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CERTAIN N-SUBSTITUTED CYCLOBUTANE CARBOXAMIDES

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ABSTRACT OF THE DISCLOSURE

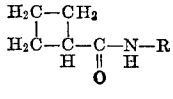
N-substituted cyclobutanecarboxamides in which the substituent is hydroxyalkanoyl, nicotinoyl, or chlorobenzoxazolyl, are useful as muscle relaxants, with lessened side-effects.

BACKGROUND OF THE INVENTION

Skeletal muscle contraction is a condition which accompanies many chronic diseases as well as some localized physical injuries. The conventional therapy has been to employ muscle relaxant (myorelaxant) compounds which relieve such contraction as their principal pharmacodynamic activity. The great majority of the known myorelaxant drugs exhibit undesirable toxicity or adverse side-effects, and some possess activity of such short duration as to render them of limited effectiveness. Thus, there has existed a need for compounds which would be less toxic and yet would be more potent muscle relaxants than the drugs commonly used in human medical practice.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided novel myorelaxants derived from cyclobutanecarboxylic acid. These are N-substituted cyclobutanecarboxamides having the formula:



wherein R is hydroxyalkanoyl containing at least 4 carbon atoms, nicotinoyl, or chlorobenzoxazolyl. The compounds of the invention are prepared by reacting cyclobutanecarbonyl chloride with a hydroxyalkanoyl amide, or with nicotinamide, or with an aminochlorobenzoxazole. The resulting products, except for the benzoxazole derivative, may be regarded functionally as imides.

Examples of the aforementioned N-substituted cyclobutanecarboxamides include:

N-γ-hydroxybutyrylcyclobutanecarboxamide
N-nicotinoylcyclobutanecarboxamide
2-N-cyclobutanecarbonylamino-5-chlorobenzoxazole

Each of the foregoing compounds possesses biological activity as a skeletal muscle relaxant. In comparison with known muscle relaxants, the compounds of the invention are less toxic and have a higher activity than those substances previously available for this type of therapeutic application. While derivatives of cyclobutanecarboxamide have been described in the patent and scientific literature, these have been useful as analgesics and sedatives but not as myorelaxants. In comparison with the known muscle relaxants, the compounds of the present invention exhibit

greatly reduced toxicity. Thus data in the literature on the efficacy and toxicity of several of the known compounds appear in the following table:

Drug	LD_{50}[1]	Myorelaxant ED_{50}[2]
Mephensin	471	355
Methocarbamol	1,320	700
Meprobamate	710	400
Carisoprodol	980	>980
Zoxazolamine	376	227
Chlorzoxazone	210	215

[1] Mg./kg.
[2] Antistrychnine potency in mice.

A widely used test for myorelaxant activity of central origin is the strychnine lethality antagonism and this test was used in the discovery of the known compounds mephenesin and meprobamate. The test for protection against strychnine lethality (ED_{50}) involves the determination of the dose of the drug which completely protects 50% of a mouse population treated with 2 mg./kg. of strychnine sulfate. Strychnine is administered intraperitoneally and 30 minutes after the test drug. Protection from death for 30 minutes is considered partial protection, and protection for 24 hours is taken as complete protection.

The potency of the compounds of the invention is demonstrated, for example, by the following comparison:

Drug: [1]	Antistrychnine potency in mg./kg. (ED_{50})
Mephenesin	355
Meprobamate	400
N-γ-hydroxybutyrylcyclobutanecarboxamide	250
N-nicotinoylcyclobutanecarboxamide [2]	400
2-N-cyclobutanecarbonylamino-5-chlorobenzoxale [2]	220

[1] Intraperitoneal injection.
[2] Oral administration.

The compound of the invention in the above comparison is very non-toxic and has shown no deaths when administered both orally and intraperitoneally at doses of 1000 mg./kg. At high doses the compound potentiates barbiturate sleeping time and at very high doses is itself capable of inducing pharamacological sleep.

The compounds of the invention may be administered by conventional methods using conventional unit dosages with or without conventional acceptable pharmaceutical carriers. The administration may be oral or parenteral, oral administration being with tablets, capsules or in liquid form including suspensions in conventional liquid carriers. The unit dosage for human beings can very over wide limits ranging from about 250 mg. to about 500 mg.

The general method of preparation of the compounds of the invention is to react cyclobutanecarbonyl chloride with the appropriate amide or amine, in molar ratio at moderately elevated temperatures, the reaction being exothermic. The reaction mixture is then acidified to approximately pH 3 and the reaction product extracted with an organic solvent and recrystallized.

The following examples illustrate the preparation of three of the compounds of the invention but are not to be regarded as limiting:

Example 1.—N-γ-hydroxybutyrylcyclobutanecarboxamide

A solution of 0.93 g. γ-hydroxybutyramide (0.009 mole) and 5–15 ml. of neutral alumina washed and potas-

sium hydroxide dried pyridine was cooled in an ice bath. To the cooled solution 1.0 g. cyclobutanecarbonyl chloride (0.009 mole) was added dropwise and with stirring. An exothermic reaction occurred and when it subsided the mixture was heated for one hour on a steam bath. At the end of this time the reaction was poured over 100 g. of crushed ice. The ice water mixture was brought to pH 3 with N hydrochloric acid and the product extracted with chloroform. The yield of imide melting at 88° and crystallized from ether was 25%. Formula: $C_9H_{15}O_3N$. Calculated: N=7.56%. Found: N=7.63%.

Example 2.—N-nicotinoylcyclobutanecarboxamide

A solution containing 1.1 g. nicotinamide (0.009 mole) and 5–15 ml. of neutral alumina washed and potassium hydroxide dried pyridine was cooled on an ice bath. To the cooled solution 1.0 g. of cyclobutanecarbonyl chloride (0.009 mole) was added dropwise with stirring. The reaction which occurred was exothermic and when it subsided the mixture was heated for one hour on a steam bath. At the end of that time the mixture was poured over 100 g. of crushed ice. The mixture was extracted with two 50 cc. fractions of chloroform. The crude product obtained by evaporation of the chloroform was crystallized from ethyl ether to yield 20% of imide, M.P. 103°. Formula: $C_{11}H_{12}O_2N_2$. Calculated: C=64.69%; H=5.92%. Found: C=64.81%; H=5.96%.

Example 3.—2-N-cyclobutanecarbonylamino-5-chlorobenzoxazole

A solution containing 1.5 g. of 2-amino-5-chlorobenzoxazole (0.009 mole) and 5–15 ml. of neutral alumina washed and potassium hydroxide dried pyridine was cooled on an ice bath. To this mixture was added 1.0 g. of cyclobutanecarbonyl chloride (0.009 mole), dropwise with stirring. The ensuing reaction was exothermic and when it subsided the solution was heated for one hour on a steam bath. At the end of that time the reaction was poured over 100 g. of crushed ice, brought to pH 3 with N hydrochloric acid and extracted with two 50 cc. fractions of chloroform. The crude product as obtained by evaporation of the chloroform was crystallized from methanol to yield 35% of amide, M.P. 160°. Formula: $C_{12}H_{11}O_2N_2Cl$. Calculated: N=11.20%. Found: N=11.16%.

MYORELAXANT ACTIVITY

Each of the compounds of Examples 1, 2 and 3 was tested for myorelaxant activity. To test for myorelaxant activity male Swiss-Webster albino mice were used. The weight range was 20–22 g. and no mouse was used more than once. The compounds were administered orally and in some cases intraperitoneally. When given orally they were administered via feeding tube and in 1% gum tragacanth. When given intraperitoneally they were administered in 0.25% methylcellulose sterile vehicle. Strychinine sulfate (2 mg./kg.) was given intraperitoneally 30 minutes after the test drug. This dose is 100% lethal and control animals die within 10–12 minutes of its administration. The ability of a test compound to protect

against strychnine induced convulsions was assessed by its Strychnine sulfate (2 mg./kg.) was given intraperitoneal-used measure of centrally originating myorelaxant activity. The number of living mice was recorded two times, after 30 minutes and 24 hours. Protection from death for 30 minutes was considered partial protection and protection for 24 hours was taken as complete. For each dose four animals were used. The results of our testing are contained in the following Table 1.

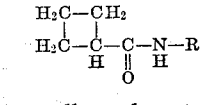
TABLE 1.—PROTECTION AGAINST STRYCHNINE LETHALITY IN MICE

Compound	LD_{50}[1]	Dose	Partial	Complete
Example 1	>1,000	[2] 1,000	3/4	3/4
		[1] 500	[4/4]	[4/4]
		[1] [3] 250	[2/4]	[2/4]
Example 2	>1,000	1,000	4/4	4/4
		400	2/4	2/4
		350	1/4	1/4
		250	0/4	0/4
		125	0/4	0/4
Example 3	>1,000	1,000	4/4	4/4
			[4] [0/4]	[0/4]
		220	2/4	2/4
		200	1/4	1/4
		125	0/4	0/4
		250	4/4	3/4

[1] Mg./kg.
[2] At 1,000 mg./kg. the compound of Example 1 shows some sedative effects in that spontaneous activity is lessened. The compounds of Examples 2 and 3 are more active and show a considerable depression of spontaneous activity at 1,000 mg./kg.
[3] At 250 mg./kg. the compound of Example 1 shows slight effect on spontaneous activity as does the compound of Example 2. The compound of Example 3 shows no effect on spontaneous activity.
[4] Values in brackets refer to the results of intraperitoneal testing.

What is claimed is:

1. A compound having the formula:



wherein R is hydroxyalkanoyl containing at least 4 carbon atoms, nicotinoyl, or chlorobenzoxazolyl.

2. N-γ-hydroxybutyryl cyclobutanecarboxamide, in accordance with claim 1.

3. N-nicotinoyl cyclobutanecarboxamide, in accordance with claim 1.

4. 2-N-cyclobutanecarbonyl amino-5-chloro benzoxazole, in accordance with claim 1.

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U.S. Cl. X.R.

260—307D, 557, 999