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Some Anticonvulsant Agents Derived from 1,3-Propanediols

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A number of mono- and dicarbamate esters of 2,2-disubstituted-1,3-propanediols have been prepared for evaluation as anticonvulsants. The dicarbamate esters were synthesized by phosgenation of the substituted propanediols followed by amidation of the bis-(chlorocarbonate) derivatives. The monocarbamate esters were obtained by ammonolysis of the cyclic carbonates prepared from the substituted propanediols.

The anticonvulsant properties of 2,2-disubstituted-1,3-propanediols, a class of compounds bearing little structural similarity to the accepted anticonvulsants, have recently been described.[1] Pharmacological studies on 2,2-diethyl-1,3-propanediol,[2] one of the more active members of this series, indicated that this compound had a powerful but short anticonvulsant action. It was also found that the action of certain of its esters was of longer duration than that resulting from the diol itself.[3] In an extension of this study, a number of mono- and dicarbamate esters of 2,2-disubstituted 1,3-propanediols have been prepared for pharmacological evaluation as potential anticonvulsant agents. This paper describes the synthesis and physical properties of these compounds. The results of the pharmacological studies carried out on these compounds will be published elsewhere.

Of the variety of procedures which have appeared in the literature for the preparation of carbamates,[4] we found the method described by Oesper, Broker and Cook[5] most suitable for the conversion of dihydric alcohols to the corresponding dicarbamate derivatives. This method consists of low temperature phosgenation of the substituted 1,3-propanediol in an inert medium in the presence of a tertiary amine, followed by conversion of the bis-(chlorocarbonate) derivative to the desired diamide. In our experience antipyrine gave consistently higher over-all yields of pure carbamates than the other tertiary amines used in the acylation reaction. Although the substituted 1,3-propanediol bis-(chlorocarbonate) derivatives could be readily isolated and purified by distillation, it was advantageous to convert them directly to the diamide by direct ammoniation of the phosgene reaction mixture.

Monocarbamate derivatives of 1,3-propanediols could be prepared in a similar manner, using an equimolar ratio of phosgene and diol, but this reaction yielded, in addition to the desired monocarbamate derivative, a considerable amount of unreacted diol and appreciable quantities of the dicarbamate and cyclic carbonate derivatives. The difficulty of separating these products could be avoided by forming the monocarbamates through ammonolysis of the cyclic carbonate esters. The latter compounds were prepared by the reaction of equimolar quantities of phosgene and propanediol in the presence of antipyrine at a temperature somewhat higher than that found most suitable for chlorocarbonate formation.

The carbamate and carbonate esters prepared in this study were white crystalline solids or high boiling liquids. Except for the lower members of the monocarbamate series, which possess considerable water solubility, these compounds are relatively insoluble in water.

Experimental[6]

Preparation of 2,2-Disubstituted 1,3-Propanediols.—2,2-Dimethyl-, diethyl-, methyl-*n*-propyl- and ethyl-*n*-butyl-1,3-propanediol were prepared by the condensation of formaldehyde with isobutyraldehyde, 2-ethylbutyraldehyde, 2-methylvaleraldehyde and 2-ethylhexaldehyde, respectively, following the procedure of Shortridge, *et al.*[7] The remaining 1,3-propanediols were obtained by reduction of the corresponding substituted malonic esters with lithium aluminum hydride.[8]

Preparation of 2,2-Disubstituted-1,3-propanediol Dicarbamates.—The following procedure illustrates the method that was adopted for the preparation of the dicarbamates listed in Table I. To a solution of 20 g. (0.2 mole) of phosgene in 200 ml. of toluene at −10° there was added with stirring a cooled solution of 13.2 g. (0.1 mole) of 2,2-diethyl-1,3-propanediol, and 38 g. (0.2 mole) of antipyrine in 100 ml. of chloroform, at such a rate that the temperature of the reaction mixture was maintained at −5 to 0°. The mixture was allowed to warm slowly to room temperature and to remain at this temperature overnight. The antipyrine hydrochloride was removed by filtration and the chlorocarbonate converted directly to the amide by treating the filtrate with gaseous ammonia with moderate cooling. The amide was separated by filtration, freed from ammonium chloride by extracting with 250 ml. of cold water and recrystallized from hot water; 17.5 g. (80%) of 2,2-diethyl-1,3-propanediol dicarbamate, m.p. 149–150°, was obtained.

To obtain the chlorocarbonate derivative, the toluene chloroform filtrate obtained on removal of the antipyrine hydrochloride was concentrated and the liquid residue purified by distillation under reduced pressure. A 75% yield of 2,2-diethyl-1,3-propanediol bis-(chlorocarbonate) was obtained as a clear, colorless liquid, b.p. 108° (4.5 mm.), $n^{25}D$ 1.4628. *Anal.* Calcd. for $C_9H_{14}O_4Cl_2$: Cl, 27.5. Found: Cl, 27.5.

The dicarbamate esters of 1,3-propanediols substituted with higher alkyl groups sometimes remained in solution following treatment with ammonia. In these cases, the amide was obtained by evaporation of the toluene–chloroform solvent under reduced pressure. All of the dicarbamates prepared were crystallized from water, and over-all yields of 60–90% of purified compound were obtained.

Preparation of N-Substituted-2,2-diethyl-1,3-propanediol Dicarbamates.—The N-methyl, N-phenyl and N,N-di-

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(2) 2,2-Diethyl-1,3-propanediol has been commonly referred to in the literature as DEP.

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(5) R. E. Oesper, W. Broker and W. A. Cook, *ibid.*, **47**, 2609 (1925).

(6) All temperatures reported are uncorrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Middle Village, Long Island, N. Y.

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TABLE I

2,2-DISUBSTITUTED-1,3-PROPANEDIOL DICARBAMATES, $RR'C(CH_2OCONH_2)_2$

Compd.	R	R'	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found
1	Methyl	Methyl	82	151.5–152.5	$C_7H_{14}N_2O_4$	14.7	14.8
2	Methyl	Ethyl	65	135–136	$C_8H_{16}N_2O_4$	13.7	13.8
3	Methyl	*n*-Propyl	90	105–106	$C_9H_{18}N_2O_4$	12.8	12.5
4	Methyl	Isopropyl	61	99–100	$C_9H_{18}N_2O_4$	12.8	13.1
5	Ethyl	Ethyl	80	149–150	$C_9H_{18}N_2O_4$	12.8	12.8
6	Ethyl	*n*-Butyl	63	117–118	$C_{11}H_{22}N_2O_4$	11.4	11.7
7	Ethyl	Phenyl	70	119–120	$C_{13}H_{18}N_2O_4$	10.5	10.3
8	*n*-Propyl	*n*-Propyl	87	152–153	$C_{11}H_{22}N_2O_4$	11.4	11.7
9	$RR' = -(CH_2)_5-$[a]		60	112–113	$C_{10}H_{18}N_2O_4$	12.2	12.2

[a] 1,1-Dicarbamoxycyclohexane. The intermediate, 1,1-bis-(hydroxymethyl)-cyclohexane, was obtained through the courtesy of Prof. C. E. Boord of The Ohio State University (see ref. 7).

ethyl derivatives of 2,2-diethyl-1,3-propanediol dicarbamate were obtained in somewhat lower over-all yields using essentially the same procedure. Upon treating the solution of 2,2-diethyl-1,3-propanediol bis-(chlorocarbonate) with the appropriate amine, the resulting amides remained in solution and were obtained by removal of the solvent. The methyl and phenyl derivatives were purified by crystallization from water and the diethyl amide by distillation under reduced pressure.

N,N'-Diacetyl-2,2-diethyl-1,3-propanediol dicarbamate was obtained by warming 5 g. of 2,2-diethyl-1,3-propanediol dicarbamate with 6 g. of acetic anhydride and two drops of sulfuric acid. The reaction mixture was poured into cold water and allowed to solidify; 4.5 g. (65%) of product was obtained as a white crystalline solid. Purification was effected by crystallization from water.

N,N'-Bis-(phenacetyl)-2,2-diethyl-1,3-propanediol dicarbamate was prepared in low yield by warming the amide with a slight excess of phenacetyl chloride in pyridine. The reaction product separated as a dark gummy solid and was purified by repeated crystallization from aqueous ethanol.

The physical constants and analytical data for these compounds are summarized in Table II.

TABLE II

N-SUBSTITUTED-2,2-DIETHYL-1,3-PROPANEDIOL DICARBAMATES, $(C_2H_5)_2C(CH_2OCONHR)_2$

R	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found
Methyl	56	85–86	$C_{11}H_{22}N_2O_4$	11.4	11.5
Phenyl[a]	67	135.5–136.5	$C_{21}H_{26}N_2O_4$	7.6	8.0
Acetyl	65	123–124	$C_{13}H_{22}N_2O_6$	9.3	9.1
Phenacetyl	20	204–205	$C_{26}H_{30}N_2O_6$	6.2	6.1
Ethyl[b]	50	.....	$C_{17}H_{34}N_2O_4$	8.5	8.1

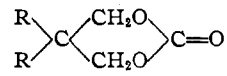
[a] Prepared also by reaction of 2,2-diethyl-1,3-propanediol and phenyl isocyanate. [b] Bis-(diethylamino) derivative, b.p. 130–132° (5 mm.), $n^{25}D$ 1.4569. *Anal.* Calcd.: C, 61.9; H, 10.0. Found: C, 61.8; H, 9.7.

Preparation of Cyclic Carbonate Esters.—The preparation of cyclic carbonate derivatives of 2,2-disubstituted-1,3-propanediols is illustrated by the synthesis of 5,5-diethyl-2-*m*-dioxanone. A cooled 10% solution of 0.1 mole of phosgene in toluene was added with stirring to a cooled solution of 13.2 g. (0.1 mole) of 2,2-diethyl-1,3-propanediol and 0.2 mole of antipyrine in a minimum volume of chloroform, at such a rate that the temperature was maintained at about 25°. The mixture was allowed to remain at this temperature overnight, then filtered to remove the antipyrine hydrochloride. The filtrate was concentrated by evaporating the bulk of the toluene–chloroform solvent, and the residue dissolved in ether. The water soluble components were removed by water extraction, the ether layer dried and concentrated by removal of the solvent. The crude ester was distilled, giving 10.5 g. (66%) of clear, viscous liquid which solidified on cooling, b.p. 131–132° (2 mm.). Further purification was effected by crystallization of the product from benzene–ligroin solution; m.p. 45–46°.

The 5,5-dimethyl- and 5-ethyl-5-phenyl-2-*m*-dioxanones were obtained in the same manner. The dioxanone derivatives prepared from 2-methyl-2-*n*-propyl- and 2-ethyl-2-*n*-butyl-1,3-propanediol were obtained as liquids whose solidification points were considerably below room temperature. The yield of distilled product was 60–85%. The physical constants and analytical data for these compounds are summarized in Table III.

TABLE III

5,5-DISUBSTITUTED-2-*m*-DIOXANONES



Parent compd.[a]	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
1	60	110–111	$C_8H_{16}O_3$	55.4	55.4	7.7	7.5
3	74	[b]	$C_9H_{18}O_3$	60.8	61.1	8.9	8.9
5	66	45–46	$C_9H_{18}O_3$	60.8	61.0	8.9	8.7
6	80	[c]	$C_{13}H_{18}O_3$	64.5	64.4	9.7	9.6
7	85	99.5–100.5	$C_{13}H_{14}O$	70.0	70.1	6.8	6.9

[a] The numbers correspond to the compound numbers in Table I. [b] B.p. 95–104° (0.25 mm.); $n^{25}D$ 1.4550. [c] B.p. 125–130° (1 mm.); $n^{25}D$ 1.4638.

Preparation of 2,2-Disubstituted-3-hydroxypropyl Carbamates.—Five grams of the 5,5-disubstituted-2-*m*-dioxanone was placed in a stainless steel pressure bomb and the vessel cooled in Dry Ice. 7.5 ml. of liquid ammonia was added and the vessel closed. Upon warming to room temperature, the contents were shaken and the mixture allowed to remain at room temperature for 48 hours. The vessel was cooled in Dry Ice, opened and the excess ammonia allowed to evaporate. The monocarbamates, obtained as low melting solids, were purified by crystallization; yields of 2–4 g. of purified product were obtained.

N-Methyl-2,2-diethyl-3-hydroxypropyl carbamate was prepared by treating 5 g. of the dioxanone with an excess of 25% methylamine in a pressure bottle at 50° for 24 hours. The mixture was evaporated under reduced pressure on a steam-bath and the residue purified by distillation under reduced pressure; 3.5 g. (59%) of product was obtained.

N,N-Diethyl-2,2-diethyl-3-hydroxypropyl carbamate was obtained by refluxing 5 g. of the dioxanone in an excess of

TABLE IV

2,2-DISUBSTITUTED-3-HYDROXYPROPYL CARBAMATES $HOCH_2CRR'CH_2OCONH_2$

Parent compd.[a]	Yield, %	M.p., °C.	Formula	Nitrogen, % Calcd.	Found
1	53	60–61[b]	$C_6H_{13}NO_3$	9.5	9.6
3	60	61.5–62.5[b]	$C_8H_{17}NO_3$	8.0	8.0
5	75	75–76[c]	$C_8H_{17}NO_3$	8.0	8.3
5	59	[d]	$C_9H_{19}NO_3$	7.4	7.0
5	55	[e]	$C_{12}H_{25}NO_3$	6.1	6.0
6	73	66.5–67.5[f]	$C_{10}H_{21}NO_3$	6.9	6.7
7	69	89–90[f]	$C_{12}H_{17}NO_3$	6.3	6.3

[a] The numbers correspond to the compound numbers in Table I. [b] Recrystn. solvent toluene–ligroin mixture. [c] Recrystn. solvent benzene. Yale, *et al.*, ref. 8, reported m.p. 69–70°. [d] N-Methyl derivative; b.p. 110–116° (0.5 mm.); $n^{25}D$ 1.4640. [e] N,N-Diethyl derivative; b.p. 104–108° (0.5 mm.); $n^{25}D$ 1.4587. [f] Recrystn. solvent water.

anhydrous diethylamine for four hours. Distillation of the crude reaction product yielded 4.0 g. (55%) of the bis-(diethylamide).

Table IV summarizes the physical constants and analytical data for these compounds.

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A New Synthesis of 1-Glycosylbenzimidazoles[1]

BY JOHN DAVOLL[2] AND GEORGE BOSWORTH BROWN

1-Glycosylbenzimidazoles are prepared in good yield by condensation of polyacetylglycosyl halides with chloromercuribenzimidazoles, followed by deacetylation of the reaction products.

The isolation of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole from hydrolysates of vitamin B_{12},[3] and the demonstration[4] that it, or the β-isomer, will elicit a vitamin B_{12}-like growth response in rats, has aroused interest in the synthesis of this compound and of analogous 1-glycosylbenzimidazoles. Of the three reported syntheses of this type of compound, two proceed by condensation of the appropriate *o*-glycosylaminoaniline with either ethyl formimino ether hydrochloride[3] or sodium dithioformate.[5a] It has also been reported[5] that 1-D-glucopyranosylbenzimidazole can be prepared, in very low yield, from the condensation product of silver 5,6-dimethylbenzimidazole and tetraacetylglucosyl bromide.[5b]

It has now been found that, as in the pure series,[6] the chloromercuri derivatives of benzimidazoles are much superior to the silver salts for use in such condensations. By deacetylation of the condensation products of chloromercuribenzimidazoles with polyacetyl glycosyl halides the 1-β-D-ribofuranosyl and 1-β-D-glucopyranosyl derivatives of benzimidazole and 5,6-dimethylbenzimidazole have been prepared in 29 to 53% yield. The properties of these compounds are set out in Table I. It is assumed that Walden inversion occurs in the condensation reaction, so that the products have the β configuration. This was verified in the case of 1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole by comparison of the picrate with authentic specimens of 1-α- and 1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole picrates.[3,7]

TABLE I

	Yield, %[a]	M.p., °C.[b]	Formula	$[\alpha]^{25}D$; c = 1% in 0.1 N HCl	Ultraviolet absorption[c] 40 mg./l. in 0.1 N HCl λm mμ	εm	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found
1-β-D-Ribofuranosylbenzimidazole	53	111–112	$C_{12}H_{14}O_4N_2$	+13°	254	5130	57.6	57.5	5.6	5.8	11.2	11.1
					262	5470						
					269	6530						
					275	5660						
1-β-D-Glucopyranosylbenzimidazole	34	141–142	$C_{13}H_{16}O_5N_2$	+19°	253	4970	55.7	56.0	5.7	5.9	10.0	9.9
					261	5290						
					268	6230						
					275	5290						
1-β-D-Ribofuranosyl-5,6-dimethylbenzimidazole	43	192–200	$C_{14}H_{18}O_4N_2$	+16°	278	7770	60.4	60.5	6.5	6.6	10.1	10.2
					286	7440						
1-β-D-Glucopyranosyl-5,6-dimethylbenzimidazole	29	167–168[d] 251–253[e]	$C_{15}H_{20}O_5N_2$	+ 7°	278	7550	58.5	58.3	6.5	6.9	9.1	9.4
					285	6930						

[a] Based upon the benzimidazole. [b] Determined on a heated microscope stage; uncorrected. [c] Determined on a Cary Recording Spectrophotometer. [d] Reference 5a gives m.p. 166–167° for the sesquihydrate. [e] Anhydrous.

Experimental

Chloromercuribenzimidazoles.—A solution of the benzimidazole in hot 10% ethanol (100 ml./g.) containing one equivalent of sodium hydroxide was treated with an ethanolic solution of one molecular proportion of mercuric chloride. After cooling, the white precipitate was collected, washed with water and dried; yield 90–100%.

Like the corresponding purine derivatives,[6] these compounds contained less chlorine than would be expected from

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(2) Fellow of the National Cancer Institute of the United States Public Health Service, Federal Security Agency.

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(5a) J. G. Buchanan, A. W. Johnson, J. A. Mills and A. R. Todd, *J. Chem. Soc.*, 2845 (1950).

(5b) When this manuscript was submitted we were not aware of the papers by P. Mamalis, V. Petrow and B. Sturgeon, *J. Pharm. Pharmacol.*, **2**, 503, 512 (1950), and G. Cooley, B. Ellis, P. Mamalis, V. Petrow and B. Sturgeon, *ibid.*, **2**, 579 (1950), describing the synthesis, from silver benzimidazoles, of 1-D-glucopyranosyl-benzimidazole and -5,6-dimethylbenzimidazole. We find a considerably lower melting point (141–142°) for 1-β-D-glucopyranosylbenzimidazole than that (212–213°) reported by the above authors, but the properties of the tetraacetyl derivative (m.p. 152–154°; $[\alpha]^{25}D$ −27° (c = 1.7% in chloroform)) and picrate (m.p. 144–147°) of our material are in fair agreement with those reported by Petrow, *et al.* For 1-tetraacetyl-β-D-glucopyranosyl-5,6-dimethyl-5,6-dimethylbenzimidazole we find m.p. 169–170°, with sintering above 126°, $[\alpha]^{25}D$ −44° (c = 1.7% in chloroform); Petrow, *et al.*, report m.p. 189.5–191°, $[\alpha]^{20}D$ −40.4° (c = 1% in chloroform).

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(7) Kindly supplied by Dr. Karl Folkers, Research Laboratories, Merck and Co., Inc., Rahway, N. J.