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Substituted Hippuramides as CNS Depressants

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Abstract □ A series of substituted hippuramides related to tricetamide was prepared, and a preliminary pharmacological evaluation was performed.

Keyphrases □ Hippuramides, substituted—synthesis and preliminary pharmacological testing □ CNS depressants, potential—synthesis and preliminary pharmacological testing of substituted hippuramides

Tricetamide (trimethoxybenzamide of glycine diethylamide), reported in 1960 by Kusserow and Drapir (1), was investigated pharmacologically and reported by Cronheim *et al.* (2, 3) to possess interesting sedative properties. Röhnert (4) also reported the synthesis of a series of *N*-substituted 3,4,5-trimethoxybenzoylglycine diethylamides. It was of interest to prepare a series of ring-substituted benzoylglycine dimethyl- and diethylamides in order to compare them to tricetamide with regard to their ability to potentiate pentobarbital sleeping time.

EXPERIMENTAL[1]

General Procedures—Two successful routes of synthesis were used. In general, the best yields were obtained by condensing the desired benzoyl chloride with glycine dimethyl- or diethylamide (Method A) (4). The synthesis of *N*-[(diethylcarbamoyl)methyl]-2,5-dimethylbenzamide is presented as an example.

In some cases it was necessary to use the mixed anhydride of the substituted hippuric acid formed from reaction with ethyl chloroformate. Dimethyl- or diethylamine was then added to the anhydride formed to give the desired amide (Method B) (5). The synthesis of *N*-[(dimethylcarbamoyl)methyl]-2,4-dichlorobenzamide is presented as an example.

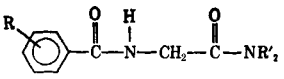
Method A: N-[(*Diethylcarbamoyl)methyl*]-*2,5-dimethylbenzamide*—A solution of 9.1 g. (0.054 mole) of 2,5-dimethylbenzoyl chloride in 70 ml. anhydrous ether and a solution of 8 g. (0.062 mole) of glycine diethylamide in 100 ml. of 8% $NaHCO_3$ solution were added slowly dropwise into a beaker at such a rate that twice the volume of aqueous solution was added per volume of ethereal solution. After the addition was complete, the mixture was stirred vigorously for another hour. The layers were allowed to separate. The ether layer was removed and dried overnight using anhydrous sodium sulfate. The solvent was removed and then the residue was recrystallized once from ethyl acetate and then twice from alcohol and water. A yield of 76% of theory based on the acid chloride was obtained.

Method B: N-[(*Dimethylcarbamoyl)methyl*]-*2,4-dichlorobenzamide*—A solution of 4.6 g. (0.022 mole) of 2,4-dichlorohippuric acid in 50 ml. of acetone and 5 ml. of 25% trimethylamine (0.034 mole) in water was cooled to about −10°.

A solution of 2 ml. (0.025 mole) of ethyl chloroformate in 10 ml. of acetone was added with stirring at such a rate that the temperature was maintained at −10°. The mixture was allowed to stand 15 min.; then 10 ml. of 25% dimethylamine (0.056 mole) in water was added with stirring, keeping the temperature near −10°. The mixture was stirred for another hour, the ice and salt bath was removed, and the mixture was allowed to stand overnight at room temperature. The solvent was then removed in a flash evaporator. The oily residue was taken up in ether, and the ether solution was washed with water and then dried overnight using anhydrous sodium sulfate. On removal of the ether, a semicrystalline mass resulted. This was recrystallized several times from ethyl acetate. The yield was 1.8 g. or 39% of theory.

[1] All melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by F. B. Strauss Microanalytical Laboratory, Oxford, England. IR spectra for all compounds were recorded on a Beckman IR-8 spectrometer and were found to be in agreement with the assigned structures. No attempt was made to optimize the yields. The method of preparation, yields, melting points, recrystallization solvents, molecular formulas, and analyses are shown in Table I.

Table I—*N*-Substituted Hippuramides



Compound Number[a]	R	R′	Method of Preparation	Melting Point	Yield, %	Recrystallization Solvent	Formula	Analysis, % Calc.	Found
1	2-CH_3; 5-CH_3	C_2H_5	A	92–93°	76	Water–ethanol	$C_{15}H_{22}N_2O_2$	C 68.67	68.56
								H 8.45	8.44
								N 10.68	10.76
2	2-Cl; 4-Cl	CH_3	B	92–92.5°	39	Ethyl acetate	$C_{11}H_{12}N_2O_2$	C 48.02	48.09
								H 4.40	4.47
								N 10.18	10.40
3	2-Cl; 4-Cl	C_2H_5	A	66–67°	14	Ethyl acetate	$C_{13}H_{16}Cl_2N_2O_2$	C 51.50	52.21
								H 5.32	5.33
								N 9.24	8.85
4	2-Cl	C_2H_5	A	86–87°	44	Ethyl acetate	$C_{13}H_{17}ClN_2O_2$	C 58.10	58.54
								H 6.38	6.59
								N 10.42	10.71
5	4-CH_3	C_2H_5	A	91–91.5°	72	Ethyl acetate	$C_{14}H_{20}N_2O_2$	C 67.72	67.50
								H 8.12	8.01
								N 11.28	11.39
6	2-CH_3; 5-CH_3	CH_3	B	113–114°	18	Water–ethanol	$C_{13}H_{18}N_2O_2$	C 66.64	66.90
								H 7.74	7.64
								N 11.96	11.88
7	4-CH_3O	C_2H_5	A, B	92–94°[b]	77	Ethyl acetate	$C_{14}H_{20}N_2O_3$	C 63.61	63.79
								H 7.63	7.55
								N 10.63	10.83

[a] IR spectra are consistent with the assigned structures. [b] Lit. (1) m.p. 80–81°.

Pharmacological Testing—Preliminary pharmacological testing was performed on mice by intraperitoneal injection of an aqueous suspension of the drug with sodium carboxymethylcellulose. A dose of test drug equivalent to 100 mg./kg. was administered. Fifteen minutes later, a dose of 45 mg./kg. of sodium pentobarbital was given by intraperitoneal injection. The mice were placed on their backs, and the time of righting reflex recovery was recorded.

RESULTS AND DISCUSSION

Several of the compounds produced moderate sleep time potentiation. However, the data were not adequate to permit any clear-cut delineation of structure–activity relationships in this group. The 2,5-dimethylhippuryl diethylamide, *o*-chlorohippuryl diethylamide, 2,5-dimethylhippuryl dimethylamide, and *p*-methylhippuryl diethylamide (Table I) showed activity similar to, or slightly greater than, that of tricetamide[2].

Selected compounds, when tested orally in rats, were inactive against pentylenetetrazol-induced seizures; in mice they showed only moderate CNS depression[3].

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