Carbamate Derivatives Related to Meprobamate

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A series of 2-substituted 1,3-propanediol dicarbamates, related chemically to meprobamate, has been prepared for central nervous system pharmacological investigation. The N-unsubstituted propanediol dicarbamates were obtained by an ester-exchange reaction between the corresponding diol and urethan, by phosgenation of the diol followed by ammoniation of the bis(chlorocarbonate) derivative, by the reaction of the diol with cyanic acid, and by ammoniation of the bis(phenylcarbonate) derivative of the appropriate diol. The symmetrically N,N′-substituted propanediol dicarbamates were synthesized by direct carbamoylation of the propanediols, and the unsymmetrically substituted derivatives by stepwise carbamoylation *via* the *m*-dioxanone and hydroxypropyl carbamate intermediates using similar carbamoylation reactions. In addition to the preparation and physical properties of these compounds, the muscle paralyzing activity, anticonvulsant activity, and toxicity of these carbamates and many of the intermediates employed in their synthesis are presented. Structure-activity relationships among these compounds are discussed.

Meprobamate, 2-methyl-2-propyl-1,3-propanediol dicarbamate, was first synthesized by Ludwig and Piech in 1951.[1] These workers prepared a series of nine dicarbamates of 2,2-disubstituted 1,3-propanediols as part of a program to modify chemically a variety of substituted propanediols and glycerol ethers. Of the carbamate derivatives prepared, 2-methyl-2-propyl-1,3-propanediol dicarbamate was unusual in possessing pronounced muscle relaxant and anticonvulsant activity and in exerting a marked taming effect on monkeys.[2] Replacement of one or more of the hydrogens of the carbamate nitrogens of propanediol dicarbamates resulted in compounds possessing central muscle relaxant action different from that of the parent carbamates. Compounds in which only one of the carbamate hydrogens was replaced by a short-chain alkyl group were found to possess potent muscle-relaxant activity. Carisoprodol, N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate, was found to be the compound of choice among these derivatives.[3]

This paper describes the preparation of a series of N-unsubstituted and N-substituted 1,3-propanediol dicarbamates related to meprobamate and carisoprodol and compares their muscle paralyzing action, anticonvulsant activity, and toxicity. The activities of the propanediols from which they are derived and many of the intermediate compounds obtained in the synthesis of the dicarbamate compounds are also presented.

The 1,3-propanediols (I) used as starting materials in the preparation of both the propanediol N-unsubstituted and N-substituted dicarbamates were obtained from commercial sources or by LAH reduction of the appropriate malonates.

The procedures employed for the conversion of these diols to the various N-unsubstituted and N-substituted carbamate esters are outlined in Scheme I. Of greatest convenience for the preparation of N-unsubstituted (II) and symmetrically N-substituted dicarbamates (III, IV) was the method described by Ludwig and Piech,[1] who used low-temperature phosgenation in the presence of a tertiary amine as acid acceptor to obtain the corresponding chlorocarbonate, generally in good yield (method A). Tetrahydrofuran also served as an excellent medium for conducting this phosgenation.[4] The bis(chlorocarbonates) could be readily isolated and purified by distillation under reduced pressure, but for most purposes they were advantageously ammoniated or aminated without isolation.

Most N-unsubstituted dicarbamates could also be formed from the diol through an ester-exchange reaction with a low molecular weight alcohol carbamate such as urethan (method B). The application of this method for the preparation of benzyl carbamate was first described by Kraft.[5] When used in the preparation of propanediol dicarbamates, the ethanol contained in 2 moles of urethan is replaced by the diol to give the desired dicarbamate in excellent yield.[6]

A third method which proved effective for the conversion of diols to N-unsubstituted dicarbamates was the use of cyanic acid formed *in situ* by the action of dry HCl on sodium cyanate suspended in chloroform or trichloroethylene at 0° (method C).[7] Loev and Kormendy[8] have reported the advantageous use of trifluoroacetic acid in place of HCl in this reaction.

Alternate methods for the formation of N-unsubstituted dicarbamates of substituted propanediols have also been explored. Reaction of the diol with urea at controlled elevated temperatures usually gave low yields of the desired carbamates whose work-up was complicated by the presence in the reaction mixture of urea condensation products and high molecular weight by-products.[9] The conversion of diols to their phenylcarbonate esters using phenylchloroformate in the presence of an acid acceptor, followed by ammonolysis, produced good yields of dicarbamates (method D). This more lengthy procedure proved to be especially suitable when applied to secondary and tertiary carbinols. McLamore, *et al.*,[10] found this procedure of value in the synthesis of unsaturated tertiary carbinol

(1) B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5779 (1951).

(2) For a description of the pharmacological properties of meprobamate and some of the related carbamate compounds described here, see (a) F. M. Berger, *J. Pharmacol. Exp. Ther.*, **104**, 229 (1952); (b) F. M. Berger, *ibid.*, **112**, 413 (1954); (c) F. M. Berger, C. D. Hendley, B. J. Ludwig and T. E. Lynes, *ibid.*, **116**, 337 (1956); (d) F. M. Berger, *Intern. Rec. Med.*, **169**, 184 (1956).

(3) (a) F. M. Berger and B. J. Ludwig, U. S. Patent 2,937,119 (1960); (b) F. M. Berger, M. Kletzkin, B. J. Ludwig, S. Margolin, and L. S. Powell, *J. Pharmacol. Exp. Ther.*, **127**, 66 (1959).

(4) (a) M. Katz and E. L. Whittbecker, U. S. Patent 2,787,630 (1957); (b) A. O. Geiszler and M. A. Spielman, U. S. Patent 2,806,053 (1957).

(5) W. M. Kraft, *J. Am. Chem. Soc.*, **70**, 3569 (1948).

(6) F. M. Berger and B. J. Ludwig, U. S. Patent 3,059,022 (1962).

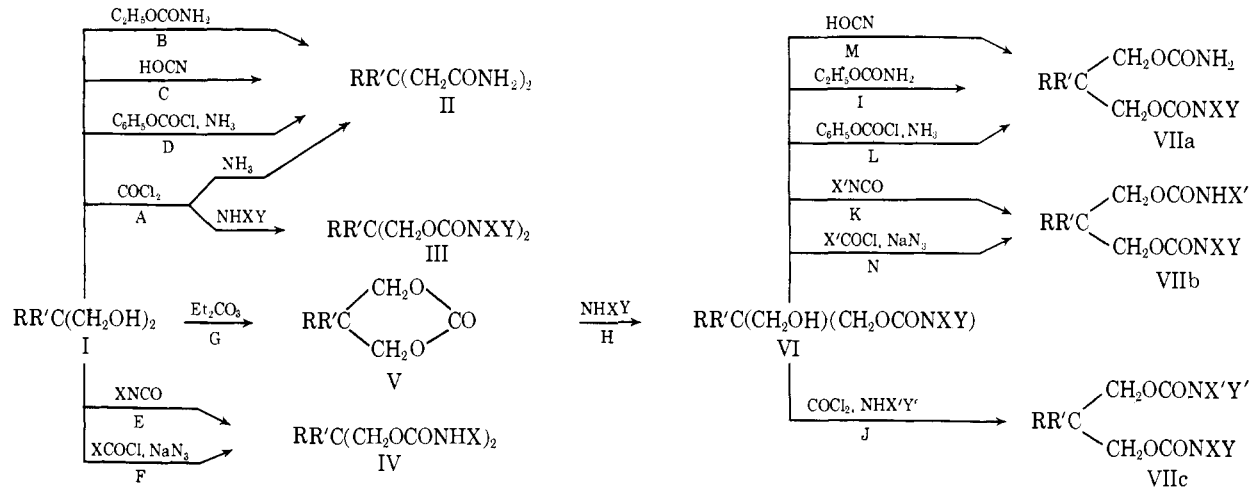
(7) Lepetit S.p.A., Swiss Patent 359,126 (1962).

(8) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).

(9) G. Ferrari, *Chim. Ind.* (Milan), **40**, 13 (1958); Y. Liwschitz, *Bull. Res. Council Israel*, **4**, 81 (1954), employed this method to obtain high yields of benzyl carbamate.

(10) W. M. McLamore, S. Y. P'an, and A. Bavley, *J. Org. Chem.*, **20**, 1379 (1955).

SCHEME I



R, R' = H, alkyl, aryl; X, X', Y, Y' = alkyl, aryl

carbamates. We were unsuccessful, however, in preparing the dicarbamate of 2-*t*-amyl-1,3-propanediol using this method, probably because of the hindering effect of the tertiary amyl group.

The formation of dicarbamates symmetrically substituted but bearing only a single substituent on each nitrogen (IV) was also accomplished by treating the diol with 2 equiv of alkyl or aryl isocyanate (method E). It is of interest that the ester-exchange method, extremely useful in preparing N-unsubstituted dicarbamates, fails when the urethan used to effect the exchange bears a nitrogen substituent. An attempted interchange between N-methylurethan and a hydroxypropyl carbamate, using aluminum isopropoxide as catalyst, failed to give the desired N-methylcarbamate but led to a disproportionation of the monocarbamate to the corresponding dicarbamate and the diol. Although the precise role of aluminum isopropoxide in this exchange reaction was not thoroughly explored, the ability of this catalyst to promote this disproportionation was confirmed in separate experiments.

Symmetrical N-monoalkylated dicarbamates of this type were also prepared by utilizing the Curtius reaction to obtain a solution of the required acyl azide which, when slowly added to a refluxing solution of the diol, is converted *in situ* to the isocyanate which in turn reacts with the diol to give the dicarbamate (method F).[11]

Monocarbamates of substituted 1,3-propanediols (VI) have been successfully prepared by controlled phosgenation of the diol followed by amidation.[1] Because of the difficulty sometimes encountered in working up the product resulting from the action of NH_3 or amines on this phosgenation reaction mixture, the hydroxypropyl carbamates were usually more readily obtained *via* the intermediate cyclic carbonate ester (*m*-dioxanone). However, the phosgene method proved to be the only means available for the preparation of the monocarbamate of 2-phenyl-1,3-propanediol. We were unable to convert this diol to its cyclic carbonate by the usual ester-exchange method.

The cyclic carbonates (V) were readily obtained by heating the diol in xylene with a slight excess of diethyl carbonate and a catalytic amount of NaOMe[3a] (method G). The carbonates were converted to the desired monocarbamates by reaction with aqueous or anhydrous NH_3 or amine (method H). The cyclic carbonates were also found to react with hydrazine in a similar manner to give the corresponding carbazates.

N-Substituted monocarbamates bearing one N substituent (VI, Y = H) were in some instances obtainable by the reaction of 2 moles of diol with 1 mole of alkyl or aryl isocyanate.

The unsymmetrical N-substituted dicarbamates (VIIa, VIIb, VIIc) were prepared from the N-unsubstituted or 3-hydroxypropyl N-substituted carbamates by carbamoylation, using ester interchange (method I), phosgenation–amidation (method J), isocyanation (method K), phenyl chloroformate–amidation (method L), cyanic acid (method M), or by the Curtius reaction described earlier (method N), the key intermediate in each case being the appropriate 2-substituted 3-hydroxypropyl carbamate (VI).

In addition to the numerous N-alkyl- and N-arylcarbamate derivatives prepared in this study, a number of N-acyl derivatives were synthesized for pharmacological evaluation (method O). Additional 1,3-propanediol dicarbamates having miscellaneous substituents attached to the carbamate nitrogens were also synthesized for evaluation. The preparation of representative compounds of these types is included in the Experimental Section.

The majority of the compounds prepared in these studies are relatively low-melting, stable crystalline solids. Many of the 1,3-propanediols were obtained as high-boiling liquids. The solubility of these diols in water ranged from about 5% downward. The hydroxypropyl carbamates are usually more water soluble than their dicarbamate counterparts. The noncrystallizable members of this group could be readily purified by distillation under reduced pressure. The 1,3-propanediol N-unsubstituted dicarbamates are crystalline solids having a limited solubility in water (0.1% or less). N-Alkyl substitution resulted in decreased water solubility and usually gave noncrystalline compounds which were purified by molecular distillation. Where acylation of these liquid derivatives is possible, readily crystallizable solids are obtained.

The water solubility of compound **62**, the tricarbamate of 2-methyl-2-β-hydroxypropyl-1,3-propanediol,

(11) L. S. Powell, U. S. Patent 3,092,656 (1963).

is of interest. The dicarbamate from which this tricarbamate is derived, 2-methyl-2-β-hydroxypropyl-1,3-propanediol dicarbamate, is the major metabolite of meprobamate.[12] Both the metabolite and its fully carbamoylated derivative dissolve in water in excess of 10% and are essentially devoid of pharmacological activity. The extreme solubility of this tricarbamate as compared to that of meprobamate supports the postulate that the 1,3-propanediol N-unsubstituted dicarbamates owe their limited water solubility to internal hydrogen bonding between the carbamate moieties.

The 1,3-propanediol mono- and dicarbamates unsubstituted or substituted at the amide nitrogen position are generally resistant to hydrolysis. Unlike urethan and similar alkyl monocarbamates, these compounds require extensive refluxing in mineral acid or strong alkali to effect complete hydrolysis.

The physical constants, analytical data, and pharmacological screening data for the numerous carbamate compounds and for the propanediols and various intermediates employed in their syntheses are summarized in Tables I-VI.

Pharmacology.—The most characteristic and best known pharmacological property of these compounds is their ability to produce relaxation of the voluntary muscles. This effect is produced by an action on the central nervous system and comes about by inhibition of the interneurons. The compounds of this study have no significant peripheral action and do not interfere with neuromuscular transmission in the myoneuronal junction. Because muscular relaxation is difficult to evaluate quantitatively, we measured instead the paralyzing effect of these compounds. Paralysis produced by these compounds is completely reversible. It is an extreme form of muscular relaxation and can be evaluated objectively by measuring the incidence and duration of the loss of righting reflex resulting from the intraperitoneal administration of drugs.[13] With this technique graded doses of the drugs are given intraperitoneally to groups of mice and the dose that produced a loss of righting reflex for a duration of more than 1 min in 50% of the animals is determined. The mortality occurring 7 days after administration of the compounds was used in calculating the LD_{50} dose.

The anticonvulsant activity of the compounds was measured by determining the dose which upon oral administration prevents the appearance of the extensor tonic phase of electroshock seizures in 50% of mice.[14]

2-Substituted 1,3-Propanediols.—The most effective paralyzing agent of this type with a single substituent was 2-(1-methylbutyl)-1,3-propanediol (**5**). Compounds with a shorter or differently branched chain were less active. None of the singly substituted compounds produced remarkable anticonvulsant action. Several of the 2,2-dialkyl-1,3-propanediols showed good paralyzing activity, and this appeared to be greatest when one of the substituents was methyl and the other a 5-alkyl (**17–20**). When one of the substituents was ethyl, maximum activity was obtained when the second substituent was a 4- or 5-alkyl (**25, 26, 29**). All of these more active paralyzing compounds also possessed some anticonvulsant action.

2-Substituted 1,3-Propanediol Dicarbamates.—None of the compounds with a single 2-substituent possessed strong paralyzing action. The *sec*-butyl, 1-methylbutyl, and 1-ethylpropyl compounds (**44, 48, 50**) were most potent in this respect. The presence of an aromatic group in the 2 position nullified all paralyzing action but in some cases enhanced anticonvulsant activity (**54**).

Some of the 2,2-dialkyl-1,3-propanediol dicarbamates possessed strong paralyzing action. Of these, the methyl-*sec*-butyl and methyl-1-ethylpropyl derivatives (**67, 73**) had the most potent action and in this respect were equal or superior to meprobamate (**61**). The greatest activity was shown by compounds having alkyl groups in the 2 position containing a total of five to seven carbon atoms. Introduction of an aromatic group in this position failed to enhance paralyzing activity, but the presence of both a methyl and a phenyl group gave a compound having greatly increased anticonvulsant activity (**75**). Compounds having substituents in the 2 position containing N, Cl, and S and those derivatives having alkylene or alkyne substituents in this position possessed insignificant paralyzing and anticonvulsant action.

2-Substituted 3-Hydroxypropyl Carbamates.—N-Unsubstituted compounds of this type having 4- or 5-alkyls showed good paralyzing activity (**110, 140, 153**). As before, one aromatic group in the 2 position gave compounds of increased anticonvulsant activity (**111**), but this substitution also resulted in a diminution of paralyzing activity.

Attaching an alkyl group to the carbamate nitrogen produced compounds with appreciable paralyzing activity, and ethyl and propyl substitution in this manner produced compounds of high activity (**119, 151**). It is of interest that the N substitution with one CH_3 or C_2H_5 group produced strong paralyzing activity in 2,2-diphenyl substituted compounds (**162, 163**). This activity contrasts with the low paralyzing action of 2,2-diphenyl-1,3-propanediol N-unsubstituted dicarbamate. N substitution with *i*-Pr or Pr (**164, 165**) or the use of tolyl in place of C_6H_5 in the 2 position (**167**) resulted in loss of activity. The N,N-dimethyl analogs of 2,2-dialkyl compounds possessed good paralyzing activity (**133, 159**), but this was lost when two groups larger than CH_3 were used. Introduction of a single allyl group improved activity (**121**), but this enhancement of activity did not occur when substitution was made with propynyl, 2-butenyl, or methallyl (**122, 126, 127**).

1,3-Propanediol N-Substituted Dicarbamates.—Replacement of one of the carbamoyl hydrogens by a single short-chain alkyl group yielded a number of compounds with good paralyzing activity (*e.g.*, **191, 211, 218, 235**) but similar substitution with Ph or $PhCH_2$ gave inactive derivatives. Introduction of a single unsaturated hydrocarbon group in this manner yielded several compounds having good paralyzing activity (such as **193, 220, 221, 226**). The intensity of this activity was affected to some extent by the nature of the 2 substituents.

The introduction of two alkyl groups on one N or a

(12) B. J. Ludwig, J. F. Douglas, L. S. Powell, M. Meyer, and F. M. Berger, *J. Med. Pharm. Chem.*, **3**, 53 (1961).

(13) (a) F. M. Berger and W. Bradley, *Brit. J. Pharmacol.*, **1**, 265 (1946); (b) F. M. Berger in "Methods in Drug Evaluation," P. Manteguzza and F. Piccinini, Ed., North-Holland Publishing Co., Amsterdam, 1966, pp 218–235.

(14) J. E. P. Toman, E. A. Swinyard, and L. S. Goodman, *J. Neurophysiol.*, **9**, 231 (1946).

TABLE I

2-SUBSTITUTED 1,3-PROPANEDIOLS[a]

$RR_1C(CH_2OH)_2$

No.	R	R_1	Yield, %	Mp or bp (mm), °C	$n^{25}D$	Formula	Analyses	Dose, mg/kg[b] PD_{50}	ED_{50}	LD_{50}
1	H	*i*-Pr	60	80–83 (0.5)	1.4482	$C_6H_{14}O_2$	C, H	>620	>280	>620
2	H	*i*-Bu	87	82–86 (0.3)	1.4470	$C_7H_{16}O_2$	C, H[c]	>280	>420	>280
3	H	*t*-Bu	59	59–61		$C_7H_{16}O_2$	C, H	>280	<420	>280
4	H	Am	73	100–106 (0.2)	1.4506	$C_8H_{18}O_2$	C; H[d]	225	>420	360
5	H	1-Methylbutyl	70	95–98 (0.5)	1.4560	$C_8H_{18}O_2$	C; H[e]	180	670	570
6	H	3-Methylbutyl	81	104–106 (0.4)	1.4482	$C_8H_{18}O_2$	C, H	280	280 (ip)	>280
7	H	1-Ethylpropyl	41	82–85 (0.02)	1.4545	$C_8H_{18}O_2$	H; C[f]	280	>180 (ip)	>280
8	H	2-Cyclopentenyl	70	38.5–40		$C_8H_{14}O_2$	H; C[g]	>420	355 (ip)	
9	H	C_6H_{13}	63	30–32		$C_9H_{20}O_2$	C; H[h]			
10	H	Cyclohexyl	80	90–92		$C_9H_{18}O_2$	C, H	>280		>250
11	H	*p*-Tolyl	34	55.5–56		$C_{10}H_{14}O_2$	C, H	355	355 (ip)	>420
12	H	3-Phenylpropyl	80	43–44		$C_{12}H_{18}O_2$	C, H	>180	>620	>280
13	Me	Allyl	82	119–120 (10)	1.4649	$C_7H_{14}O_2$	C, H	>280	>280	>280
14	Me	2-Propynyl	71	68.5–69.5		$C_7H_{12}O_2$	C, H	>420	>420	>420
15	Me	*i*-Bu	82	87–92 (0.3)		$C_8H_{18}O_2$	H; C[i]	310	490	780
16	Me	*t*-Bu	75	192.5–194		$C_8H_{18}O_2$	C, H	355	345	570
17	Me	Am	50	51–52.5		$C_9H_{20}O_2$	C, H	130	550	260
18	Me	1-Methylbutyl	90	150–151 (14)		$C_9H_{20}O_2$	H; C[j]	120	375	390
19	Me	3-Methylbutyl	78	68–70.5		$C_9H_{20}O_2$	C, H	149	389	>280
20[k]	Me	1-Ethylpropyl	70	45–48		$C_9H_{20}O_2$		147	295	>280
21	Me	Cyclohexyl	87	79–80		$C_{10}H_{20}O_2$	C, H			
22	Me	*p*-$ClC_6H_4CH_2$	67	67–68		$C_{11}H_{15}O_2Cl$	C, H			
23[l]	Et	$ClCH_2$	9	65.5–66		$C_6H_{13}O_2Cl$	Cl			
24[m]	Et	Pr	74	37–39		$C_8H_{18}O_2$		185	295	550
25	Et	*sec*-Bu	84	90–91 (0.08)	1.4665	$C_9H_{20}O_2$	C, H	120	330	420
26	Et	*i*-Bu	83	95–97 (0.1)	1.4598	$C_9H_{20}O_2$	C, H	150	510	250
27	Et	Am	77	91–94 (0.025)	1.4585	$C_{10}H_{22}O_2$	C, H	280	>280	>280
28	Et	3-Methylbutyl	75	41–42		$C_{10}H_{22}O_2$	C, H	>280	>280	>280
29[k]	Et	1-Ethylpropyl	87	76–77 (0.02)	1.4643	$C_{10}H_{22}O_2$		138	280	>280
30	Et	Cyclohexyl	60	59.5–61		$C_{11}H_{22}O_2$	C, H	230	>180 (ip)	>280
31	Et	PhO	80	51–53		$C_{11}H_{16}O_3$	H; C[n]			
32[l]	Et	*p*-NO_2Ph	35	98–100		$C_{11}H_{15}NO_4$	N	340	225	>420
33[l]	Et	*p*-H_2NPh	53	188–190 dec[o]		$C_{11}H_{18}NO_2Br$	Br	>620	280 (ip)	>620
34[p]	Et	*p*-ClPh	41	97–99		$C_{11}H_{15}O_2Cl$	C, H	212		680
35[l]	Et	*p*-Butylmercaptophenyl		64–65		$C_{18}H_{24}O_2S$	C, H, S	>620	>620	>620
36[l]	Pr	Dimethylaminomethyl		95–97 (0.02)	1.4637	$C_9H_{21}NO_2$	N	325		325
37	Pr	1-Ethylpropyl	92	86–88 (0.02)	1.4666	$C_{11}H_{24}O_2$	H; C[q]	212		810
38[l]	*p*-Tolyl	*p*-Tolyl	38	119–120		$C_{17}H_{20}O_2$	C, H	>280	>280	>280

[a] Prepared from corresponding malonate unless otherwise noted. [b] The PD_{50} is the dose that produces a loss of righting reflex for a duration of more than 1 min in 50% of the animals. The ED_{50} is the oral dose preventing the appearance of the extensor tonic phase of electroshock seizures in 50% of the animals. The LD_{50} was calculated by the mortality occurring 7 days after the administration of compounds. See the text for more information. [c] C: calcd, 63.60; found, 64.49. H: calcd, 12.20; found, 11.63. [d] H: calcd, 12.41; found, 11.93. [e] H: calcd, 12.41; found, 11.90. [f] C: calcd, 65.71; found, 66.47. [g] C: calcd, 67.57; found, 66.25. [h] H: calcd, 12.58; found, 12.09. [i] C: calcd, 65.71; found, 64.99. [j] C: calcd, 67.45; found, 67.88. [k] F. M. Berger and B. J. Ludwig, U. S. Patent 3,059,022 (1962). [l] See Experimental Section. [m] See ref 3a. [n] C: calcd, 67.32; found, 68.19. [o] HBr salt. [p] Prepared by the crossed Cannizzaro reaction of α-*p*-chlorophenylbutyraldehyde and HCHO by the method of F. C. Whitmore, A. H. Popkin, H. I. Bernstein, and J. P. Wilkins, *J. Am. Chem. Soc.*, **63**, 124 (1941). [q] C: calcd, 70.16; found, 71.34.

single alkyl group on each N failed to yield compounds of significant effectiveness. The use of bulky groups such as xanthyl (**285**, **286**) likewise did not increase effectiveness. Introduction of three or four alkyl substituents attached to the carbamate nitrogens as a rule did not yield compounds having interesting activities, with the exception of a tetramethyl derivative (**304**) which showed good paralyzing activity. N-Acylated derivatives of N-unsubstituted and N-substituted dicarbamate compounds were invariably inactive. Compounds wherein the carbamate N was substituted with a carboxy-, hydroxy-, or haloalkyl possessed insignificant activity, and, with the exception of the isopropylcarbazates (**315**, **319**), none of the N-amino-, N-alkoxy-, N-hydroxy-, N-carbamyl-, N-nitro-, or N-sulfonylcarbamates displayed interesting paralyzing or anticonvulsant activity.

Experimental Section[15]

All melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

Preparation of Substituted 1,3-Propanediols (I).—The diols obtained from commercial sources were used without further purification. Most of the diols used in this study, including those not previously described, were prepared by LAH reduction of the corresponding malonate esters.[16] The crossed Cannizzaro reaction of the appropriate aldehyde with HCHO was also employed.[17] The preparation of those diols requiring special methods is described individually. Table I lists the diols prepared for this study which are unreported in the literature.

2-Ethyl-2-*p*-nitrophenyl-1,3-propanediol (32).—The diacetate of 2-ethyl-2-phenyl-1,3-propanediol was prepared by refluxing the diol for 20 min with excess Ac_2O containing a trace of H_2SO_4; bp 132–134° (0.1 mm), $n^{25}D$ 1.4975. Nitration of this ester according to the method of Bousquet and Adams[18] gave 2-ethyl-2-*p*-nitrophenyl-1,3-propanediol diacetate which was hydrolyzed to the corresponding diol by refluxing in an excess of 10% HCl for 1.5 hr. The product was purified by crystallization (C_6H_6).

2-Ethyl-2-*p*-aminophenyl-1,3-propanediol (33).—2-Ethyl-2-*p*-nitrophenyl-1,3-propanediol diacetate was reduced at 2 atm of H_2 using PtO_2 catalyst. The product was saponified without isolation by refluxing with aqueous KOH for 5 hr to obtain the amine which was isolated as the HBr salt.

2-Ethyl-2-(*p*-*n*-butylmercaptophenyl)-1,3-propanediol (35).—

(15) Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Galbraith Laboratories, Inc., Knoxville, Tenn.

(16) W. G. Brown, *Org. Reactions*, **6**, 469 (1951).

(17) R. W. Shortridge, R. A. Craig, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **70**, 946 (1948).

(18) E. W. Bousquet and R. Adams, *ibid.*, **52**, 224 (1930).

TABLE II

2-SUBSTITUTED 1,3-PROPANEDIOL DICARBAMATES

$RR_1C(CH_2OCONH_2)_2$

No.	R	R_1	Method	Yield, %	Mp, °C	Formula	Analyses	Dose, mg/kg — PD_{50}	ED_{50}	LD_{50}
39	H	Me	B	60	187–188	$C_6H_{12}N_2O_4$	N	>3200	>3200	>3200
40	H	Et	B	64	178–179	$C_7H_{14}N_2O_4$	N	>3200	1200	>3200
41	H	Pr	B	30	118–120	$C_8H_{16}N_2O_4$	N	660	140	1100
42	H	*i*-Pr	B	58	164–165	$C_8H_{16}N_2O_4$	N	>3200	630	>3200
43[b]	H	Bu	B	46	137–138.5	$C_9H_{18}N_2O_4$	N	1215	162	1920
44[b]	H	*sec*-Bu	B	43	113–115	$C_9H_{18}N_2O_4$	N	530	225	1100
45[b]	H	*i*-Bu	B	55	145–146.5	$C_9H_{18}N_2O_4$	N	1280	190	3200
46[b]	H	*t*-Bu	C	90	109–111	$C_9H_{18}N_2O_4$	N	760	420	1140
47	H	Am	B	70	131–132	$C_{10}H_{20}N_2O_4$	N[c]	730	260	1650
48	H	1-Methylbutyl	B	50	113–115	$C_{10}H_{20}N_2O_4$	N	585	330	1160
49	H	3-Methylbutyl	B	45	151.5–153	$C_{10}H_{20}N_2O_4$	N	>3200	855	>3200
50	H	1-Ethylpropyl	B	30	110–111	$C_{10}H_{20}N_2O_4$	N	420	<180	>420
51	H	C_8H_{13}	B	51	124–125.5	$C_{11}H_{22}N_2O_4$	N	1725	1400	3200
52	H	C_7H_{15}	B	60	134–135	$C_{12}H_{24}N_2O_4$	N	>280	>280	>280
53	H	2-Cyclopentenyl	B	22	148–149.5	$C_{10}H_{16}N_2O_4$	N[d]	>420	280 (ip)	>420
54[e]	H	Ph	B	40	151–152	$C_{11}H_{14}N_2O_4$		2200	52	4000
55	H	PhO	B	40	134–135	$C_{10}H_{14}N_2O_5$	N[f]	>620	>620	>620
56	H	Cyclohexyl	B	38	170.5–172	$C_{11}H_{20}N_2O_4$	N	>3200	>3200	>3200
57	H	*p*-Tolyl	B	37	153–154	$C_{12}H_{16}N_2O_4$	N	>420	>420	>420
58	H	$PhCH_2$	B	93	176–176.5	$C_{12}H_{16}N_2O_4$	N[g]	>3200	620	>3200
59	H	3-Phenylpropyl	B	36	118–120	$C_{14}H_{20}N_2O_4$	N	>3200	620	>3200
60	Et	$ClCH_2$	C	75	188–188.5	$C_6H_{13}ClN_2O_4$	N	>620	>620	>620
61[h]	Me	Pr	A		105–106	$C_8H_{16}N_2O_4$		235	165	800
62	Me	2-Carbamoyloxypropyl	C	35	72–74	$C_9H_{17}N_3O_6$	C, H, N			
63	Me	1-Propenyl	C	40	151–152	$C_9H_{16}N_2O_4$	N	620	280	>620
64	Me	Allyl	B	19	116–118	$C_8H_{14}N_2O_4$	N[i]	>280	>280 (ip)	>280
65	Me	2-Propynyl	B	50	124–125.5	$C_9H_{14}N_2O_4$	N[j]	>420	>420	>420
66	Me	Bu	B	42	112–113	$C_{10}H_{20}N_2O_4$	N	530	285	1050
67[k]	Me	*sec*-Bu	B	66	77–79	$C_{10}H_{20}N_2O_4$		175	290	460
68	Me	*i*-Bu	B	24	77–79	$C_{10}H_{20}N_2O_4$	N	280	235	660
69	Me	*t*-Bu	B	13	118–119	$C_{10}H_{20}N_2O_4$	N	440	345	690
70	Me	1-Methylallyl	C	73	83–86	$C_9H_{16}N_2O_4$	N			
71	Me	Am	B	61	94–96	$C_{11}H_{22}N_2O_4$		360	340	1500
72	Me	1-Methylbutyl	B	19	107–109	$C_{11}H_{22}N_2O_4$		390	375	800
73[l]	Me	1-Ethylpropyl	B	7	118–120	$C_{11}H_{22}N_2O_4$		175	280	490
74	Me	3-Methylbutyl	B	40	112–114	$C_{11}H_{22}N_2O_4$		475	470	2600
75	Me	Ph	C	75	110–111.5	$C_{12}H_{16}N_2O_4$	N[m]	380	102	620
76[n]	Me	*p*-$ClPhCH_2$	B	35	181–183	$C_{19}H_{17}N_2O_4Cl$		>420	>420	>420
77[o]	Me	Cyclohexyl	B	72	153–155	$C_{12}H_{22}N_2O_4$		>420	>420 (ip)	>420
78[p]	Me	$PhCH_2$	C	25	170–171	$C_{13}H_{18}N_2O_4$		>620	>620	
79	Me	O_2N	A	35	151–153	$C_7H_{13}N_3O_8$	N			
80	Et	Diethylaminomethyl	C	36	115	$C_{12}H_{25}N_3O_4$	N	>620	>420	420
81	Et	EtO	B	50	142–143	$C_8H_{16}N_2O_5$	N	>1400		>1400
82	Et	Pr	B	61	115–117	$C_9H_{18}N_2O_4$	N	620	365	590
83	Et	*i*-Pr	B	33	109–110	$C_9H_{18}N_2O_4$	N	250	320	700
84	Et	Allyl	C	62	106–108	$C_9H_{16}N_2O_4$	N	420		720
85	Et	*sec*-Bu	B	56	119–120	$C_{11}H_{22}N_2O_4$	N	315	360	700
86	Et	*i*-Bu	B	34	115–116	$C_{11}H_{22}N_2O_4$	N	525	770	1100
87	Et	Am	B	15	128–129	$C_{12}H_{24}N_2O_4$		730	315	1010
88	Et	1-Methylbutyl	D	19	108–109	$C_{12}H_{24}N_2O_4$		300	225	510
89	Et	3-Methylbutyl	B	20	149–150	$C_{12}H_{24}N_2O_4$		>420	>420	>420
90[l]	Et	1-Ethylpropyl	B	33	119–121	$C_{12}H_{24}N_2O_4$		>420	>420	>420
91	Et	Cyclohexyl	B	48	168–170	$C_{13}H_{24}N_2O_4$	N	>420	>420 (ip)	>420
92	Et	3-Thienyl	B	38	110–113	$C_{11}H_{16}N_2O_4S$	N, S	>420	>420 (ip)	>420
93	Et	*p*-O_2NPh	D	14	160–163	$C_{19}H_{17}N_3O_8$	N	>620	>620	
94	Et	*p*-H_2NPh	G	30	136–138	$C_{19}H_{19}N_3O_4$	N	>620	>620	
95	Et	*p*-Butylmercaptophenyl	C	40	71–76	$C_{17}H_{26}N_2O_4S$	C, H, S	620		735
96	Pr	Cl	C	65	125–126	$C_8H_{15}ClN_2O_4$	C, H, N, Cl			
97	*i*-Pr	*i*-Pr	B	20	139–140	$C_{10}H_{22}N_2O_4$	N	900	670	770
98	Bu	Bu	B	70	157–158	$C_{12}H_{26}N_2O_4$	N	>3200	>3200	>3200
99	Ph	Ph	D	76	167–168	$C_{17}H_{18}N_2O_4$	C, H, N	>3200	1400	4700
100	*p*-MePh	*p*-MePh	D	27	210–212	$C_{19}H_{22}N_2O_4$	N	>420	>420	>420
101	$PhCH_2$	$PhCH_2$	B	13	168.5–170	$C_{19}H_{22}N_2O_4$	N	>3200	>3200	>3200
102	Propylidene		C	40	130–131	$C_9H_{14}N_2O_4$	N	1060		160
103	$(CH_2)_2$		D	Poor	216–218	$C_7H_{12}N_2O_4$	N			
104	$(CH_2)_3$		D	70	189–191	$C_8H_{14}N_2O_4$	N			
105[b]	$(CH_2)_4$		B	50	165–166	$C_9H_{16}N_2O_4$	N	1570	490	2400

[a] Footnote *b* in Table I. [b] Reference 2c reported the central depressant and anticonvulsant activity but not the preparation of these compounds. [c] N: calcd, 12.06; found, 12.53. [d] N: calcd, 12.27; found, 13.03. [e] F. M. Berger and B. J. Ludwig, U. S. Patent 2,884,444 (1959). [f] N: calcd, 11.02; found, 11.54. [g] N: calcd, 11.10; found, 11.63. [h] Mephobamate, see ref 1. [i] N: calcd, 12.95; found, 13.50. [j] N: calcd, 13.08; found, 13.50. [k] Mebutamate [F. M. Berger and B. J. Ludwig, U. S. Patent 2,878,280 (1959); F. M. Berger, J. F. Douglas, M. Kletzkin, B. J. Ludwig, and S. Margolin, *J. Pharmacol. Exp. Ther.*, **134**, 356 (1961)] has been isolated in dimorphic crystalline forms, mp 77–79° and 91–93°. [l] See ref 6. [m] N: calcd, 11.10; found, 10.57. [n] G. Ferrari and C. Casagrande, *Farmaco, Ed. Sci.*, **18**, 780 (1963). [o] Prepared by PtO_2-catalyzed hydrogenation of **93**.

Diethyl ethylphenylmalonate was converted to the *p*-nitro derivative using 90% fuming HNO_3 according to the method of Bousquet and Adams;[18] bp 170° (0.4 mm), $n^{31}D$ 1.5067. Hydrogenation of the nitro compound (PtO_2) gave diethyl 2-ethyl-2-(*p*-aminophenyl)malonate, bp 150–153° (0.10 mm), $n^{25}D$ 1.5231. The amine was converted *via* the diazonium salt to the xanthate ester following the procedure of Campaigne and Osborn.[19] Reduction of this ester with LAH afforded 2-ethyl-2-(*p*-mercaptophenyl)-1,3-propanediol in an over-all yield from the amine of 39%. The thiol was converted to the Bu ether by treating it with

[19] E. Campaigne and S. W. Osborn, *J. Org. Chem.*, 22, 561 (1957).

TABLE III

2-SUBSTITUTED 3-HYDROXYPROPYL CARBAMATES[a]

$RR_1C(CH_2OH)(CH_2OCONR_2R_3)$

No.	R	R_1	R_2	R_3	Yield, %	Mp or bp (mm), °C	$n^{25}D$	Formula	Analyses	Dose mg/kg[b] PD50	ED50	LD50
106	H	Et	H	H	95	105–112 (0.02)	1.4663	$C_8H_{15}NO_3$	N	>620	510	
107	H	Et	H	Me	60	96–97 (0.06)	1.4548	$C_7H_{13}NO_3$	N	>420	>420 (ip)	
108	H	Et	Me	Me	68	72–75 (0.02)	1.4522	$C_8H_{15}NO_3$	N	482		>620
109	H	Et	H	Ph	40	132–136 (0.01)	1.5346	$C_{12}H_{17}NO_3$	N	>420	355 (ip)	>420
110	H	Bu	H	H	80	74–75		$C_8H_{17}NO_3$	N	235		580
111[c]	H	Ph	H	H	16	73–75		$C_{10}H_{13}NO_3$	N	355	154	>420
112	Me	Me	H	Me	30	89–90 (0.04)	1.4548	$C_7H_{15}NO_3$	N			
113	Me	Me	Me	Me	74	65–68 (0.06)	1.4486	$C_8H_{17}NO_3$	N	>420	>420	
114[d]	Me	Et	H	H	60	43–45		$C_7H_{15}NO_3$				
115	Me	Et	H	Me	83	104–107 (0.04)	1.4594	$C_8H_{17}NO_3$	N	>620	420 (ip)	
116	Me	Et	H	Pr	72	107–112 (0.04)	1.4590	$C_{10}H_{21}NO_3$	N	225	235 (ip)	
117	Me	Pr	H	Me	75	112–115 (0.3)	1.4594	$C_9H_{19}NO_3$	N	255	341	>620
118[d]	Me	Pr	H	Et	55	115–120 (0.3)	1.4589	$C_{10}H_{21}NO_3$		280	>280	>280
119[d]	Me	Pr	H	Pr	80	114–117 (0.02)	1.4579	$C_{11}H_{23}NO_3$		201	355	900
120[d]	Me	Pr	H	*i*-Pr	55	86–88 (0.01)	1.4543	$C_{11}H_{23}NO_3$		>420	420 (ip)	>420
121[d]	Me	Pr	H	Allyl	86	102–104 (0.05)	1.4683	$C_{11}H_{21}NO_3$		149	230 (ip)	
122[d]	Me	Pr	H	2-Propynyl	30	120–125 (0.06)	1.4663	$C_{11}H_{19}NO_3$		355	>420	
123[d]	Me	Pr	H	Bu	88	107–108 (0.01)	1.4579	$C_{12}H_{25}NO_3$		171	500	900
124	Me	Pr	H	*sec*-Bu	30	104–105 (0.01)	1.4556	$C_{12}H_{25}NO_3$	N	280	355(ip)	>420
125[d]	Me	Pr	H	*i*-Bu	61	118–119 (0.06)	1.4586	$C_{12}H_{25}NO_3$		246	>280 (ip)	800
126	Me	Pr	H	2-Butenyl	73	120–130 (0.04)	1.4710	$C_{12}H_{23}NO_3$	N	355	355 (ip)	
127	Me	Pr	H	2-Methylallyl	21	115–116 (0.06)	1.4654	$C_{12}H_{23}NO_3$	N	355	280 (ip)	420
128	Me	Pr	H	Pentyl	68	144–146 (0.07)	1.4591	$C_{13}H_{27}NO_3$	N	620	420	>620
129	Me	Pr	H	3-Methylbutyl	72	130–136 (0.07)	1.4580	$C_{13}H_{27}NO_3$	N	620	520 (ip)	
130[c]	Me	Pr	H	Ph	84	85–86		$C_{14}H_{21}NO_3$	N	>420		>420
131	Me	Pr	H	$PhCH_2$	25	173–175 (0.02)	1.5032	$C_{15}H_{23}NO_3$	N	420	180 (ip)	>420
132	Me	Pr	H	*p*-HO_2CPh	40	183–185		$C_{15}H_{21}NO_5$	N	1185		1180
133[e]	Me	Pr	Me	Me	72	78–80 (0.02)	1.4542	$C_{10}H_{21}NO_3$		238	230 (ip)	650
134	Me	Pr	Et	Et	75	112–116 (0.03)	1.4491	$C_{12}H_{25}NO_3$	N	280		<420
135	Me	Pr	$-(CH_2)_2O(CH_2)_2-$		70	102–104 (0.02)	1.4726	$C_{12}H_{13}NO_4$	N	>280		>280
136	Me	Pr	Me	1-Phenyl-2-propyl	55	160–162 (0.07)	1.5008	$C_{18}H_{29}NO_3$	N	1345		2050
137	Me	Pr	Bu	Bu	60	114–115 (0.01)	1.4546	$C_{16}H_{33}NO_3$	C, H	>420	>420	>420
138[d]	Me	*o*-Pr	H	H	70	73–74		$C_8H_{17}NO_3$		520	280 (ip)	1550
139	Me	*i*-Pr	H	Me	42	101–103 (0.07)	1.4655	$C_9H_{19}NO_3$	N	>420	>280	
140[d]	Me	Bu	H	H	64	65–66		$C_9H_{19}NO_3$		193	319	520
141[d]	Me	Bu	H	Me	63	96–99 (0.04)	1.4592	$C_{10}H_{21}NO_3$				
142	Me	*sec*-Bu	H	H	65	35–37		$C_9H_{19}NO_3$	N			
143[d]	Me	*sec*-Bu	H	Pr	80	127–132 (0.07)	1.4655	$C_{12}H_{25}NO_3$				
144[d]	Me	*sec*-Bu	H	*i*-Pr	71	126–128 (0.07)	1.4631	$C_{12}H_{25}NO_3$		182		>280
145[d]	Me	*sec*-Bu	H	Allyl	71	147–148 (0.07)	1.4742	$C_{12}H_{23}NO_3$				
146[d]	Me	*sec*-Bu	H	2-Propynyl	50	123–126 (0.04)	1.4790	$C_{12}H_{21}NO_3$		235		440
147	Me	*sec*-Bu	H	Bu	88	145–147 (0.07)	1.4650	$C_{13}H_{27}NO_3$	N			
148	Me	*i*-Bu	H	H	71	122–127 (0.2)	1.4652	$C_9H_{19}NO_3$	N	280		480
149	Me	Ph	H	H	55	*f*	1.5465	$C_{11}H_{15}NO_3$	N			
150[c]	Et	$ClCH_2$	H	H	38	86–87		$C_{17}H_{14}ClNO_3$	N	420	420 (ip)	
151	Et	Et	H	Et	68	109–110 (0.1)	1.4624	$C_{11}H_{21}NO_3$	N[g]	210	280 (ip)	
152	Et	Et	H	Ph	80	73–74		$C_{14}H_{21}NO_3$	N	>420	280 (ip)	>420
153	Et	Pr	H	H	60	71–73		$C_9H_{19}NO_3$	N	138	212	710
154[d]	Et	Pr	H	*i*-Pr	81	130–132 (0.5)	1.4619	$C_{12}H_{25}NO_3$				
155[d]	Et	Bu	H	Me	81	128–130 (0.06)	1.4645	$C_{11}H_{23}NO_3$		215	280 (ip)	
156	Et	Bu	H	Et	70	104–106 (0.03)	1.4627	$C_{12}H_{25}NO_3$	N	250	180 (ip)	950
157[d]	Et	*i*-Pr	H	H	58	58–60		$C_9H_{19}NO_3$				
158	Et	Bu	H	Pr	79	132–136 (0.01)	1.4625	$C_{13}H_{27}NO_3$	N	420		>420
159	Et	Ph	Me	Me	60	127–128 (0.06)	1.5235	$C_{14}H_{21}NO_3$	C, H	185	340	680
160	Et	PhO	H	H	15	98–100		$C_{12}H_{17}NO_4$	C, H	482		>620
161[h]	Ph	Ph	H	H	65	121–122		$C_{16}H_{17}NO_3$		720	152	1400
162[i]	Ph	Ph	H	Me	93	87–89		$C_{17}H_{19}NO_3$		168	210	1280
163	Ph	Ph	H	Et	64	*f*		$C_{18}H_{21}NO_3$	C, H	155	318 (ip)	180
164	Ph	Ph	H	Pr	86	90–91		$C_{19}H_{23}NO_3$	H; C[j]	420	280 (ip)	>420
165	Ph	Ph	H	*i*-Pr	70	112–115		$C_{19}H_{23}NO_3$	N	630		>2100
166	*p*-Tolyl	*p*-Tolyl	H	H	90	133–136		$C_{18}H_{21}NO_3$	H; C[k]			
167	*p*-Tolyl	*p*-Tolyl	H	Me	70	106–107		$C_{19}H_{23}NO_3$	C; H[l]	>1400	>1400	>1400

[a] Prepared from the corresponding dioxanone (method H) unless otherwise noted. [b] See footnote *b* in Table I. [c] See Experimental Section. [d] See ref 3a. [e] See ref 11. [f] Compound was purified by short-path distillation at 100–120° bath temperature (0.001 mm). [g] N: calcd, 6.89; found, 7.54. [h] F. M. Berger and B. J. Ludwig, U. S. Patent 2,656,378 (1953). [i] F. M. Berger and B. J. Ludwig, U. S. Patent 3,222,392 (1965). [j] C: calcd, 72.82; found, 73.24. [k] C: calcd, 72.22; found, 71.56. [l] H: calcd, 7.40; found, 6.84.

2 moles of *n*-BuBr in EtOH in the presence of 1 mole of NaOMe. Recrystallization (CH_2Cl_2–pentane) gave a 50% yield of purified compound.

2-Chloromethyl-2-ethyl-1,3-propanediol (23).—3-Ethyl-3-oxetanemethanol, prepared by the method of Pattison,[20] was treated in $CHCl_3$ with an excess of dry HCl at 0° for 4 hr. The excess HCl was removed by aspiration, and the product was distilled at 92–102° (0.02 mm). It was purified by recrystallization (PhMe).

2-Propyl-2-diethylaminomethyl-1,3-propanediol (36) was prepared by the Mannich condensation of 0.3 mole of diethyl propylmalonate, 0.3 mole of Et_2NH, and 0.33 mole of 37% HCHO in 200 ml of EtOH. Vacuum distillation of the crude product gave the desired malonate in 80% yield, bp 87–88° (0.04 mm). Reduction of the malonate with LAH afforded the corresponding diol in 81% yield.

2,2-Di(*p*-tolyl)-1,3-propanediol (38).—A mixture of 0.41 mole of 4,4′-dimethylhydrobenzoin and 500 ml of 90% HCO_2H was refluxed for 4 hr. The H_2O and excess acid were removed under reduced pressure, the residue, dissolved in Et_2O, was washed (saturated $NaHCO_3$, saturated NaCl), and the solvent was removed. The crude 2,2-di-*p*-tolylacetaldehyde was added to 300 ml of 37% HCHO containing 30.3 g of K_2CO_3. This mixture was refluxed for 22 hr during which time sufficient EtOH was added to

(20) D. B. Pattison, *J. Am. Chem. Soc.*, **79**, 3455 (1957).

TABLE IV

2-SUBSTITUTED 1,3-PROPANEDIOL N-MONOSUBSTITUTED DICARBAMATES

$RR_1C(CH_2OCONH_2)(CH_2OCONHR_2)$

No.	R	R_1	R_2	Method	Yield, %	Mp or bp (mm), °C	$n^{25}D$	Formula[a]	Dose, mg/kg[b] PD50	ED50	LD50
168	H	Et	Me	I	79	110.5–111		$C_8H_{16}N_2O_4$	>420	360 (ip)	420
169	H	Et	Pr	K	76	93–94		$C_{10}H_{20}N_2O_4$	236	500	831
170	H	Et	Ph	K	65	118–119		$C_{13}H_{18}N_2O_4$	>420	>420 (ip)	
171	H	1-Methylbutyl	2-Propynyl	J	88	81–82		$C_{12}H_{22}N_2O_4$	<420		>420
172	H	Ph	Me	J	60	96–98.5		$C_{12}H_{16}N_2O_4$	355	52	
173	H	Ph	Pr	J	64	58–62		$C_{14}H_{20}N_2O_4$	305	150	
174	H	Ph	Ph	K	90	147–148.5		$C_{17}H_{18}N_2O_4$	>620	>620	>620
175	Me	Me	Me	M	60	88–91		$C_8H_{16}N_2O_4$	>620	765	
176	Me	Me	Pr	K	95	110–113		$C_{10}H_{20}N_2O_4$	420	420	
177	Me	Me	Ph	K	65	112–114		$C_{13}H_{18}N_2O_4$	>420	224	
178	Me	Et	Me	M	73	78–79.5		$C_9H_{18}N_2O_4$	520	280 (ip)	620
179	Me	Et	Et	L	50	87–89		$C_{10}H_{20}N_2O_4$	235	590	800
180[c]	Me	Et	Pr	M	72	71.5–73.5		$C_{11}H_{22}N_2O_4$	165	265	580
181[c]	Me	Et	*i*-Pr	K	86	86–88		$C_{11}H_{22}N_2O_4$	150	385	730
182[c]	Me	Et	Allyl	L	23	51–52		$C_{11}H_{20}N_2O_4$	180	585	510
183	Me	Et	2-Propynyl	L	5	*d*	1.4998	$C_{11}H_{18}N_2O_4$	510		1000
184[c]	Me	Et	Bu	K	77	*d*	1.4682	$C_{12}H_{24}N_2O_4$	136	265	570
185	Me	Et	Ph	K	33	88–90		$C_{14}H_{20}N_2O_4$	520	315	
186	Me	Pr	Me	I	63	148–150 (0.05)	1.4662	$C_{10}H_{20}N_2O_4$	295	460	730
187[c]	Me	Pr	Et	I	72	154–156 (0.05)	1.4677	$C_{11}H_{22}N_2O_4$	170	400	700
188[c]	Me	Pr	Vinyl	N	36	90–92		$C_{11}H_{20}N_2O_4$	180	>280	620
189	Me	Pr	$2\text{-}HOCH_2CH_2$	J	20	120–140 (0.02)	1.4809	$C_{11}H_{22}N_2O_6$	>420		
190	Me	Pr	COMe	K	80	88–89		$C_{11}H_{20}N_2O_5$	213	180	761
191[c]	Me	Pr	Pr	I, J	72	144–147 (0.02)	1.4694	$C_{12}H_{24}N_2O_4$	146	326	790
192[c,f]	Me	Pr	*i*-Pr	I	63	89–91.5		$C_{12}H_{24}N_2O_4$	153	280	790
193[c]	Me	Pr	Allyl	I	62	110–130 (0.025)	1.4760	$C_{12}H_{22}N_2O_4$	114	154	500
194[c]	Me	Pr	2-Propynyl	I	35	94–96		$C_{12}H_{20}N_2O_4$	172	154	650
195	Me	Pr	Cyclopropyl	J	60	79–81		$C_{12}H_{22}N_2O$	138	215	452
196[c,g]	Me	Pr	Bu	I	18	49–51		$C_{12}H_{24}N_2O_4$	940	198	514
197	Me	Pr	*sec*-Bu	I	41	96–98		$C_{13}H_{26}N_2O_4$	>420	280	>420
198[c]	Me	Pr	*i*-Bu	I	33	100–110 (0.01)	1.4645	$C_{13}H_{26}N_2O_4$	175	690	>940
199[c]	Me	Pr	2-Butenyl	I	66	88–89		$C_{12}H_{24}N_2O_4$	385	940	>940
200	Me	Pr	2-Methylallyl	I	40	64–65		$C_{12}H_{24}N_2O_4$	253	180 (ip)	900
201	Me	Pr	2-Furyl	N	5	84–86		$C_{14}H_{20}N_2O_5$	630		630
202	Me	Pr	Pentyl	M	70	79–81		$C_{14}H_{28}N_2O_4$	450	>940	>940
203	Me	Pr	3-Methylbutyl	I	30	*d*	1.4664	$C_{14}H_{28}N_2O_4$	620		>940
204	Me	Pr	1,1-Dimethyl-2-propynyl	J	10	123–125 (0.01)	1.4774	$C_{13}H_{24}N_2O_4$	240		490
205	Me	Pr	Ph	K	92	98–99		$C_{15}H_{22}N_2O_4$	>420		>420
206	Me	Pr	$PhCH_2$	I	50	131–132		$C_{16}H_{24}N_2O_4$	>1400		>1400
207	Me	Pr	$PhCOCH_2$	*h*	5	116–118		$C_{17}H_{24}N_2O_6$	510	420 (ip)	
208	Me	Pr	3-Pyridyl	J	50	136–138[c]		$C_{14}H_{22}ClN_3O_4$	210		>280
209	Me	*i*-Pr	Me	M	56	*d*	1.4750	$C_{10}H_{20}N_2O_4$[i]	520	373	>620
210	Me	*i*-Pr	Pr	K	46	58–60		$C_{12}H_{24}N_2O_4$	236	480	765
211[c]	Me	*i*-Pr	*i*-Pr	J	50	58		$C_{12}H_{24}N_2O_4$	130	510	760
212[c]	Me	*i*-Pr	Allyl	J	60	120–125 (0.02)	1.4824	$C_{12}H_{22}N_2O_4$	197	304	530
213	Me	*i*-Pr	2-Propynyl	J	63	*d*	1.4872	$C_{12}H_{20}N_2O_4$	225	255	530
214[c]	Me	*i*-Pr	Bu	J	73	63–65		$C_{13}H_{26}N_2O_4$	160	240	560
215	Me	*i*-Pr	Ph	K	85	96–98		$C_{15}H_{22}N_2O_4$	>420	280	>420
216[c]	Me	Bu	Me	M	70	75–77		$C_{10}H_{22}N_2O_4$	160	280	515
217	Me	Bu	Et	J	17	91–92		$C_{12}H_{24}N_2O_4$	225	580	660
218[c]	Me	Bu	Pr	K	62	62–64		$C_{14}H_{26}N_2O_4$	114	305	532
219[c]	Me	Bu	*i*-Pr	L	15	74–76.5		$C_{13}H_{26}N_2O_4$	102	>420	840
220[c]	Me	Bu	Allyl	J	74	62–63		$C_{13}H_{24}N_2O_4$	136	280	345
221[c]	Me	Bu	2-Propynyl	J	17	55–57		$C_{13}H_{22}N_2O_4$	136	90	345
222	Me	Bu	Bu	J	50	54–57		$C_{14}H_{28}N_2O_4$	305	900	760
223	Me	Bu	Ph	K	94	112–113		$C_{16}H_{22}N_2O_4$	>620	620 (ip)	>620
224[c]	Me	*sec*-Bu	Pr	M	50	61–63		$C_{13}H_{26}N_2O_4$	105	380	620
225[c]	Me	*sec*-Bu	*i*-Pr	M	95	89–90		$C_{13}H_{26}N_2O_4$	92	225	750
226[c]	Me	*sec*-Bu	Allyl	M	50	*d*	1.4830	$C_{13}H_{24}N_2O_4$	102	142	344
227[c]	Me	*sec*-Bu	2-Propynyl	M	55	120–125 (0.01)	1.4862	$C_{13}H_{22}N_2O_4$	171	130	510
228	Me	*i*-Bu	Bu	M	60	*d*	1.4714	$C_{14}H_{28}N_2O_4$	320		760
229	Me	*i*-Bu	2-Propynyl	J	77	47–49		$C_{13}H_{22}N_2O_4$	305		>420
230	Me	Ph	Pr	J	43	113–114		$C_{16}H_{22}N_2O_4$	280	180	586
231	Me	Ph	2-Propynyl	J	42	*d*	1.5409	$C_{16}H_{18}N_2O_4$	530		>940
232	Me	Ph	Ph	K	80	113–114		$C_{18}H_{20}N_2O_4$	520	280 (ip)	520
233	Et	Et	Et	I	57	111–113		$C_{11}H_{22}N_2O_4$	530		>940
234[c]	Et	Et	Pr	I	42	83–84		$C_{12}H_{24}N_2O_4$	147	490	760
235[c]	Et	Et	*i*-Pr	J	45	91–93		$C_{12}H_{24}N_2O_4$	130	530	1280
236[c]	Et	Et	Allyl	L	50	84–85		$C_{12}H_{22}N_2O_4$	205	370	330
237	Et	Et	2-Propynyl	J	75	75–78		$C_{12}H_{20}N_2O_4$	305		
238	Et	Et	Bu	J	81	62–64		$C_{13}H_{26}N_2O_4$	255	305	820
239	Et	Et	Ph	K	86	98.5–100		$C_{15}H_{22}N_2O_4$	510	420	
240[c]	Et	Pr	*i*-Pr	M	58	82–84		$C_{13}H_{26}N_2O_4$	225	470	880
241[c]	Et	*i*-Pr	*i*-Pr	J	55	72–74		$C_{13}H_{26}N_2O_4$	120	480	730
242[c]	Et	Bu	Me	I	60	74–75.5		$C_{12}H_{24}N_2O_4$	170	246	509
243	Et	Bu	Et	I	50	79–81		$C_{13}H_{26}N_2O_4$	235	680	800
244	Et	Bu	Pr	I	69	81.5–83		$C_{14}H_{28}N_2O_4$	420		
245[c]	Et	Bu	2-Propynyl	J	30	61–64		$C_{14}H_{24}N_2O_4$	153	150	510
246	Et	Bu	Ph	K	95	128–130.5		$C_{17}H_{26}N_2O_4$	>420	>420	>420
247	Et	Ph	Et	L	50	69–71		$C_{13}H_{20}N_2O_4$	280		>280

TABLE IV (*Continued*)

No.	R	R_1	R_2	Method	Yield, %	Mp or bp (mm), °C	$n^{25}D$	Formu.[a]	Dose, mg/kg[b] PD_{50}	ED_{50}	LD_{50}
248	Et	Ph	Ph	K	90	137–138		$C_{19}H_{20}NO_4$	>620	>620	>620
249	Ph	Ph	Me	M	30	103–105[k] 132–135		$C_{18}H_{21}NO_4$	>620	>620	>620
250	Ph	Ph	Pr	K	83	145–146		$C_{20}H_{24}N_2O_4$	>420	>420	>420
251	Ph	Ph	Ph	K	90	201–202.5		$C_{23}H_{22}N_2O_4$	>420	>420	>420

[a] All previously unreported compounds were analyzed for N. [b] See footnote *b* in Table I. [c] See ref 3a. [d] See footnote *f*, Table III. [e] Polymerizes on heating at melting point or on standing at 50°. See ref 11. [f] Carisoprodol; see ref 3b. [g] Tybamate; see F. M. Berger, M. Kletzkin, and S. Margolin, *Med. Exp.*, **10**, 327 (1964). [h] Prepared by the reaction of meprobamate and NaH in DMF with phenylacetyl chloride. [i] HCl salt. [j] N: calcd, 12.06; found, 11.50. [k] Dimorphic crystalline forms.

maintain the reactants in solution. The solvents and excess HCHO were removed under reduced pressure and the residue was heated on the steam bath with 10% NaOH for 5 hr. The mixture was extracted into Et_2O and the crude product obtained upon removal of the solvent was purified by recrystallization (PhMe).

Preparation of 2-Substituted 1,3-Propanediol Dicarbamates (II).—The majority of the 2-substituted 1,3-propanediol dicarbamates listed in Table II were prepared by either the phosgenation procedure[1] (method A) or the ester-exchange method[6] (method B) previously described. Other methods employed for this purpose were as follows.

Sodium cyanate procedure (method C) is illustrated by the preparation of **2-allyl-2-ethyl-1,3-propanediol dicarbamate (84)**. A mixture of 18.7 g (0.13 mole) of the diol, 18.8 g (0.29 mole) of anhydrous NaOCN, and 400 ml of dry $CHCl_3$ was stirred and maintained at 0° while dry HCl was passed into the mixture for a period of 6 hr. The mixture was allowed to warm to room temperature and to stand overnight, and the HCl and the $CHCl_3$ were removed by distillation under reduced pressure. Recrystallization of the residue (H_2O) yielded 24.4 g (85%) of purified product.

Phenyl Chlorocarbonate Procedure (Method D).—The use of the intermediate phenyl carbonate in the synthesis of dicarbamates is illustrated by the preparation of **2,2-diphenyl-1,3-propanediol dicarbamate (99)**. 2,2-Diphenyl-1,3-propanediol[21] (20 g, 0.088 mole) was dissolved in 100 ml of $CHCl_3$ to which 40 g (0.5 mole) of pyridine had been added. To this was then added 31.2 g (0.2 mole) of phenyl chlorocarbonate in 50 ml of $CHCl_3$. The reaction mixture was refluxed for 1 hr and then poured into ice water. The $CHCl_3$ layer was washed (10% HCl, 10% NaOH, H_2O) and the $CHCl_3$ was distilled. The crude 2,2-diphenyl-1,3-propanediol bis(phenylcarbonate) was added to 200 ml of NH_4OH and 50 ml of EtOH. This mixture was treated with NH_3 for 2 hr under reflux and then poured into 300 ml of H_2O. The solid which separated was recrystallized from 3 l. of 90% Me_2CO and yielded 21 g (76%) of white crystalline product.

Condensation with Urea.—We were unable to obtain yields comparable to those of Paquin[22] who reported 78% of 1,3-butylene glycol dicarbamate from the glycol, using urea and $Zn(OAc)_2$ catalyst at 175–185°. When 66 g (0.5 mole) of 2-methyl-2-propyl-1,3-propanediol, 120 g (2.0 mole) of urea, and 6 g of $Zn(OAc)_2$ were stirred and heated at an internal temperature of 150° for 7.5 hr, a 25% yield of meprobamate was obtained. Several variations in the ratio of reactants, time, temperature, and choice of catalyst failed to improve the yield. The isolation of the product obtained in this manner was complicated by the presence in the reaction mixture of urea decomposition products.

Cyclic Carbonates (V, Method G).—The cyclic carbonate esters used as intermediates in the synthesis of the monocarbamates were obtained substantially by the procedure of Berger and Ludwig.[3a]

Previously undescribed 5-substituted *m*-dioxanones prepared by this method were 5-ethyl-*m*-dioxanone, bp 80–83° (0.02 mm), $n^{25}D$ 1.4523; 5-butyl-, 178–180° (0.3 mm), 1.4448; 5-methyl-5-isobutyl-, 114–117° (0.02 mm), 1.4558; 5-methyl-5-phenyl-, mp 97–98°; and 5,5-di-*p*-tolyl-, mp 168–171°.

1,3-Propanediol Monocarbamates (VI).—The N-unsubstituted-3-hydroxypropyl carbamates and most of the N-alkyl(aryl) monocarbamates described in Table III were produced from the corresponding *m*-dioxanone and NH_3 or the appropriate amine by the method described earlier[3a] (method H). Procedures for the preparation of other compounds of this type requiring special methods are as follows.

2-Ethyl-2-chloromethyl-3-hydroxypropyl carbamate (150) was formed along with 2-ethyl-2-chloromethyl-1,3-propanediol dicarbamate and 2-ethyl-2-chloromethyl-1,3-propanediol when 1 mole of 3-ethyl-3-oxetanemethanol[20] was treated in $CHCl_3$ with 1 mole of NaOCN and excess dry HCl. The 2-ethyl-2-chloromethyl-1,3-propanediol dicarbamate (38%) remained insoluble in the $CHCl_3$ and was filtered off. The filtrate was distilled and separated into two fractions. Fraction 1, bp 92–100° (0.02 mm), was recrystallized (CH_2Cl_2) to a constant melting point of 65.5–66° and proved to be 2-ethyl-2-chloromethyl-1,3-propanediol (24%). Fraction 2, bp 102–150° (0.02 mm), after recrystallization (CH_2Cl_2) melted at 86–87°. Analysis showed it to be 2-ethyl-2-chloromethyl-3-hydroxypropyl carbamate (38%).

2-Phenyl-3-hydroxypropyl Carbamate (111).—Since the cyclic carbonate of 2-phenyl-1,3-propanediol could not be obtained by method G, the desired monocarbamate was prepared by an alternate route. 2-Phenyl-1,3-propanediol (0.4 mole) in 500 ml of THF was treated at room temperature with 0.42 mole of $COCl_2$ in 100 ml of THF. The reaction mixture was stirred 2 hr and then poured with cooling into 250 ml of concentrated NH_4OH. The THF layer was separated and the solvent was removed by distillation. The residue was dissolved in Et_2O and the solution was washed (10% HCl, H_2O). After removal of the Et_2O, the residue was recrystallized (Me_2CO–$CHCl_3$). The dicarbamate of 2-phenyl-1,3-propanediol, which also formed in the reaction, crystallized out first (mp 148–150°), and by adding petroleum ether to the filtrate the monocarbamate was obtained, mp 71–74°. After recrystallization (PhMe), the monocarbamate melted at 73–75°.

N-Phenyl-2-methyl-2-propyl-2-hydroxypropyl Carbamate (130).—A solution of 26.4 g (0.2 mole) of 2-methyl-2-propyl-1,3-propanediol in 400 ml of dry C_6H_6 was heated to reflux and 11.8 g (0.1 mole) of phenyl isocyanate in dry C_6H_6 was added slowly with stirring over a period of 1 hr. The C_6H_6 was then removed and the residue was distilled. Unreacted diol (12 g), bp 80° (0.1 mm), was obtained. The residue was recrystallized from heptane; yield 20.7 g (84%).

1,3-Propanediol N-Monosubstituted Dicarbamates (VIIa, Y = H, Table IV).—The urethan-exchange method (method I), the phosgenation-amidation procedure (method J), and the cyanic acid reaction (method M) were employed in the synthesis of these compounds.[3a]

2-Substituted 1,3-Propanediol N,N′-Di-, -Tri- and -Tetrasubstituted Dicarbamates (IV, VIIa, VIIb, VIIc, Table V). 2-Methyl-2-propyl-1,3-propanediol N-(3-Methylbutyl)-N′-butyldicarbamate (279, Method K).—A mixture of 24.5 g (0.1 mole) of 2-methyl-2-propyl-3-hydroxypropyl N-(3-methylbutyl)carbamate and 11 g (0.11 mole) of butyl isocyanate in 100 ml of dry C_6H_6 was refluxed for 6 hr and then concentrated to an oil. The residue was distilled at 165–170° (0.0015 mm) to yield 30.5 g (88%) of a viscous liquid.

1,3-Propanediol N,N′-Alkyl(aryl)dicarbamates. Isocyanate Procedure (Method E).—The use of alkyl or aryl isocyanates in the preparation of symmetrically N,N′-substituted dicarbamates is illustrated in the preparation of **2-methyl-2-propyl-1,3-propanediol N,N′-diphenyldicarbamate (281)**. 2-Methyl-2-propyl-1,3-propanediol (10 g) was mixed with 95% of the theoretical quantity of phenyl isocyanate (17.1 g) and the mixture was warmed. A vigorous reaction took place and, after subsiding, the mixture set to a viscous gum. Crystallization of the product (EtOH–H_2O) gave 17.2 g (79%) of purified compound.

Acyl Azide Procedure (Method F).[11]—This method, useful for the laboratory preparation of selected N-substituted dicarbamates, is illustrated by the preparation of **2-methyl-2-propyl-1,3-propanediol N,N′-diisopropyldicarbamate (271)**. A solution of 26.8 g (0.25 mole) of isobutyryl chloride in PhMe (60 ml) was added to a stirred solution of 18.8 g (0.29 mole) of NaN_3 in 50 ml of H_2O maintained at 0–10°. The mixture was stirred rapidly for 0.5 hr and then the PhMe layer was removed and washed

(21) D. G. Markees and A. Burger, *J. Am. Chem. Soc.*, 71, 2031 (1949).
(22) A. M. Paquin, *Z. Naturforsch.*, 1, 518 (1946).

Table V

2-Substituted 1,3-Propanediol N-Polysubstituted Dicarbamates

$RR_1C(CH_2OCONR_2R_3)(CH_2OCONR_4R_5)$

No.	R	R_1	R_2	R_3	R_4	R_5	Method	Yield, %	Mp or bp (mm), °C	n_D^{25}	Formula	Analyses	Dose, mg/kg[a] PD_{25}	ED_{50}	LD_{50}
252	H	Et	H	H	Me	Me	M	65	58–60		$C_{15}H_{18}N_2O_3$	N	520	>420	>620
253	H	Ph	H	H	Me	Me	J	50	90–92		$C_{19}H_{18}N_2O_4$	N	247	126	
254	Me	Me	H	H	Me	Me	M	49	95–97		$C_9H_{16}N_2O_4$	N	620	355 (ip)	520
255	Me	Pr	H	H	Me	Me	I	50	99–103		$C_{14}H_{22}N_2O_4$	N	570		900
256	Me	Pr	H	H	Me	Pr	J	56	43–46		$C_{16}H_{26}N_2O_3$	N	180	>280	<620
257	Me	Pr	H	H	Et	Et	I	45	78–80		$C_{16}H_{26}N_2O_4$	N	370		735
258	Me	Pr	H	H	$-(CH_2)_2O(CH_2)_2-$		I	62	74–76		$C_{13}H_{21}N_2O_5$	N	245	>420	700
259	Me	*i*-Pr	H	H	Me	Me	J	50	76–78		$C_{17}H_{32}N_2O_4$	N	420	420	
260	Me	Bu	H	H	Me	Me	J	30	76–78		$C_{17}H_{34}N_2O_4$	N	265		650
261	Me	*sec*-Bu	H	H	Me	Me	J	58	55–57		$C_{17}H_{34}N_2O_4$	N	272		710
262	Et	Pr	H	H	Me	Me	M	40	92–93		$C_{15}H_{22}N_2O_4$	N	420	280 (ip)	
263[b]	H	$PhCH_2$	H	Ph	H	Ph	E	88	150		$C_{21}H_{18}N_2O_4$	N	>620	>1800	
264	Me	Pr	H	Me	H	Me	A	50	160–162 (0.2)	1.4640	$C_{13}H_{22}N_2O_4$	N	315	315	730
265	Me	Pr	H	Et	H	Et	A	70	152–156 (0.2)	1.4608	$C_{15}H_{26}N_2O_4$	N	560		1020
266	Me	Pr	H	$ClCH_2CH_2$	H	$ClCH_2CH_2$	A	88	c	1.4849	$C_{15}H_{24}Cl_2N_2O_4$	N	>420	>420 (ip)	>420
267	Me	Pr	H	Ac	H	Ac	O	80	125–126.5,[d] 135–136		$C_{15}H_{22}N_2O_6$	N	620		>620
268	Me	Pr	H	HO_2CCH_2	H	HO_2CCH_2	e	65	133–140[f]		$C_{15}H_{18}N_2O_8$	N	>940	>940	>940
269	Me	Pr	H	$ClCH_2CO$	H	$ClCH_2CO$	O	3	141–142.5		$C_{15}H_{20}Cl_2N_2O_6$	N	>620	<620	
270	Me	Pr	H	2,2,2-Trichloro-hydroxyethyl	H	2,2,2-Trichloro-hydroxyethyl	e	82	105–107		$C_{15}H_{20}Cl_6N_2O_6$	C, H	>1400		1045
271[g,h]	Me	Pr	H	*i*-Pr	H	*i*-Pr	F	87	69–73		$C_{15}H_{30}N_2O_4$	N	>620	420 (ip)	>620
272[h]	Me	Pr	H	Et	H	2-Butenyl	N	37	c	1.4732	$C_{15}H_{28}N_2O_4$	C, H[c]	720		1460
273	Me	Pr	H	*i*-Pr	H	EtCO	O	75	94–95.5		$C_{15}H_{28}N_2O_5$	N	270	665	>1400
274	Me	Pr	H	Acryloyl	H	Acryloyl	e	30	170–171		$C_{15}H_{22}N_2O_6$	N	1400		<1400
275	Me	Pr	H	EtCO	H	EtCO	O	75	164–166		$C_{15}H_{26}N_2O_6$	N	>1400		>1400
276	Me	Pr	H	2-Bromo-propionyl	H	2-Bromo-propionyl	e	70	140–141		$C_{15}H_{24}Br_2N_2O_6$	C, H, N	>1400		>1400
277	Me	Pr	H	Bu	H	Bu	A	80	164–168 (0.01)	1.4619	$C_{17}H_{34}N_2O_4$	N			
278	Me	Pr	H	EtO_2CCH_2	H	EtO_2CCH_2	E	96	c	1.4652	$C_{17}H_{30}N_2O_8$	N	>620	>620	>620
279	Me	Pr	H	Bu	H	3-Methyl-butyl	K	88	c	1.4613	$C_{19}H_{38}N_2O_4$	C, H, N	>620	>520	>620
280	Me	Pr	H	2-Glucosyl	H	2-Glucosyl	A	55	100		$C_{29}H_{52}N_2O_{14}$	C, H, N	>420	>420	>420
281	Me	Pr	H	Ph	H	Ph	E	79	118–119		$C_{19}H_{26}N_2O_4$	N	>620	>1700	
282	Me	Pr	H	$PhCH_2$	H	$PhCH_2$	A	50	73–74		$C_{21}H_{30}N_2O_4$	N	>420	>420	
283	Me	Pr	H	*p*-EtOPh	H	*p*-EtOPh	E	90	173.5–176.5		$C_{23}H_{34}N_2O_6$	N	2000	<1400 (ip)	1710
284	Me	Pr	H	$PhCOCH_2$	H	$PhCOCH_2$	j	9	200–201		$C_{21}H_{22}N_2O_6$	N	>620	>620	
285	Me	Pr	H	*i*-Pr	H	9-Xanthyl	e	30	137–139		$C_{23}H_{32}N_2O_5$	C, H, N	>620	>620	
286	Me	Pr	H	9-Xanthyl	H	9-Xanthyl	e	70	184–184.5		$C_{33}H_{34}N_2O_6$	C, H	>1400	>420	
287	Me	*i*-Pr	H	Me	H	Me	A	50	110–112		$C_{19}H_{32}N_2O_4$	N	>620	>1700	
288	Me	*i*-Pr	H	Ac	H	Ac	O	80	149–150		$C_{23}H_{36}N_2O_6$	N	1740		2340
289	Me	*i*-Pr	H	Ph	H	Ph	E	57	142–143		$C_{21}H_{26}N_2O_4$	N	>620	>1700	
290	Me	*sec*-Bu	H	Ac	H	Ac	O	95	146–147		$C_{19}H_{34}N_2O_6$	N	690		>4700
291	Me	*sec*-Bu	H	EtCO	H	EtCO	O	75	147–149		$C_{21}H_{38}N_2O_6$	N	>1400		>1400
292	Et	Et	H	Et	H	Et	A	65	70–72		$C_{13}H_{28}N_2O_4$	N	457		800
293	Et	Et	H	$PhCH_2$	H	$PhCH_2$	A	25	100–101		$C_{21}H_{30}N_2O_4$	N	>280		>280
294	Et	Pr	H	Ac	H	Ac	O	80	120–122		$C_{17}H_{32}N_2O_6$	N	1290		1725
295	Et	Pr	H	EtCO	H	EtCO	O	75	163–165		$C_{19}H_{36}N_2O_6$	N	>1400		>1400
296	Et	Bu	H	Ph	H	Ph	E	60	107–109		$C_{23}H_{34}N_2O_4$	N	>620	>1800	
297	Et	Ph	H	Ph	H	Ph	E	55	138–139		$C_{25}H_{26}N_2O_4$	N	>620	>1900	
298	Me	Pr	H	*i*-Pr	H	Et_2NCH_2	k	60		1.4677	$C_{19}H_{39}N_3O_4$	N			
299	Me	Pr	H	Et	Me	Me	K	45	126–128 (0.03)	1.4575	$C_{19}H_{38}N_2O_4$	N[i]	420		420
300	Me	Pr	H	Pr	Me	Me	K	60	146–148 (0.075)	1.4578	$C_{21}H_{42}N_2O_4$	N	342		>420
301[h]	Me	Pr	H	*i*-Bu	Me	Me	N	46	110 (0.012)	1.4600	$C_{23}H_{46}N_2O_4$		405		1525
302	Me	Pr	H	Et	Et	Et	L	63	126–127 (0.02)	1.4581	$C_{23}H_{50}N_2O_4$	N	>420	235	>420
303	Me	Pr	H	Pr	Et	Et	K	62	132–137 (0.03)	1.4568	$C_{25}H_{54}N_2O_4$	N	>420	355 (ip)	>420
304	M	Pr	Me	Me	Me	Me	e	58	114–118 (0.06)	1.4561	$C_{13}H_{26}N_2O_4$	N	180	>420	
305	Me	Pr	$-CH_2CH_2-$		$-CH_2CH_2-$		A	52	119–122 (0.01)	1.4676	$C_{13}H_{22}N_2O_4$	N			
306	Me	Pr	Et	Et	Et	Et	A	74	119–125 (0.02)	1.4537	$C_{17}H_{34}N_2O_4$	N	>1400		1000
307	Me	Pr	$ClCH_2CH_2$	$ClCH_2CH_2$	CH_2CH_2Cl	CH_2CH_2Cl	A	45	155–165 (0.01)	1.4950	$C_{17}H_{34}Cl_4N_2O_4$	Cl[j]	>620	>620	>620
308	Me	Pr	$-(CH_2)_2O(CH_2)_2-$		$-(CH_2)_2O(CH_2)_2-$		A	47	162–163 (0.02)	1.4863	$C_{17}H_{30}N_2O_6$	N	95		362

TABLE V (*Continued*)

No.	R	R_1	R_2	R_3	R_4	R_5	Method	Yield, %	Mp or bp (mm), °C	$n^{25}D$	Formula	Analyses	Dose, mg/kg[a] PD_{50}	ED_{50}	LD_{50}
309	Me	Pr	$-(CH_2)_5-$		$-(CH_2)_5-$		A	60	158–160 (0.02)	1.4858	$C_{19}H_{34}N_2O_4$	N	>420		>420
310	Et	Et	Et	Et	Et	Et	A	40	129–132 (0.5)		$C_{15}H_{34}N_2O_4$	C; H[n]	810		720

[a] See footnote *b* in Table I. [b] H. Adkins and H. R. Billica [*J. Am. Chem. Soc.*, **70**, 3121 (1948)] reported mp 68–70°. [c] See footnote *f* Table III. [d] Dimorphic crystalline forms: mp 125–126.5° from EtOH–H_2O, mp 135–136° from PhMe. [e] See Experimental Section. [f] Monoammonium salt. [g] Pharmacological properties reported by R. Inoki, K. Otori, and I. Komura, *Folia Pharmacol. Japon.*, **57**, 280 (1961). [h] See ref 11. [i] H: calcd, 9.40; found, 9.88. [j] See footnote *h*, Table IV. [k] Prepared from 2-methyl-2-propyl-1,3-propanediol N-isopropyldicarbamate, Et_2NH, and 37% HCHO. [l] N: calcd, 10.21; found, 10.68. [m] Cl: calcd, 30.29; found, 29.87. [n] H: calcd, 10.37; found, 9.74.

(Na_2CO_3, H_2O). The toluene solution was dried ($CaCl_2$) at 5° for 1 hr and was added slowly to 13.2 g (0.1 mole) of 2-methyl-2-propyl-1,3-propanediol dissolved in 100 ml of anhydrous PhMe. The solution was heated at reflux during the addition and for an additional 8 hr. PhMe was removed under reduced pressure and the residue was crystallized from hexane; yield 26.3 g (87%), mp 72–73°.

The unsymmetrical 1,3-propanediol N,N′-tri- and -tetrasubstituted dicarbamates listed in Table V were prepared from the appropriate 3-hydroxypropyl N-substituted carbamates using the various carbamoylation reactions described earlier.

2-Methyl-2-propyl-1,3-propanediol N,N′-bis(2,2,2-trichlorohydroxyethyl)dicarbamate (270) was prepared in 82% yield by stirring a mixture of 0.1 mole of 2-methyl-2-propyl-1,3-propanediol dicarbamate and 0.25 mole of chloral on the steam bath for 1 hr. The reaction product was recrystallized (C_6H_6), mp 105–107°.

2-Methyl-2-propyl-1,3-propanediol N,N′-Bis(9-xanthyl)dicarbamate (286).—Following the procedure of Sawicki and Oliverio,[23] 2.75 g of 2-methyl-2-propyl-1,3-propanediol dicarbamate was dissolved in 15 ml of EtOH–AcOH (1:1) and mixed with 5 g of xanthydrol dissolved in 15 ml of the same solvent. The solution was warmed and allowed to stand overnight. The product (4.5 g) was recrystallized (PhMe), mp 184–184.5°.

The monoxanthyl derivative of 2-methyl-2-propyl-1,3-propanediol N-isopropyldicarbamate (**285**) also prepared by this method was obtained in crystalline form in low yield.

2-Methyl-2-propyl-1,3-propanediol N,N′-bis(carboxymethyl)-dicarbamate monoammonium salt (268) was prepared by treating 1 mole of 2-methyl-2-propyl-1,3-propanediol with 2 moles of carbethoxymethyl isocyanate in C_6H_6. The reactants were refluxed for 3 days, the solvent was removed by distillation, and the residue was distilled in a molecular still. The fraction distilling at 162–187° (0.001 mm) was collected, $n^{25}D$ 1.4652. This intermediate, 2-methyl-2-propyl-1,3-propanediol N,N′-bis(carbethoxymethyl)dicarbamate (**278**) was saponified by refluxing 1 hr with excess NaOMe in EtOH. The EtOH was removed by distillation, and the residue was taken up in H_2O and extracted with Et_2O, discarding the Et_2O extracts. The aqueous solution was acidified with HCl, the product was extracted into Et_2O, and the solution was dried ($CaSO_4$) and distilled to dryness to give a viscous residue. The product was isolated as the monoammonium salt by dissolving the gum in anhydrous *i*-Pr_2O and introducing NH_3. It was crystallized from *i*-PrOH saturated with NH_3, mp 133–140°.

2-Methyl-2-propyl-1,3-propanediol N,N,N′,N′-tetramethyldicarbamate (304) was prepared by the reaction of 1 mole of the diol with 2 moles of dimethylcarbamoyl chloride in PhMe, using 2.5 moles of pyridine as the acid acceptor. The reaction mixture was refluxed for 20 hr and then poured into ice H_2O. Et_2O was added and the Et_2O layer was washed with dilute HCl, dried, and concentrated. Distillation of the residue gave a fraction boiling at 114–118° (0.06 mm), $n^{25}D$ 1.4561, in a yield of 58%.

1,3-Propanediol N-Acylated Dicarbamates (Method O).—The diacyl derivatives of N-unsubstituted and N-monosubstituted dicarbamates were prepared by treating 1 part of dicarbamate with 2 parts of the appropriate acid anhydride to which a trace of concentrated H_2SO_4 had been added. After 0.5 hr, the reaction mixture was poured into excess H_2O and the diacyl derivative was collected and recrystallized from dilute alcohol or other solvent. The acyl derivatives requiring special methods are described individually.

2-Methyl-2-propyl-1,3-propanediol N-Acetyldicarbamate (190).—One mole of acetyl isocyanate, prepared by the method of Hill and Degnan,[24] was treated with 1 mole of 2-methyl-2-propyl-3-hydroxypropyl carbamate dissolved in anhydrous C_6H_6. The product, insoluble in C_6H_6, was crystallized (H_2O); mp 88–89°, yield 80%.

2-Methyl-2-propyl-1,3-propanediol N,N′-Bis(β-bromopropionyl)dicarbamate (276).—One mole of β-bromopropionyl isocyanate, prepared by the method of Johnson,[25] was mixed with 0.5 mole of 2-methyl-2-propyl-1,3-propanediol in $CHCl_3$. The reaction mixture was heated at reflux for 2 hr and then the solvent was removed by distillation under reduced pressure. A 70% yield of product, mp 138–139°, was obtained; after recrystallization (EtOH), mp 140–141°.

2-Methyl-2-propyl-1,3-propanediol N,N′-diacryoyldicarbamate (274) was prepared in 30% yield from the above compound by dehydrohalogenation with excess Et_3N in PhMe. The mixture was warmed on the steam bath and allowed to stand 1 hr. The amine·HBr was separated by filtration and the excess Et_3N was removed by warming. The product crystallized on cooling. Repeated crystallization (EtOH–H_2O) gave a product melting at 170–171°.

The preparation of the miscellaneous N-substituted dicarbamates appearing in Table VI which required special procedures are given below.

2,2-Diethyl-3-hydroxypropyl allophanate (328) was prepared in low yield by treating a dioxane solution of the diol with HOCN, obtained by the thermal depolymerization of cyanuric acid. It was isolated by diluting the dioxane solution with H_2O and was crystallized from EtOH, mp 154.5–156°. The 2,2-dimethyl analog (**327**) was also prepared by this method.

2,2-Diethyl-1,3-propanediol diallophanate (338) was prepared in 66% yield by treating 1 mole of the diol bis(chlorocarbonate) with 2 moles of urea in C_6H_6 solution. A trace of H_2SO_4 was added and the mixture was refluxed for 18 hr. The product was crystallized from EtOH, mp 191–193°. The 2-methyl-2-propyl analog (**337**) was prepared in a similar manner.

2,2-Diethyl-1,3-propanediol N,N′-Dinitro-N,N′-diethyldicarbamate (334).—Following the method of Curry and Mason,[26] 2,2-diethyl-1,3-propanediol N,N′-diethyldicarbamate was nitrated using a mixture of 90% fuming HNO_3 and Ac_2O (1:3), prepared at 0–10°. The dicarbamate was added to this mixture at such a rate as to maintain its temperature under 10°. After stirring for 0.5 hr, the mixture was poured into excess H_2O to precipitate the dinitro derivative. It was recrystallized from EtOH, mp 43.5–44.5°. The same procedure was employed to prepare **2-methyl-2-propyl-1,3-propanediol N,N′-dinitrodicarbamate (333).**

The preparation of 2-substituted 3-hydroxypropyl carbazates (method H) is illustrated by the preparation of **2-methyl-2-propyl-3-hydroxypropyl carbazate (311).** One mole of 5-methyl-5-propyl-2-*m*-dioxanone was treated at room temperature with 1 mole of hydrazine (85% hydrazine hydrate) for 12 hr. The product was crystallized from $CHCl_3$, mp 75–77° (60%).

2-Methyl-2-propyl-1,3-propanediol Dicarbazate (321).—2-Methyl-2-propyl-1,3-propanediol bis(methylcarbonate) was prepared by reaction of 2 moles of MeOH with 0.5 mole of 2-methyl-2-propyl-1,3-propanediol bis(chlorocarbonate) in 2 moles of pyridine. The mixture was warmed on the steam bath for 3 hr and the upper layer, containing the carbonate, was combined with the Et_2O extract of the acidified lower layer. The Et_2O solution

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TABLE VI

MISCELLANEOUS 1,3-PROPANEDIOL CARBAMATES

$RR_1C(CH_2OCONR_2R_3)(CH_2OCONR_4R_5)$

No.	R	R_1	R_2	R_3	R_4	R_5	Method	Yield, %	Mp or bp (mm), °C	$n^{25}D$	Formula	Analyses	---Dose, mg/kg[a]--- PD$_{50}$	ED$_{50}$	LD$_{50}$
311	Me	Pr	*b*		H	NH_2	H	60	75–77		$C_8H_{18}N_2O_4$	N			
312	Et	Et	*b*		H	NH_2	N	76	82–83		$C_8H_{16}N_2O_4$	N[c]			
313	Me	Pr	*b*		H	$PhCH{=}N$	*d*	67	116–118		$C_{15}H_{22}N_2O_4$	C, H, N			
314	Me	Pr	*b*		H	*i*-PrNH	*d*	60	*e*		$C_{11}H_{24}N_2O_4$	C, H, N	350		350
315	Me	Bu	*b*		H	*i*-PrNH	*d*	85	125–130 (0.01)	1.4661	$C_{12}H_{26}N_2O_4$	N	980		980
316	Et	Pr	*b*		H	NH_2	H	80	131–132		$C_{10}H_{22}N_2O_4$	C, H, N			
317	Ph	Pr	*b*		H	NH_2	H	92	145–146		$C_{14}H_{22}N_2O_4$	N			
318	Me	Pr	H	H	H	NH_2	J	21	92–96		$C_9H_{20}N_2O_4$	N[f]			
319	Me	Bu	H	H	H	*i*-PrNH	*d*	85	83–85		$C_{12}H_{28}N_2O_4$	N	180		278
320	Me	sec-Bu	H	H	H	NH_2	J	58	129–131		$C_{10}H_{24}N_2O_4$	C, H, N			
321	Me	Pr	H	NH_4	H	NH_2	*d*	60	228–229[g]		$C_9H_{22}N_4O_4S$	N, S[h]			120
322	Et	Et	H	NH_2	H	NH_2	A	27	54–56		$C_9H_{20}N_4O_4$	N	> 1400		195
323	Me	Pr	H	H	H	*i*-PrNH	M	17	96–98		$C_{12}H_{28}N_2O_4$	C, H, N	280		<280
324	Me	Pr	H	*i*-PrNH	H	*i*-PrNH	*d*	30	191–192[i]		$C_{16}H_{30}Cl_2N_2O_4$	Cl	550		> 620
325	Me	Pr	H	$Me_2C{=}N$	H	$Me_2C{=}N$	*d*	50	180–182		$C_{15}H_{28}N_4O_4$	C, H, N	> 620		420
326	Me	Pr	H	$PhCH{=}N$	H	$PhCH{=}N$	*d*	52	195–196		$C_{25}H_{32}N_4O_4$	N	> 620	> 620	
327	Me	Me	*b*		H	Carbamoyl	*d*	20	168–169.5		$C_{11}H_{22}N_4O_6$	N			
328	Et	Et	*b*		H	Carbamoyl	*d*	30	154.5–156		$C_{13}H_{26}N_4O_6$	N	> 1400		
329	Et	Et	*b*		MeO	Me	H	37	127–134 (0.1)	1.4572	$C_{10}H_{21}NO_5$	C, H, N	> 420		460
330	Me	Pr	H	H	H	OH	*d*	65	100 dec		$C_8H_{18}N_2O_4$	C, H, N			
331	Me	Pr	Me	MeO	Me	MeO	A	81	153–159 (1.5)	1.4503	$C_{12}H_{26}N_2O_5$	C, H, N	325		> 420
332	Et	Et	Me	MeO	Me	Me	A	30	130–135 (0.02)	1.4537	$C_{13}H_{28}N_2O_6$	C, H, N	620	420 (ip)	
333	Me	Pr	H	O_2N	H	NO_2	*d*	25	116–118		$C_8H_{16}N_4O_8$	C, H, N	> 420	> 420	< 420
334	Et	Et	Et	O_2N	Et	NO_2	*d*	85	43.5–44.5		$C_{12}H_{24}N_4O_8$	C, H, N	> 620	420	
335	Me	Pr	H	H	H	$PhSO_2$	K	60	124–125		$C_{21}H_{32}N_2O_8S$	H, N; C, S[j]			
336	Me	Pr	H	H	H	Sulfamoyl	*k*	25	135–136		$C_{11}H_{24}N_4O_8S$	C, H, N, S			
337	Me	Pr	H	Carbamoyl	H	Carbamoyl	*d*	25	200–201		$C_9H_{18}N_4O_6$	N	> 620		
338	Et	Et	H	Carbamoyl	H	Carbamoyl	*d*	66	191–193		$C_{10}H_{20}N_4O_6$	N		> 940	
339	Et	Et_2NCH_2	H	H	H	Carbamoyl	*l*	20	148–150		$C_{13}H_{29}N_5O_5$	N	> 620		

[a] See footnote *b* in Table I. [b] Compound is a 3-hydroxypropyl N-substituted carbamate. [c] N: calcd, 14.72; found, 15.17. [d] See Experimental Section. [e] See footnote *f*, Table III. [f] N: calcd, 18.01; found, 17.50. [g] H_2SO_4 salt. [h] S: calcd, 9.25; found, 8.78. [i] HCl salt. [j] C: calcd, 50.25; found, 50.67. S: calcd, 8.93; found, 8.44. [k] Prepared from the product of the reaction of 2-methyl-2-propyl-3-hydroxypropyl carbamate and $COCl_2$, without purification, with 1 equiv of monosodium sulfamide. [l] Obtained as a by-product in the preparation of **80** (Table II).

was washed (10% HCl, H_2O), dried (Na_2SO_4), and distilled. The fraction, bp 95–98° (0.07 mm), weighed 92.4 g (75%). This carbonate was converted to the desired dicarbazate by treating it with 2 equiv of hydrazine hydrate for 16 hr at room temperature. It was isolated as the sulfate by treating the *i*-PrOH solution of the base with a slight excess of H_2SO_4. Crystallization from EtOH–H_2O gave a product, mp 228–229°.

The N-alkylene- and N-alkylcarbazates listed in Table VI were prepared from the corresponding carbazates by treatment with the appropriate aldehyde or ketone followed by catalytic reduction. Typical examples of the preparation of these compounds are as follows.

2-Methyl-2-propyl-1,3-propanediol N,N′-bis(isopropylimino)-dicarbamate (325) was obtained by treating the corresponding amino compound with Me_2CO. The two materials were warmed on the steam bath for a short time and then diluted (H_2O). After recrystallization (EtOAc), the product melted at 180–182°.

2-Methyl-2-propyl-1,3-propanediol N,N′-Bis(isopropylamino)-dicarbamate (324).—The corresponding imino compound was hydrogenated in EtOH using PtO_2 catalyst at 3 atm of H_2. It was isolated as the HCl salt and recrystallized from dioxane–EtOAc (1:2), mp 191–192°.

2-Methyl-2-propyl-1,3-propanediol N,N′-bis(benzylimino)di-carbamate (326) was readily formed when the corresponding diamino compound was treated with benzaldehyde in the presence of a trace of HCl. It crystallized from EtOH, mp 195–196°.

The corresponding monocarbazate **313** was obtained in a similar manner by the reaction of 2-methyl-2-propyl-3-hydroxypropyl carbazate with benzaldehyde, and **314**, **315** and **319** by reaction of the monocarbazate with Me_2CO followed by catalytic reduction.

2-Methyl-2-propyl-1,3-propanediol N-Hydroxydicarbamate (330).—The reaction product of molar equivalents of 2-methyl-2-propyl-3-hydroxypropyl carbamate and $COCl_2$ in THF was isolated in the crude form by removal of the solvent at 40°. Its solution in Et_2O was stirred for 2 hr with excess benzyloxyamine, and the excess amine was removed under reduced pressure. The residual oil was dissolved in EtOH and reduced at 2 atm of H_2 using 5% Pd–C. The product was isolated as an oil by removal of the EtOH under reduced pressure and was purified by sublimation at 0.01 mm.

2-Methyl-2-(2-hydroxypropyl)-1,3-propanediol Tricarbamate (62).—The synthesis of α-methyl-α-carbethoxy-γ-valerolactone was achieved according to the method of Seidel and Stoll,[27] using propylene oxide in place of ethylene oxide. A 75% yield of lactone, bp 55–57° (0.02 mm), was obtained. *Anal.* ($C_9H_{14}O_4$) C, H.

The lactone was reduced to 2-methyl-2-(2-hydroxypropyl)-1,3-propanediol using LAH. A yield of 37%, bp 105–109° (0.02 mm), was obtained. *Anal.* ($C_7H_{16}O_3$) C, H.

The tricarbamate was prepared by treating this triol with 3 equiv of NaOCN and dry HCl. Crystallization was effected using EtOAc, mp 72–74°.

Attempted Transesterification Reaction Using an N-Substituted Urethan.—2-Methyl-2-propyl-3-hydroxypropyl carbamate (17.5 g, 0.1 mole) and N-methylurethan (11.3 g, 0.11 mole) were dissolved in excess PhMe. The system was dried by the distillation of a small amount of PhMe, cooled to room temperature, 2 g of aluminum isopropoxide was added, and distillation was continued. After heating for 11 hr, only 3.0 ml of EtOH had distilled, which is approximately the volume which can be liberated from the aluminum isopropoxide employed. The reaction mixture was worked up in the usual manner and 6 g of an oily product was obtained. Fractional distillation (0.01–0.02 mm) gave two fractions: (1) bp 88–120°, (2) bp 120–160°. From 1 there was obtained 1.35 g of crystalline 2-methyl-2-propyl-1,3-propanediol, identified by ir and mixture melting point with an authentic sample of this material. From 2 there was obtained 3 g of 2-methyl-2-propyl-1,3-propanediol dicarbamate, also identified by ir and mixture melting point with an authentic sample. Fraction 2 also yielded a small quantity (1 g) of unchanged monocarbamate.

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