PATENT SPECIFICATION

NO DRAWINGS

873,908

Date of Application and filing Complete Specification: April 24, 1958.
No. 13078/58.
Application made in United States of America on April 24, 1957.
Application made in United States of America on April 18, 1958.
Complete Specification Published: Aug. 2, 1961.

Index at acceptance:—Classes 2(3), C2B40(A: C: G: J3), C3A14A(3B: 8A); and 81(1), B2H.
International Classification:—C07c. A61k.

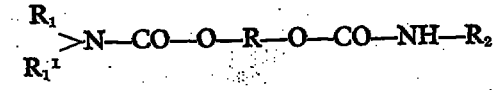
COMPLETE SPECIFICATION

Improvements in or relating to 2-Methyl-2-*n*-Propyl-N-Monosubstituted-1:3-Propanediol Dicarbamates and method of Manufacture

We, CARTER PRODUCTS, INC., a corporation organized under the laws of the State of Maryland, one of the United States of America, of 2 Park Avenue, City and State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel organic compounds and has for its object the provision of new compounds possessing muscle relaxant action of high activity.

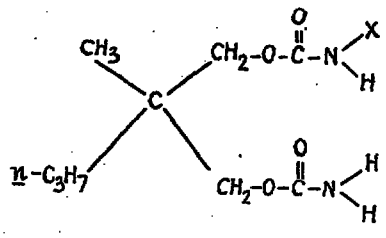
Prior to this invention, many drugs have been used for the purpose of relieving muscle spasm caused by different disorders, such for example, as rheumatic and related disorders, cerebral palsy, and various neurological conditions. For many years, salicylates were used for this purpose but they were not generally effective for they relieved aching discomfort for only a short time. Later, mephenesin (3 - *o* - toloxy - 1,2 - propanediol) became widely used in a variety of conditions where muscle spasm is a factor. The very short duration of action of mephenesin is its greatest drawback. The most recent drug which has had wide acceptance for relieving muscle spasm is meprobamate (2 - methyl - 2 - *n* - propyl - 1,3-propanediol dicarbamate). The muscle relaxant action of meprobamate is similar to that of mephenesin but of greater potency and longer duration. Specification No. 751,841 discloses dicarbamates of the general formula



wherein R is an aliphatic hydrocarbon radical, R_1 and R_1^1 are hydrogen, alkyl, aryl, aralkyl or cycloalkyl, and R_2 is alkyl, aryl, aralkyl or cycloalkyl, with the proviso that if one of R_1 and R_1^1 is hydrogen, the other of these is different from R_2.

This invention is based on the discovery that certain novel compounds falling within the general formula shown above possess muscle relaxant action of greater potency than any of the heretofore used muscle relaxant agents. The invention also includes a novel method for producing the N-substituted dicarbamates of this invention.

The compounds of the present invention are 2 - methyl - 2 - *n* - propyl - N - monosubstituted - 1,3 - propanediol dicarbamates having the general formula:

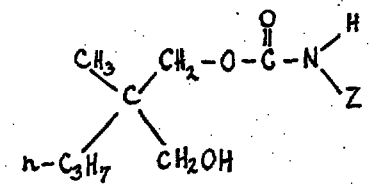


wherein X is an ethyl, *n*-propyl, *iso*propyl-*n*-butyl, *iso*butyl or allyl radical. Thus the compounds of this invention are N - *n* - propyl - 2 - methyl - 2 - *n* - propyl - 1,3-propanediol dicarbamate, N - *iso*propyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate, N - *n* - butyl - 2 - methyl - 2 - *n* - propyl - 1,3-propanediol dicarbamate, N - ethyl-2-methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate, N - *iso*butyl - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate, and N-allyl-2 - methyl - 2 - *n* - propyl - 1,3 - propanediol dicarbamate.

In accordance with the invention, there is provided a method of manufacturing N-monosubstituted dicarbamates having the general formula shown above, which method comprises reacting a monocarbamate of the general formula:

[*Price 3s. 6d.*]

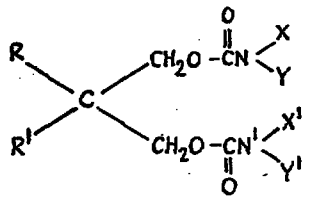
Price 4s 6d.



wherein Z is a hydrogen atom or an aliphatic hydrocarbon radical selected from an ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl or alkyl radical, with a carbamating agent, the carbamating agent being an alkyl isocyanate or phosgene followed by an aliphatic amine containing from 2 to 4 carbon atoms in the case where Z is a hydrogen atom, and the carbamating agent being cyanic acid, a carbamic ester of a low boiling alcohol, or phosgene followed by ammonia in the case where Z is an aliphatic hydrocarbon radical.

The N-monosubstituted dicarbamates of this invention possess unexpected intense muscle relaxing activity. This is shown by the results of Table 1 giving mean paralyzing doses and mean lethal doses obtained in mice after intraperitonial administration of a number of related propanediol dicarbamate compounds. The PD_{50} and LD_{50} doses are expressed in millimoles (mm) of active ingredient per kilogram (kg) of mouse. The compounds listed below in Table 1 comprise 2,2-disubstituted - N - monosubstituted - 1,3-propanediol dicarbamate which include the novel compounds of this invention; 2 - 2-disubstituted - N,N - disubstituted - 1,3-propanediol dicarbamates; 2,2 - disubstituted-N,N^1 - disubstituted - 1,3 - propanediol dicarbamates; 2,2 - disubstituted - N,N,N^1,N^1-tetrasubstituted - 1,3 - propanediol dicarbamates, and as a control, meprobamate, which is a 2,2 - disubstituted - N - unsubstituted-1,3 - propanediol dicarbamate.

TABLE 1



R	R^1	X	Y	X^1	Y^1	PD_{50}	LD_{50}
CH_3	*n*-C_3H_7	H	H	H	H	235	800
CH_3	*n*-C_3H_7	CH_3	H	H	H	290	730
CH_3	*n*-C_3H_7	C_2H_5	H	H	H	170	700
CH_3	*n*-C_3H_7	*n*-C_3H_7	H	H	H	146	790
CH_3	*n*-C_3H_7	*iso*C_3H_7	H	H	H	153	790
CH_3	*n*-C_3H_7	*n*-C_4H_9	H	H	H	94	514
CH_3	*n*-C_3H_7	*iso*C_5H_{11}	H	H	H	620	940
CH_3	*n*-C_3H_7	benzyl	H	H	H	1400	1400
C_2H_5	C_2H_5	C_2H_5	H	H	H	530	940
CH_3	*n*-C_3H_7	CH_3	H	CH_3	H	315	730
CH_3	*n*-C_3H_7	C_2H_5	H	C_2H_5	H	560	1020
CH_3	*n*-C_3H_7	CH_3	CH_3	H	H	570	900
CH_3	*n*-C_3H_7	C_2H_5	C_2H_5	H	H	370	735
C_2H_5	C_2H_5	C_2H_5	C_2H_5	C_2H_5	C_2H_5	convulsant	650
CH_3	*n*-C_3H_7	C_2H_5	C_2H_5	C_2H_5	C_2H_5	convulsant	940
CH_3	*n*-C_3H_7	C_2H_5	H	C_2H_5	H	560	1020
CH_3	*n*-C_3H_7	*iso*C_4H_9	H	H	H	175	940
CH_3	*n*-C_3H_7	CH_2=$CHCH_2$ (allyl)	H	H	H	114	500

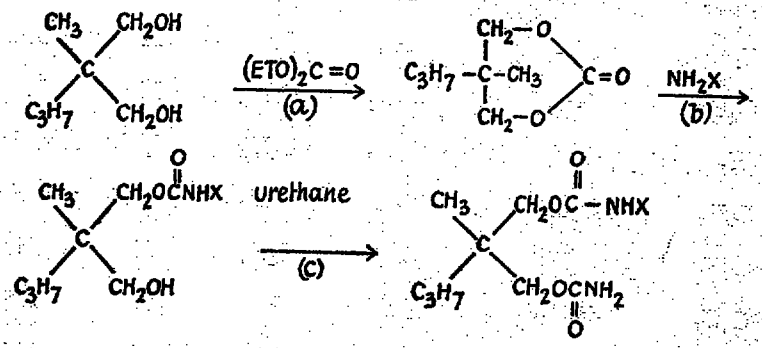
The results summarized in Table 1 show the unexpected muscle relaxant activity of the compounds of this invention. From a study of these results, it appears that enhanced activity of N and/or N^1 substituted dicarbamates over meprobamate appears to be dependent upon the substitution of one and not more than one of the four hydrogen atoms attached to the carbamate nitrogens with an aliphatic group. Secondly, the nature of the aliphatic group affects the activity. It is seen, therefore, that not every 2 - methyl - 2-*n* - propyl - N and/or N^1 - substituted - 1,3-propanediol dicarbamate has improved activity over meprobamate but only the compounds of this invention. As a matter of fact, as shown by the results of Table 1, it has been found that in general substituting aliphatic groups for more than one of the four hydrogens attached to the two carbamate nitrogens of meprobamate decreases rather than enhances muscle relaxant activity. Moreover, the unexpected improved muscle relaxant activity possessed by the compounds of this invention is clearly shown by the fact that other members of the very specific class, i.e., 2,2-disubstituted N-monosubstituted propanediol carbamates, to which the compounds of this invention belong, possess muscle relaxant action far inferior to that possessed by mepro-

bamate and of course even more inferior to the unique muscle relaxant activity of the compounds of this invention.

The compounds covered by this application are colorless liquids of high boiling point or low melting solids. They are soluble in most organic solvents but only slightly soluble in water at ordinary room temperature. They are readily hydrolyzed by hot caustic or strong acid solution to give the corresponding diol, ammonia, primary amine and carbon dioxide.

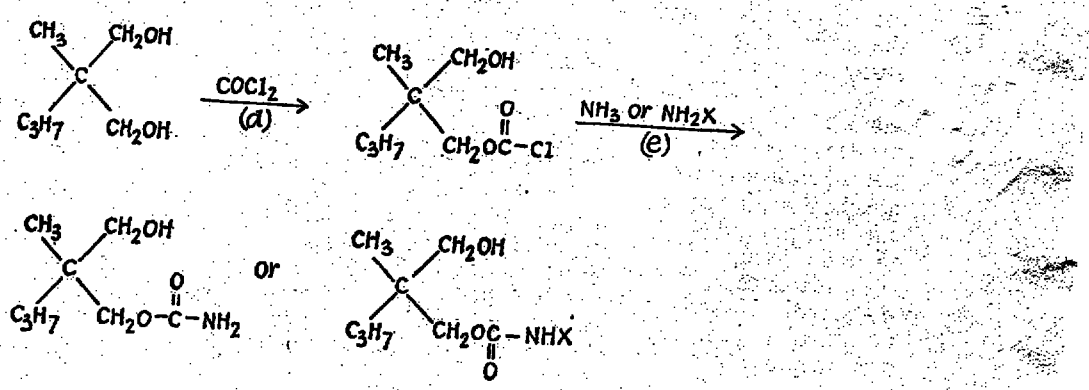
The compounds of this invention may be prepared by many different methods. One method involves reacting an appropriate N-substituted hydroxyalkyl carbamate with a carbamate of a low boiling alcohol (e.g., alcohols having from 1 to 4 carbon atoms) or cyanic acid. Cyanic acid is a compound formed by the treatment of an alkali metal cyanate such, for example, as sodium cyanate with anhydrous hydrogen chloride. The N-substituted hydroxyalkyl carbamate employed in the above reactions may be prepared by any of the known methods, some of which are described hereinlater. Another method for producing the compounds of this invention involves the conversion of an appropriate N-unsubstituted hydroxyalkyl carbamate to the desired compound by reacting it with the appropriate organic isocyante. The N-unsubstituted hydroxyalkyl carbamate used in this reaction may be prepared by any of the known methods, some of which are described hereinafter. Another method for preparing the compounds of this invention involves the phosgenation of the N-unsubstituted hydroxyalkyl carbamate followed by amination using the desired primary amine.

In order to describe more particularly a number of methods which may be employed for producing both the intermediate N-substituted monocarbamate (i.e., hydroxyalkyl carbamates) and N-unsubstituted monocarbamates, as well as the compounds of this invention produced therefrom, the following explanation is given. In all instances, the compounds of this invention are prepared from an unsubstituted or N-mono-substituted 2 - methyl - 2 - *n* - propyl - 1,3 - propanediol monocarbamate. One method of preparation of the compounds of this invention involves, (a) conversion of the diol to the corresponding cyclic carbonate ester (*m*-dioxanone) using diethyl carbonate, (b) treatment of the cyclic carbonate ester with the appropriate amine HNHX, either in aqueous solution or in the anhydrous form, to give the N-substituted monocarbamate, and (c) reaction of the latter compound with a carbamate of a low boiling alcohol such, for example, as urethane, in an ester exchange reaction to give the desired compound. These reactions are summarized in the following reaction scheme.



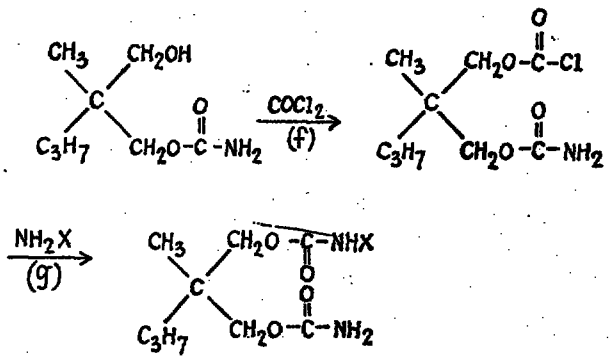
Alternatively the dicarbamate product of step (c) may be prepared by reacting the monocarbamate of step (b) with cyanic acid HOCN.

The monocarbamate obtained from step (b) above may also be prepared by the controlled action of phosgene on the diol (d) followed by amidation with ammonia or the desired amine, NH_2X (e):

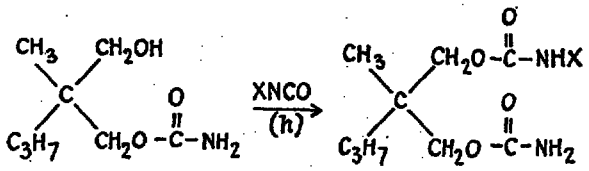


In the process of step (b), if ammonia (NH_3) is used instead of an amine (NH_2X), an N-unsubstituted monocarbamate is formed.

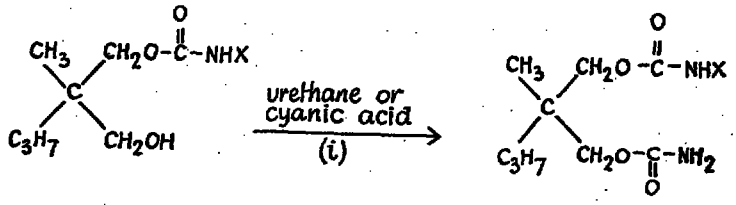
When the product of step (e) or the product of step (b) obtained by using ammonia is the N-unsubstituted amide it may be converted to the desired product by phosgenation (f) followed by amidation using the desired primary amine NH_2X (g):



An alternative method for making the product of step (g) when the product of step (e) is the N-unsubstituted amide is to react said monocarbamate with the appropriate aliphatic isocyanate (XNCO) (h):



When the product of step (e) is the N-aliphatic amide, it may be converted to the final product by either the phosgenation-amidation steps (f) and (g) using ammonia as the amidation agent, or by an ester exchange reaction using a carbamate of a low boiling alcohol such as, for example, urethane, or by reacting the monocarbamate with cyanic acid (i).



In order to illustrate the preparation of the compounds of this invention the following examples are given illustrating various methods of preparation. Unless otherwise indicated the parts given are by weight. Examples A—I illustrate the preparation of intermediate compounds for forming the novel compounds of this invention. Examples 1—10 illustrate the preparation of novel compounds of this invention.

Example A illustrates the preparation of an intermediate 5 - methyl - 5 - *n* - propyl-2 - *m* - dioxanone by step (a) described above wherein the diol is converted to the cyclic carbonate ester using diethyl carbonate. Examples B—F illustrate the preparation of a number of intermediates of the compounds of this invention employing step (b) described above by treatment of the cyclic carbonate ester with an appropriate amine or ammonia to give either the N-substituted or N-unsubstituted monocarbamate respectively. Example G illustrates a method for preparing the intermediate chlorocarbonate by step (d) described above by controlled action of phosgene on the diol, while Examples H and I illustrate the preparation of intermediate monocarbamates by a method, step (e) described above, different from the method of Examples B—F, by amidation of a chlorocarbonate with the desired amine. Examples 1—6 illustrate the preparation of the compounds of this invention employing steps (c) and (i) described hereinbefore, i.e., reaction of N-substituted monocarbamate with a carbamate of a low boiling alcohol in an ester exchange reaction. Examples 7 and 8 illustrate different methods for the preparation of one of the compounds of this invention utilizing steps (f) and (g) described above.

In Example 7 an N-unsubstituted monocarbamate is converted to the desired compound by phosgenation followed by amidation with the appropriate primary amine. In Example 8 the same compound is obtained by phosgenation of the N-substituted monocarbamate and reaction of the monochlorocarbonate with ammonia. Example 9 illustrates a method for the praparation of one of the compounds of this invention employing step (h). In this Example an N-unsubstituted monocarbamate is converted to the desired compound by reaction with an appropriate organic isocyanate. Example 10 illustrates a method for preparing one of the compounds of this invention employing step (i). In this Example an N-unsubstituted monocarbamate is reacted with cyanic acid.

PREPARATION OF INTERMEDIATE COMPOUNDS

EXAMPLE A

PREPARATION OF 5 - methyl - 5 - *n* - propyl-2 - *m* - dioxanone:

132 parts of 2 - methyl - 2 - *n* - propyl-1,3 - propanediol and 113 parts of diethyl carbonate were mixed in a suitable vessel equipped with an efficient distillation column. The mixture was freed from moisture by distillation of a small portion of the diethyl carbonate. After cooling, approximately one part of sodium ethylate was added. Distillation was continued until substantially the theoretical quantity of ethanol was distilled at about 78° C. A further quantity of 10 parts of diethyl carbonate was added and distillation continued until ethanol removal was complete. The mixture was cooled and diluted with an equal volume of diethyl ether. This solution was washed with dilute hydrochloric acid saturated with sodium chloride and then with water. It was dried using a suitable drying agent and the solvent was removed. The residue was distilled under reduced pressure. The fraction distilling at 125—130° C. at about 0.1 mm was collected as a clear, colorless, oily liquid n_D^{25} 1.4506. A yield of 80% of the theoretical amount of 5 - methyl - 5 - *n* - propyl - 2 - *m* - dioxanone was obtained.

EXAMPLE B

PREPARATION OF 2 - methyl - 2 - *n* - propyl-3 - hydroxypropyl carbamate:

5 parts of 5 - methyl - 5 - *n* - propyl - 2-*m* - dioxanone and 7.5 parts of liquid ammonia were placed in a cooled stainless steel pressure bomb and the vessel sealed. The vessel was permitted to warm to room temperature and allowed to remain at this temperature with occasional shaking for 24 to 48 hours. The vessel was cooled, opened, and the excess ammonia allowed to evaporate. The monocarbamate which was obtained as a low melting solid was purified by crystallization from a toluene-ligroin mixture. Approximately four parts of the purified product were obtained in the form of a colorless crystalline solid, slightly soluble in water, melting point 61.5—62.5° C.

EXAMPLE C

PREPARATION OF N - *n* - propyl - 2 - methyl-2 - *n* - propyl - 3 - hydroxypropyl carbamate:

55 parts of 5 - methyl - 5 - *n*- propyl - 2-*m* - dioxanone and 41 parts of *n* - propylamine were mixed in a suitable vessel equipped with a reflux condenser. The mixture was heated slowly and permitted to reflux for two hours. The excess amine was removed by distillation and the residue distilled under reduced pressure. The fraction boiling at 114—117° C. at 0.02 mm was collected in a yield of 80% of theoretical. This product was a viscous, colorless oil having the physical constants and analysis as given in Table 2.

EXAMPLE D

PREPARATION OF N - ethyl - 2 - methyl - 2-*n* - propyl - 3 - hydroxypropyl carbamate:

158 parts of 5 - methyl - 5 - *n* - propyl - 2-*m* - dioxanone were stirred at room temperature with 75 parts of a 70% solution of ethylamine in water, until reaction was complete. The excess amine was removed by dissolving the mixture in ether and extracting with dilute hydrochloric acid. The ether was removed from the organic layer and the residue purified by distillation at reduced pressure. The fraction distilling at 110—112° C. at 0.02 mm. was collected. It had the physical constants and analysis as listed in Table 2.

EXAMPLE E

PREPARATION OF N - *iso*butyl - 2 - methyl - 2-*n* - propyl - 3 - hydroxypropyl carbamate:

55 parts of 5 - methyl - 5 - *n* - propyl-2 - *m* - dioxane, 51 parts of *iso*butylamine and 75 parts ethanol are permitted to remain at room temperature overnight. The ethanol and excess amine are then removed by distillation under reduced pressure. The oily residue remaining is dissolved in ethyl ether and extracted with dilute hydrochloric acid to remove the remaining amine and then extracted with water. The ether solution is dried over a suitable drying agent and freed from solvent by evaporation. The crude N-*iso*butyl - 2 - methyl - 2 - *n* - propyl - 3-hydroxypropyl carbamate is purified by distillation under reduced pressure; the fraction boiling at 118—119° C. at 0.06 mm. pressure is collected. A yield of 50 parts (62% of theoretical) of purified compound is obtained having the analytical values and physical constants listed in Table 2.

EXAMPLE F

PREPARATION OF N - allyl - 2 - methyl - 2-*n* - propyl - 3 - hydroxypropyl carbamate:

57 parts of allylamine are added slowly with stirring to 52 parts of 5 - methyl - 2-*n* - propyl - 2 - *m* - dioxanone. After addition is completed, the reaction mixture is heated for two hours on a steam bath. The excess allylamine is then removed by distillation

under reduced pressure and the residue purified by vacuum distillation. A yield of 40 parts of purified product distilling at 102—104° C. at 0.05 mm. pressure is obtained having the analytical values and physical constants listed in Table 2.

EXAMPLE G

PREPARATION OF 2 - methyl - 2 - *n* - propyl-3 - hydroxypropylchlorocarbonate:

A cooled 10% solution of 1 mole of phosgene in toluene was added with stirring to a cooled solution of 1 mole of 2 - methyl - 2-*n* - propyl - 1,3 - propanediol and 2 moles of dimethylaniline also dissolved in toluene, at such a rate that the temperature of the mixture was maintained at about 25° C. The mixture was allowed to remain at this temperature for several hours, then cooled and extracted with cold 5% hydrochloric acid solution to remove the dimethylaniline. The toluene layer was dried using a suitable drying agent and the chlorocarbonate used in subsequent reactions in the form of its solution in anhydrous toluene.

EXAMPLE H

PREPARATION OF N - *n* - butyl - 2 - methyl-2 - *n* - propyl - 3 - hydroxypropyl carbamate:

A quantity of solution obtained as described in Example G containing 0.1 mole of the chlorocarbonate was treated with 0.2 mole of anhydrous *n*-butylamine and allowed to react at ordinary room temperature. The solution was cooled, extracted with dilute hydrochloric acid and the organic layer concentrated by evaporation of the solvent. The crude monocarbamate was purified by distilling at 107—108° C. at about 0.01 mm. It was a clear, viscous liquid having the physical constants and analysis as listed in Table 2.

EXAMPLE I

PREPARATION OF N - *iso*propyl - 2 - methyl-2 - *n* - propyl - 3 - hydroxypropyl carbamate:

This compound was prepared from 2-methyl - 2 - *n* - propyl - 3 - hydroxypropyl chlorocarbonate and *iso*propyl amine by the method used in Example H. The product has the physical constants and analysis as listed in Table 2.

TABLE 2

N-substituted-2-methyl-2-*n*-propyl-3-hydroxypropyl carbamates

N-alkyl Group	Formula	Anal. Calc.	Nitrogen Found	Refractive Index n_D^{25}	B.P. °C. (mm)
ethyl	$C_{10}H_{21}O_3N$	6.89	6.83	1.4589	110—112 (0.02)
n-propyl	$C_{11}H_{23}O_3N$	6.45	6.76	1.4579	114—117 (0.02)
*iso*propyl	$C_{11}H_{23}O_3N$	6.45	6.21	1.4543	86—88 (0.01)
n-butyl	$C_{12}H_{25}O_3N$	6.06	6.06	1.4579	107—108 (0.01)
*iso*butyl	$C_{12}H_{25}O_3N$	6.06	5.96	1.4586	118—119 (0.06)
allyl	$C_{11}H_{21}O_3N$	6.51	6.80	1.4683	102—104 (0.05)

PREPARATION OF COMPOUNDS OF INVENTION

EXAMPLE 1

PREPARATION OF N - *n* - propyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

22 parts of N - *n* - propyl - 2 - methyl - 2-*n* - propyl - 3 - hydroxypropyl carbamate and 10 parts of ethyl urethane were dissolved in 250 parts of anhydrous xylene in a suitable vessel equipped with an efficient distillation column. Two parts of aluminium isopropylate were added and the mixture heated to boiling and distillation continued until substantially the theoretical quantity of ethanol had been distilled in the form of an azeotrope with xylene. The bulk of the solvent was removed by distillation under reduced pressure. 100 parts of water were added and distilled under reduced pressure to remove the final traces of xylene. 50 parts of isopropanol were added and distilled to remove residual water, and the residue taken up in 100 parts isopropanol. The solution was clarified by filtration, concentrated by evaporation of the isopropanol and the residue subjected to distillation under reduced pressure. The fraction distilling at 144—147° C. at 0.02 mm. was collected. This product was obtained in a yield of 72% of theoretical in the form of a somewhat viscous, clear, oily liquid having the properties listed in Table 3.

EXAMPLE 2

PREPARATION OF N - *iso*propyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

One mole of N - *iso*propyl - 2 - methyl - 2-*n* - propyl - 3 - hydroxypropyl carbamate and 1.1 moles of ethyl urethane were reacted in an ester interchange reaction as described in Example 1. The product obtained on removal of the isopropanol solvent was recovered as a crystalline solid which was purified by recrystallization from aqueous isopropanol solution. It had the properties and analysis as listed in Table 3.

EXAMPLE 3

PREPARATION OF N - *n* - butyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

This compound was prepared from N - *n*-butyl - 2 - methyl - 2 - *n* - propyl - 3-hydroxypropyl carbamate and ethyl urethane by the method described in Example 1. The properties and analysis of the purified product are listed in Table 3.

EXAMPLE 4

PREPARATION OF N - ethyl - 2 - methyl - 2-*n* - propyl - 1,3 - propanediol dicarbamate:

22 parts of N - ethyl - 2 - methyl - 2 - *n*-propyl - 3 - hydroxypropyl carbamate were reacted in an ester exchange reaction with 15 parts of ethyl urethane using aluminium isopropylate as catalyst in anhydrous toluene in a vessel equipped with a distillation column as described in Example 1. The product obtained had the properties and analysis as listed in Table 3.

EXAMPLE 5

PREPARATION OF N - *iso*butyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

22.1 parts of N - *iso*butyl - 2 - methyl-2 - *n* - propyl - 3 - hydroxypropyl carbamate and 9.8 parts of urethane are dissolved in 300 parts of anhydrous xylene in a suitable vessel equipped with an efficient distillation column. Xylene is distilled to remove traces of water from the mixture. 2.3 parts of aluminium isopropylate are added and distillation is continued until substantially the theoretical quantity of ethanol has been distilled at about 78° C. The reaction mixture is then freed from xylene by distillation under reduced pressure. Approximately 100 parts of water are added and the mixture again freed of solvent by distillation under reduced pressure. 100 parts of trichloroethylene are added, the solution filtered to remove insoluble matter and the solution freed of solvent by evaporation. The residual oil is purified by molecular distillation at a pressure of about 0.01 mm. 8.7 parts (35% of theoretical yield) of purified N - *iso*butyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate are obtained in the form of a viscous colorless oil having the analytical values and physical constants listed in Table 3.

EXAMPLE 6

PREPARATION OF N - allyl - 2 - methyl - 2 - *n*-propyl - 1,3 - propanediol dicarbamate:

A solution of 18.8 parts of N - allyl - 2-methyl - 2 - *n* - propyl - 3 - hydroxypropyl carbamate, 8.9 parts of urethane and 200 parts of xylene are distilled to removed all traces of residual water. The mixture is allowed to cool and one part of aluminium isopropylate is added. The mixture is distilled until substantially the theoretical quantity of alcohol has been removed in the form of its azeotrope with xylene. The xylene is removed by distillation under reduced pressure and 100 parts of water are added. The water is distilled under reduced pressure and the residue dissolved in 150 parts of isopropanol. The insoluble material is removed by filtration and the isopropanol removed by distillation. The residual oil is purified by molecular distillation using a bath temperature of about 110—135° C. and a pressure of about 0.025 mm. A yield of 14 parts of purified product is obtained having the analytical values and physical constants given in Table 3.

EXAMPLE 7

PREPARATION OF N - *n* - propyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

A cooled 10% solution of 0.1 mole of phosgene in toluene was added with stirring to a cooled solution of 0.1 mole of 2 - methyl-2 - *n* - propyl - 3 - hydroxypropyl carbamate and 0.11 mole of pyridine also dissolved in toluene, at such a rate that the temperature of the mixture was maintained at about 0 to 5° C. The mixture was allowed to warm to 25° C. and was stirred for several hours. The pyridine hydrochloride was filtered off, the toluene was removed by distillation under reduced pressure and the residue dissolved in an anhydrous ether. The solution was filtered and the chlorocarbonate used in the subsequent reactions in the form of its solution in anhydrous ether. To this solution there was added 0.2 mole of *n*-propylamine and the mixture was allowed to react at room temperature. The excess amine was removed by extracting with dilute hydrochloric acid solution, and the ether layer concentrated by evaporation of the solvent. The residue was purified by distillation under reduced pressure giving a product identical to that obtained in Example 1.

EXAMPLE 8

PREPARATION OF N - *n* - propyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

N - *n* - propyl - 2 - methyl - 2 - *n* - propyl-3 - hydroxypropyl carbamate was converted to its chlorocarbonate derivative employing phosgene and pyridine as described in Ex-

ample 7. A solution of this chlorocarbonate in ether was treated at room temperature with an excess of dry ammonia gas by bubbling the gas into the stirred solution of the chlorocarbonate while cooling. The mixture was alowed to warm to room temperature and stired for about one hour. The excess ammonia was removed by extracting with dilute hydrochloric acid and the isolation and purification effected as described in Example 7. The product obtained was identical to that obtained in Examples 1 and 7.

Example 9

Preparation of N - *n* - butyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

175 parts of 2 - methyl - 2 - *n* - propyl-3 - hydroxypropyl carbamate and 108 parts of *n*-butyl isocyanate are added to 1250 parts of anhydrous benzol and the mixture boiled under reflux for about 8 hours. The solvent is removed by distillation under reduced pressure and the residue dissolved in approximately 1800 parts of warm trichloroethylene-hexane (1:2) solvent. On cooling, the product separates in the form of colorless crystals, which after removal from the solvent and drying, melts at 49 to 51° C. The yield of the purified compound is about 80% of theoretical. Analysis: Calculated for $C_{13}H_{26}O_4N_2$, nitrogen 10.21%. Found: nitrogen 10.42%. This compound may also be purified by distillation under reduced pressure. The compound distills at approximately 150—152° C. at a pressure of 0.06 mm. The product obtained by distillation can be converted to a crystalline solid by subjecting it to the crystallization procedure indicated above.

Example 10

Preparation of N - *iso*propyl - 2 - methyl-2 - *n* - propyl - 1,3 - propanediol dicarbamate:

21.7 grams (0.1 mole) of N - *iso*propyl-2 - methyl - 2 - *n* - propyl - 3 - hydroxypropyl carbamate and 7.5 grams (0.11 mole) of anhydrous sodium cyanate are stirred in 200 mls. anhydrous chloroform in a suitable vessel equipped with a gas inlet tube, stirrer and thermometer. While cooling the vessel, anhydrous hydrogen chloride is passed into the stirred mixture slowly for 5 hours maintaining the temperature between 0 and 5° C. The mixture is then allowed to stand at room temperature overnight. The solid material is separated by filtration and the chloroform solution concentrated to an oil under reduced pressure. The oil is dissolved in 50 mls. of trichloroethylene, the solution treated with charcoal, filtered and the filtrate added to 125 ml. of hexane. The crystalline material which forms on standing at refrigerator temperature is removed by filtration, washed with light petroleum ether and dried at about 50° C. Approximately 20 grams of product are obtained. On recrystallizing from trichloroethylene-hexane, 17.8 grams of purified compound are obtained, melting point 89—91° C. The product from this reaction is identical to that obtained from the reaction described in Example 2.

Table 3

N-substituted-2-methyl-2-*n*-propyl-1,3-propanediol dicarbamates

N-alkyl Group	Formula	Anal. Calc.	Nitrogen Found	Refractive Index n_D^{25}	B.P. or m.p. (mm) °C.
ethyl	$C_{11}H_{22}O_4N_2$	11.38	11.06	1.4677	154—156 (0.05 mm.)
n-propyl	$C_{12}H_{24}O_4N_2$	10.76	10.71	1.4694	144—147 (0.02 mm.)
*iso*propyl	$C_{12}H_{24}O_4N_2$	10.76	10.76		m.p. 89—91°
n-butyl	$C_{13}H_{26}O_4N_2$	10.21	10.42		m.p. 49—51°
*iso*butyl	$C_{13}H_{26}O_4N_2$	10.21	10.47	1.4645	100—110 (0.01 mm.)*
allyl	$C_{12}H_{22}O_4N_2$	10.85	11.03	1.4760	110—135 (0.25 mm.)*

* Compound purified by distillation at temperature and pressure indicated.

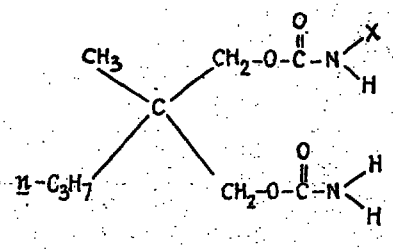
In addition to possessing unique muscle relaxant action so as to be extremely useful as a drug for the relief of muscle spasm, the marked central depressant properties of the compounds of this invention suggest that some of these compounds may be of further therapeutic value as tranquilizers, sedatives, hypnotics and agents influencing abnormal behavior.

The novel compounds of this invention are

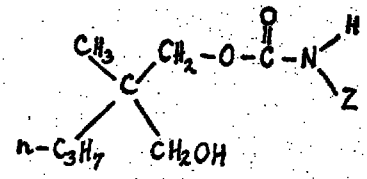
preferably administered orally in the form of pills, tablets or capsules, formed by well-known procedures. A typical composition comprises the active ingredient, intermixed in a dry pulverulent state with gelatin, starch, magnesium stearate and alginic acid, pressed into a tablet. The active ingredient may also be dissolved in a suitable solution. An effective dose of the active ingredient generally is in the range of 0.05 grams to 2.0 grams.

WHAT WE CLAIM IS:—

1. Method of manufacturing N-monosubstituted dicarbamates of the general formula:



wherein X is an ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl or allyl radical, which method comprises reacting a monocarbamate of the general formula:



wherein Z is a hydrogen atom or an aliphatic hydrocarbon radical selected from an ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl or allyl radical, with a carbamating agent, the carbamating agent being an alkyl isocyanate or phosgenes followed by an aliphatic amine containing from 2 to 4 carbon atoms in the case where Z is a hydrogen atom, and the carbamating agent being cyanic acid, a carbamic ester of a low boiling alcohol, or phosgene followed by ammonia in the case where Z is an aliphatic hydrocarbon radical.

2. N - *n* - propyl - 2 - methyl - 2 - *n*-propyl - 1,3 - propanediol dicarbamate.

3. N - *iso*propyl - 2 - methyl - 2 - *n*-propyl - 1,3 - propanediol dicarbamate.

4. N - *n* - butyl - 2 - methyl - 2 - *n*-propyl - 1,3 - propanediol dicarbamate.

5. N - ethyl - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate.

6. N - *iso*butyl - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate.

7. N - allyl - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate.

8. The method of manufacturing an N-monosubstituted - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate substantially as hereinbefore described with reference to any one of Examples 1 to 10.

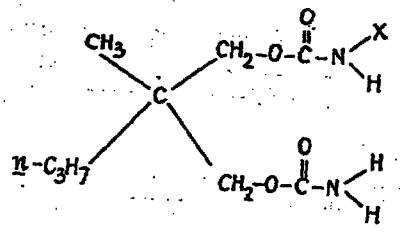
HASELTINE, LAKE & CO.,
Chartered Patent Agents,
28, Southampton Buildings,
Chancery Lane, London, W.C.2,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1961.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

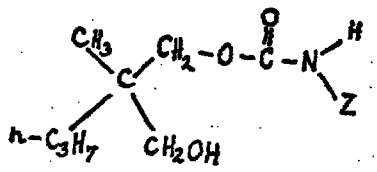
preferably administered orally in the form of pills, tablets or capsules, formed by well-known procedures. A typical composition comprises the active ingredient, intermixed in a dry pulverulent state with gelatin, starch, magnesium stearate and alginic acid, pressed into a tablet. The active ingredient may also be dissolved in a suitable solution. An effective dose of the active ingredient generally is in the range of 0.05 grams to 2.0 grams.

WHAT WE CLAIM IS:—

1. Method of manufacturing N-monosubstituted dicarbamates of the general formula:



wherein X is an ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl or allyl radical, which method comprises reacting a monocarbamate of the general formula:



wherein Z is a hydrogen atom or an aliphatic hydrocarbon radical selected from an ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl or allyl radical, with a carbamating agent, the carbamating agent being an alkyl isocyanate or phosgenes followed by an aliphatic amine containing from 2 to 4 carbon atoms in the case where Z is a hydrogen atom, and the carbamating agent being cyanic acid, a carbamic ester of a low boiling alcohol, or phosgene followed by ammonia in the case where Z is an aliphatic hydrocarbon radical.

2. N - *n* - propyl - 2 - methyl - 2 - *n*-propyl - 1,3 - propanediol dicarbamate.

3. N - *iso*propyl - 2 - methyl - 2 - *n*-propyl - 1,3 - propanediol dicarbamate.

4. N - *n* - butyl - 2 - methyl - 2 - *n*-propyl - 1,3 - propanediol dicarbamate.

5. N - ethyl - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate.

6. N - *iso*butyl - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate.

7. N - allyl - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate.

8. The method of manufacturing an N-monosubstituted - 2 - methyl - 2 - *n* - propyl-1,3 - propanediol dicarbamate substantially as hereinbefore described with reference to any one of Examples 1 to 10.

HASELTINE, LAKE & CO.,
Chartered Patent Agents,
28, Southampton Buildings,
Chancery Lane, London, W.C.2,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1961.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

