O-Diazoacetyl-D-serine.—To a solution of 15 g. (0.075 mole) of O-glycyl-D-serine monohydrochloride in 1500 ml. of water and ice was added 13.1 g. (0.14 mole) of sodium nitrite. The resulting solution was allowed to stand overnight at 25°, *p*H 4.7–5.2. The solution was degassed under vacuum and put on a column consisting of 100 g. of Darco G-60 and 100 g. of Celite 545. The column was washed with 2 l. of water and eluted with water containing 2% acetone and the eluate, having a yellow color and positive ninhydrin, was collected (500 ml.), shell-frozen and lyophilized. This gave a yellow solid, 2.6 g., $E^{1\%}_{1\,cm}$ 1124 at $\lambda^{H_2O}_{max}$ 250 mμ. It was recrystallized from water–ethanol yielding yellow crystals, 1.7 g. (13%), m.p. 153–155° dec., $[\alpha]^{26}D$ +0.4° (*c* 5.57 in water), $E^{1\%}_{1\,cm}$ 1140 at $\lambda^{H_2O}_{max}$ 250 mμ. The infrared spectrum was identical with that of azaserine.[1]

Anal. Calcd. for $C_5H_7O_4N_3$: C, 34.69; H, 4.08; N, 24.27. Found: C, 34.94; H, 4.34; N, 24.42.

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Aminomethyloxazolidones Derived from Substituted Diamino-2-propanols

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RECEIVED JANUARY 20, 1954

A series of substituted 1,3-diamino-2-propanols and the aminomethyloxazolidones obtained from them have been prepared for pharmacological evaluation. The methods of preparation, evidence for the chemical structure of the oxazolidones and the physical properties of the compounds are described.

Pharmacological evaluation of compounds structurally related to the muscle paralyzing drug mephenesin (3-*o*-toloxy-1,2-propanediol) has revealed that substitution of the ether oxygen with an –NH– linkage gives a compound completely devoid of paralyzing action but possessing moderate convulsant activity.[1] Extension of this modification to substituted diamino-2-propanols has led to the synthesis of a group of compounds possessing striking convulsant properties.[2]

This paper describes the synthesis and physical properties of a number of substituted 1,3-diamino-2-propanols which have been prepared for pharmacological evaluation. It also describes the preparation, properties and structural proof of some substituted 5-aminomethyl-2-oxazolidones obtained by ethyl carbonate cyclization of these diaminopropanols. The oxazolidones were of interest because of the favorable enhancement of pharmacological activity observed earlier on carbamylation of certain anticonvulsant and muscle paralyzing propanediols and toloxypropanols.[3]

The symmetrically substituted 1,3-diamino-2-propanols were prepared by condensation of epichlorohydrin with an excess of the appropriate primary or secondary amine. The unsymmetrical members were obtained by stepwise amination of epichlorhydrin, usually without isolation of the intermediate 1-amino-3-chloro-2-propanol. Conversion of the diaminopropanols to the cyclic carbamates was accomplished by distilling a mixture of the compound and an excess of ethyl carbonate with a catalytic amount of sodium methylate until the theoretical volume of ethanol had been removed.

Cyclization of the symmetrically monosubstituted diaminopropanols in this manner leads to the formation of a single oxazolidone (I, R = R′). However, the unsymmetrical monosubstituted diaminopropanols under the same conditions are theoretically convertible to two isomeric oxazolidones, I and II. The high yield and relative homogeneity of the product obtained from the condensation of ethyl carbonate and alkylaminoarylaminopropanols definitely indicated the formation of only one isomer. Proof for the identity of this isomer was obtained from another set of reactions.

The product obtained from the reaction of ethyl carbonate and 1-anilino-3-*n*-butylamino-2-propanol was *n*-butylated to give either III or IV, where R = *n*-butyl and R′ = phenyl. The butylated adduct was compared to samples of III and IV prepared by the unambiguous condensation of ethyl carbonate with 1-*n*-butylamino-3-N-*n*-butylanilino-2-propanol and 1-anilino-3-di-*n*-butylamino-2-propanol, respectively, and was found to be identical with III. Also, on acid hydrolysis, the butylated product yielded 1-*n*-butylamino-3-N-*n*-butylanilino-2-propanol rather than the isomeric compound 1-anilino-3-di-*n*-butylamino-2-propanol which would result from the hydrolysis of IV. In the condensation of ethyl carbonate with the trifunctional diaminopropanol, cyclization occurs exclusively through the hydroxyl group and the more basic alkylamino group. It is probable that the cyclization of unsymmetrical bis-(alkylamino)- or bis-(arylamino)-propanols, where little if any difference in base strength existed, would lead to a mixture of the two possible isomers.

It is of interest that no evidence was found to indicate the formation of a cyclic ureide through condensation of ethyl carbonate with both amino groups. This condensation would lead to the formation of the 1,3-disubstituted-4-hydroxytetrahydro-2-pyrimidone (V).

The substituted diaminopropanols prepared in this study are low melting crystalline solids. Except for the two lowest members of the series, these compounds are relatively insoluble in water. They are readily convertible to their soluble hydrochloride salts. The substituted aminomethyloxazolidones also possess limited solubility in water, and are readily cleaved by strong acid or alkali. The strik-

(1) W. A. Lott, *Trans. N. Y. Acad. Sci.*, [2] **11**, 1 (1948); F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **93**, 470 (1948).

(2) (a) F. M. Berger, *ibid.*, **107**, 250 (1953); (b) F. M. Berger and T. E. Lynes, *ibid.*, **109**, 407 (1953).

(3) (a) B. J. Ludwig and E. C. Piech, THIS JOURNAL, **73**, 5779 (1951); (b) **73**, 5894 (1951); (c) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **104**, 229 (1952); (d) **104**, 468 (1952).

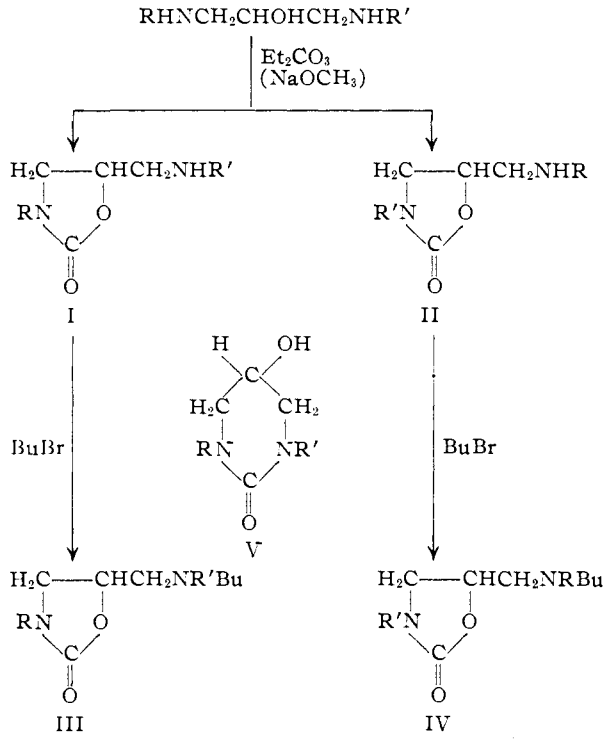
ing convulsant action characteristic of the substituted diaminopropanols is completely lacking in the oxazolidones derived from them.

Acknowledgment.—The authors wish to acknowledge the valuable technical assistance of E. C. Piech of these laboratories.

TABLE I

Compd.	R_1	R_2	R_3	Yield,[a] %	M.p. or b.p. (mm.), °C.[b]	Empirical formula	Nitrogen, % Calcd.	Found
			Substituted 1,3-diamino-2-propanols, $R_1R_2NCH_2CHOHCH_2NHR_3$					
1	*n*-Propyl	H	*n*-Propyl	53	53–54.4[ca]	$C_9H_{22}N_2O$	16.07	15.80
2	*n*-Butyl	H	*n*-Butyl	51	43–44[ca]	$C_{11}H_{26}N_2O$	13.85	13.45
					114–119(0.5)			
3	*n*-Hexyl	H	*n*-Hexyl	58	58–60[cb]	$C_{15}H_{34}N_2O$	10.83	11.23
4	*n*-Butyl	H	Phenyl	47	80–81[cb]	$C_{13}H_{22}N_2O$	12.60	12.44
					170–175(1.4)			
5	Ethyl	H	*p*-Tolyl	56	76.5–78[cb]	$C_{12}H_{20}N_2O$	13.43	13.49
6	*n*-Propyl	H	*p*-Tolyl	59	106–108[cc]	$C_{13}H_{22}N_2O$	12.60	12.64
7	*n*-Butyl	H	*o*-Tolyl	16	75.5–77.5[ca]	$C_{14}H_{24}N_2O$	11.86	11.53
					165–171(1.0)			
8	*n*-Butyl	H	*m*-Tolyl	70	82–83[cb]	$C_{14}H_{24}N_2O$	11.86	12.01
					160–164(0.5)			
9	*n*-Butyl	H	*p*-Tolyl	69	94–94.5[cb]	$C_{14}H_{24}N_2O$	11.86	11.75
10	*s*-Butyl	H	*p*-Tolyl	63	50.5–51.5[cd]	$C_{14}H_{24}N_2O$	11.86	11.93
11	Isobutyl	H	*p*-Tolyl	56	80–81[cd]	$C_{14}H_{24}N_2O$	11.86	12.09
12	*n*-Amyl	H	*p*-Tolyl	52	66.5–67.5[cd]	$C_{15}H_{26}N_2O$	11.18	11.16
13	Isoamyl	H	*p*-Tolyl	44	80–81[cd]	$C_{15}H_{26}N_2O$	11.18	11.34
14	*n*-Hexyl	H	*p*-Tolyl	52	76–77[cc]	$C_{16}H_{28}N_2O$	10.58	10.34
15[c]	*p*-Tolyl	H	*p*-Tolyl		113.5–114[cc]	.....	...	...
16	*n*-Butyl	H	*p*-Chlorophenyl	49	84–86[cc]	$C_{13}H_{21}N_2OCl$	10.92	10.62
17	*n*-Butyl	H	*p*-Chloro-*o*-tolyl	43	59–61[cd]	$C_{14}H_{23}N_2OCl$	10.36	10.22
18	Ethyl	Ethyl	*p*-Tolyl	22	[d]	$C_{14}H_{24}N_2O$	...	...
					138–143(1.0)			
19	*n*-Butyl	*n*-Butyl	Phenyl	49	50–51[cb]	$C_{17}H_{30}N_2O$	10.06	10.19
					168–173(1.0)			
20	*n*-Butyl	*n*-Butyl	*p*-Tolyl	63	50–51[cb]	$C_{18}H_{32}N_2O$	9.58	9.30
21	*n*-Butyl	Phenyl	*n*-Butyl	71	38–40[cd]	$C_{17}H_{30}N_2O$	10.06	10.21
					193–196(4.0)			
22	Ethyl	*o*-Tolyl	*n*-Butyl	59	140–143(0.9)[e]	$C_{16}H_{28}N_2O$	10.58	10.72
			Substituted 1-amino-3-(4-morpholinyl)-2-propanols, $R_1R_2NCH_2CHOHCH_2N(CH_2CH_2)_2O(CH_2CH_2)$					
23	*n*-Butyl	H[f]		56	250[cg]	$C_{11}H_{26}N_2O_2Cl_2$	9.66	9.45
24	Phenyl	H		74	124–125	$C_{13}H_{21}N_2O_2$	[g]	...
25	*p*-Tolyl	H		81	110–111.5[cf]	$C_{14}H_{22}N_2O_2$	11.20	11.45
26	Ethyl	Ethyl[f]		82	>250[cg]	$C_{11}H_{26}N_2O_2Cl_2$	9.66	9.49
27	Phenyl	Phenyl		16	170–175(0.08)	$C_{19}H_{24}N_2O_2$[h]	8.96	8.70
28	4-Morpholinyl[f]			56	246–248[cg]	$C_{11}H_{24}N_2O_3Cl_2$	9.30	9.20
			Substituted 5-aminomethyl-2-oxazolidones, $H_2C(N(R_3)C(=O)O)CHCH_2NR_1R_2$					
29	Phenyl	H	*n*-Butyl	86	74–76[ca]	$C_{14}H_{20}N_2O_2$	11.28	11.55
30	*p*-Tolyl	H	Ethyl	91	67–68[cc]	$C_{13}H_{18}N_2O_2$	11.96	11.70
31	*p*-Tolyl	H	*n*-Propyl	90	94–96[cc]	$C_{14}H_{20}N_2O_2$	11.28	11.55
32	*m*-Tolyl	H	*n*-Butyl	94	55.5–56.5[cc]	$C_{15}H_{22}N_2O_2$	10.68	10.87
33	*p*-Tolyl	H	*n*-Butyl	96	73.5–74.5[cc]	$C_{15}H_{22}N_2O_2$	10.68	10.44
34	*p*-Tolyl	H	*n*-Amyl	92	81–82[cc]	$C_{16}H_{24}N_2O_2$	10.01	10.04
35	*p*-Chlorophenyl	H	*n*-Butyl	78	81.5–82.5[cc]	$C_{14}H_{19}N_2O_2Cl$	9.92	9.78
36	*p*-Tolyl	H	*p*-Tolyl	87	157–158.5[cc]	$C_{18}H_{20}N_2O_2$	9.46	9.46
37	*n*-Butyl	*n*-Butyl	Phenyl	87	32–33[cd]	$C_{18}H_{28}N_2O_2$	9.21	9.14
38	*n*-Butyl	Phenyl	*n*-Butyl	64	214–216(1.5)[i]	$C_{18}H_{28}N_2O_2$	9.21	9.46
39	4-Morpholinyl		*p*-Tolyl	96	119.5–120.5[cc]	$C_{15}H_{20}N_2O_3$	10.14	9.89

[a] Yields are based on material of reasonable purity and do not take into account the recovery of starting materials. [b] M.p data are for analytically pure samples. Superscripts indicate crystallization solvent: [ca] ether; [cb] ligroin; [cc] ligroin–benzene; [cd] ether–petroleum ether; [ce] ethanol; [cf] water; [cg] ether–ethanol. [c] P. Cohn and P. Friedlander, *Ber.*, **37**, 3034 (1904). [d] $n^{25}D$ 1.5300. Calcd.: C, 71.14; H, 10.23. Found: C, 71.06; H, 9.92. [e] $n^{25}D$ 1.5105. [f] Dihydrochloride. [g] Calcd.: C, 65.80; H, 8.92. Found: C, 66.06; H, 8.58. [h] Calcd.: C, 73.10; H, 7.74. Found: C, 73.25; H, 7.91. [i] $n^{25}D$ 1.5286.



Experimental[4]

Preparation of Symmetrically Substituted 1,3-Diamino-2-propanols.—These compounds were prepared in a manner similar to the following procedure for the *n*-propyl analog.

1,3-Bis-(*n*-propylamino)-2-propanol.—To a vigorously stirred, refluxing solution of 118.0 g. (2.0 mole) of *n*-propylamine, there was added 46.3 g. (0.5 mole) of epichlorohydrin over a period of four hours. Refluxing was continued for 16 hours and the excess propylamine removed by distillation. The residue was shaken with 100 ml. of 20% sodium hydroxide solution and extracted with four 100-ml. portions of ether. The combined ethereal extracts were dried over potassium carbonate and concentrated. The residual oil solidified on standing and was crystallized from ether to yield 46.1 g. (53%) of product, m.p. 53–54.5°.

Preparation of Substituted 1-Amino-3-chloro-2-propanols.—To a stirred and refluxing solution of arylamine in an equal volume of ethanol (95%), there was added an equimolar quantity of epichlorohydrin over a period of 30 minutes. Refluxing was continued for one hour following the addition, the solution concentrated at 50° under diminished pressure, and the residual oil used in subsequent reactions without further purification.

Preparation of Substituted 1,3-Diamino-2-propanols.—A solution of 0.5 mole of 1-arylamino-3-chloro-2-propanol and 2.0 moles of alkylamine was refluxed for 18 hours. The excess alkylamine was distilled, and the residual oil shaken with ether and a 10% sodium hydroxide solution. The ether layer was separated, dried over potassium carbonate and concentrated. The residue was either crystallized to a constant melting point or purified by distillation under reduced pressure.

1-Chloro-3-(4-morpholinyl)-2-propanol.—Epichlorohydrin was added dropwise with stirring to an equimolar quantity of morpholine, the temperature being maintained at 40–50° by external cooling. Stirring was continued for one hour. The product was used in subsequent reactions without further purification.

Preparation of Substituted 1-Amino-3-(4-morpholinyl)-2-propanols.—These compounds were prepared in a manner similar to that described for substituted 1,3-diamino-2-propanols. Those which could not be induced to crystallize were isolated as their dihydrochlorides and were recrystallized from ethanol–ether.

Preparation of Substituted Aminomethyl-2-oxazolidones.—The substituted 1,3-diamino-2-propanol and a three molar excess of ethyl carbonate were introduced into a flask fitted with a Vigreux column and several ml. of ethyl carbonate was distilled to ensure a dry reaction medium. Sodium methylate (about 0.2% by weight of the reaction mixture) was added and the theoretical quantity of ethanol removed by distillation. After concentration, the residue was either crystallized to a constant melting point or purified by distillation under diminished pressure.

3-*n*-Butyl-5-(N-*n*-butylanilinomethyl)-2-oxazolidone (III, R = *n*-Butyl).—In order to elucidate the nature of the ring closure occurring on cyclization of the diaminopropanols with ethyl carbonate, the oxazolidone obtained from 1-anilino-3-*n*-butylamino-2-propanol (compound 29) was alkylated with *n*-butyl bromide as follows: A solution of 12.4 g. (0.05 mole) of 3-*n*-butyl-5-anilinomethyl-2-oxazolidone and 25.0 g. (0.18 mole) of *n*-butyl bromide was refluxed for 72 hours. The excess butyl bromide was removed by distillation, the residue dissolved in 50 ml. of ether and extracted with five 100-ml. portions of 3 *N* hydrochloric acid. The combined aqueous extracts were made strongly alkaline with 40% sodium hydroxide and extracted with two 100-ml. portions of ether. After drying over potassium carbonate, the ether solution was concentrated and distilled under diminished pressure to yield 6.7 g. (44%) of the desired product, b.p. 209–211° (1.0 mm.), $n^{25}D$ 1.5286. *Anal.* Calcd. for $C_{18}H_{28}N_2O_2$: N, 9.21. Found: N, 9.41.

The physical properties of this product are identical to those of compound 38, prepared by the condensation of ethyl carbonate and 1-*n*-butylamino-3-N-*n*-butylanilino-2-propanol. When seeded with a crystal of compound 37, prepared from 1-anilino-3-di-*n*-butylamino-2-propanol, crystallization failed to take place. Further proof of the identity of the butylated product was afforded by an examination of the acid hydrolysis product. On warming in moist ether solution saturated with hydrogen chloride, a hygroscopic oil separated which decomposed to give bluish crystals, m.p. 130–132.5° from benzene–ligroin. When mixed with an authentic sample of 1-*n*-butylamino-3-N-*n*-butylanilino-2-propanol dihydrochloride, m.p. 130–132.5°, there was no depression of the melting point.

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

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(4) All temperatures reported are uncorrected. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.