related compounds. This report summarizes the results of such an investigation, in which four pharmacologically active 1,3-propanediol dicarbamates were used. The compounds examined for their ability to bind with human plasma were: carisoprodol, N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate; mebutamate, 2-methyl-2-*sec*-butyl-1,3-propanediol dicarbamate; meprobamate, 2-methyl-2-propyl-1,3-propanediol dicarbamate; tybamate, N-*n*-butyl-2-methyl-2-propyl-1,3-propanediol dicarbamate.

MATERIALS AND METHODS

Human blood plasma from outdated blood, obtained from Middlesex General Hospital, New Brunswick, N.J., was prepared for use by dialyzing against standard buffer (0·01 M potassium phosphate and 0·15 M NaCl in distilled water, pH 7·1) at 5°, overnight. The methods used to synthesize the dicarbamates are described in the publications cited: carisoprodol-^{14}C,[6] mebutamate-^{14},[7] meprobamate-^{14}C,[8] and tybamate.[9]

The equilibrium dialysis technique used was essentially that developed by Klotz *et al.*[10] and Anton[11] and modified as needed for the apparatus available. Three ml of dialyzed plasma was added to dialysis bags and the latter placed in glass vials containing 7 ml of standard buffer and a known quantity of dicarbamate. The vials were shaken for 16 hr at 20° ± 2° to ensure equilibration of the contents.

Analyses of the contents were performed either by the N,N-dimethyl-*p*-aminobenzaldehyde colorimetric procedure[7, 12] or by using ^{14}C-labeled dicarbamate and counting the residue from a portion of the exterior fluid. The latter was counted at infinite thinness in a thin-window flow counter (model D-47, Nuclear Chicago) at 1350 V after plating on 1·25-in. diameter stainless steel sample pans with concentric rings (Atomic Accessories).

Partition coefficients between cottonseed oil and water were determined as described previously.[6]

RESULTS AND DISCUSSION

The extent of the interaction of the four dicarbamates with plasma protein under the conditions of the investigation is given in Table 1. These data show that protein binding varies among the compounds

TABLE 1. BINDING OF PHARMACOLOGICALLY ACTIVE DICARBAMATES BY PLASMA PROTEINS

Dicarbamate	Concentration (μg/ml)	Bound (%)	Partition coefficient cottonseed oil–water
Carisoprodol-^{14}C	10	55	4·8
	20	55	
Mebutamate-^{14}C	5	0	0·4
	10	0	
	20	0	
Meprobamate-^{14}C	5	0	0·3
	10	0	
	20	0	
Tybamate	5	81	>20·0
	15	79	
	50	77	

studied and is related to the partition coefficient between oil and water. Thus tybamate, with the highest partition coefficient, binds to the greatest extent and meprobamate to the least. This type of interaction is reminiscent of that found in other homologous series of compounds such as fatty acids,[13] where an increase in lipid solubility of compounds in the series is accompanied by an increase in plasma protein interaction.

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A comparative study of chlorpromazine and its demethylated derivatives: Potency and tissue distribution

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A PREVIOUS STUDY from our laboratory[1] showed the N-demethylated derivatives of chlorpromazine*—namely Nor_1CP and Nor_2CP—less potent than CP in inducing sedation in rats and rabbits, as seen both in behavioral and electroencephalographic experiments. Nor_1CP and CP appeared to be equally potent as based upon the electroencephalographic parameter of elevating recruitment threshold (rabbits). Data from rat experiments included only behavioral evaluations at a 90-min postinjection period and rat brain phenothiazine quantitation again for this 90-min period. Drug doses used in this former study ranged from 0·042–0·126 mmoles/kg.[1]

In the present study we have extended our work, using rats. Behavioral evaluations and brain phenothiazine determinations were made at 90 min and at 20 min after i.p. injection of a single equimolar drug dose level (0·084 mmole/kg). This was done in order to confirm whether or not the comparative potencies of Nor_1CP and CP differed on a temporal basis in rats, as had been the case with rabbits.[1] We have refined our evaluation of pharmacological effectiveness further by quantifying the pharmacological potency of these drugs in terms of an index. In addition, the drug tissue distributions were determined in liver, fat, and brain and compared with the respective chloroform-buffer and benzene-buffer partition coefficients.

METHODS AND MATERIALS

The methods used in behavioral evaluation of rat as well as quantitation of phenothiazine and phenothiazine sulfoxide have been presented in the previous publication.[1] Depressions of reactivity are denoted by a negative sign, and statistical evaluations were not attempted on the behavioral judgments. A general discussion of methods used in animal behavioral evaluation are available.[2,3]

The depression of reactivity was divided by the drug level found in the brain. This quotient is referred to as an index of pharmacological effectiveness and represents the depression of reactivity which theoretically results from a brain drug level of 1 μmole drug/g brain. The higher this index of pharmacological effectiveness, the greater the potency of a compound in producing sedation, as judged by our parameters.

Statistical analysis of mean drug values per gram of tissue included the F test for homogeneity of variance and Student's 't' test. All P values have been calculated from Student's 't' table based on size of samples.[4,5]

Chloroform-buffer and benzene-buffer partition coefficients were established by shaking the drug derivative in a solution of 0·1 M phosphate buffer (pH 7·4) at room temperature with an equal volume of chloroform or benzene for 1 hr. Fat tissue was taken from perirenal and testicular depots.

* The following abbreviations are used: chlorpromazine (tertiary amine) CP; desmonomethyl chlorpromazine (secondary amine) Nor_1CP; desdimethyl chlorpromazine (primary amine) Nor_2CP; chlorpromazine sulfoxide, CPSO.