

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

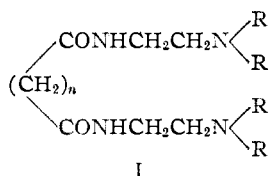
Dicarboxylic Acid Bis- β -tertiaryaminoalkyl Amides and their Quaternary Ammonium Salts as Curare Substitutes. II¹

BY ARTHUR P. PHILLIPS

A series of bis- β -tertiaryaminoalkyl amides of aliphatic dicarboxylic acids and the corresponding bis-quaternary ammonium salts have been made for examination with respect to their ability to prolong the duration of the curare-like activity of diacetylcholine.

A recent preliminary report¹ presented a few bis- β -tertiaryaminoethyl amides of aliphatic dicarboxylic acids which had been made and found to prolong the duration of the block of neuromuscular transmission produced by diacetylcholine² in the cat. This paper presents the results of the more complete study of these series with regard to variation in chain length and its effect upon activity for the aminoamides studied.

The compounds described can be illustrated by the general formula, I, in which n was varied be-



tween the limits 0 (for the oxalic acid amides) and 8, and $\text{N} \begin{array}{l} \diagup \text{R} \\ \diagdown \text{R} \end{array}$ represents dimethylamino, diethylamino and morpholino. Both the tertiary aminoalkyl amides and their bis-methiodides were made in most cases while bis ethiodides or bis-benzyl chlorides were made in only a few instances.

The amides were obtained by refluxing the appropriate dicarboxylic acid methyl or ethyl ester with at least two molecular equivalents of the tertiary-aminoethylamine. On the basis of simple inductive effects these unsymmetrical ethylenediamines should be expected to be less reactive as nucleophilic reagents (in amide formation) than analogous simple aliphatic monoprimary amines. However, as the boiling points of the substituted ethylenediamines were all above 100°, reactions could be carried out readily and successfully by

TABLE I

(A) AMIDES AND QUATERNARY AMMONIUM SALTS FROM DIMETHYLETHYLENEDIAMINE AND ALIPHATIC DICARBOXYLIC ACIDS

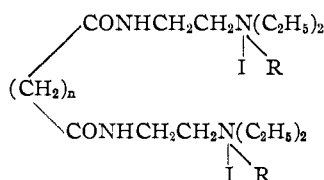
Comp. no.	n	R	Reaction conditions ^a		Yield, ^b %	Crystn. solvent ^c	M.p., ^d °C.	Analyses, %			
			Time, hr.	Temp., °C.				Carbon		Hydrogen	
							Calcd.	Found	Calcd.	Found	
1	0		19	100	100	Æ.H	123-124	52.1	52.1	9.6	9.6
2	0	CH ₃	1	65	100	Aq.M.Ac	288-290	28.0	28.2	5.5	5.5
3	0	C ₂ H ₅	6	65	85	M	258-260	I, 49.4	I, 49.3	5.9	5.9
4	1		23	150	50	M.Æ ^d	185-186	I, 46.9	I, 46.6	8.2	8.0
5	1	CH ₃	18	65	85	M.Æ	Softens 179- 181, final melting	41.6	42.0	5.7	5.7
6	2		17	150	100	Æ.H	134-135	29.5	29.2	10.1	9.9
7	2	CH ₃	2	65	100	M	251-252	55.8	55.6	5.9	5.9
8	2	C ₂ H ₅	17	65	100	M.Æ	189-190	I, 46.9	I, 46.8	6.4	6.1
9	2	C ₆ H ₅ CH ₂ ^e	18	65	90	M.Æ	206-207	33.7	33.7		
10	3		6	150	80	Æ.H	87-88	I, 44.5	I, 44.4		
11	3	CH ₃	2	65	70	M.Æ	190-191	N, 11.0	N, 10.9		
12	3	C ₂ H ₅	4	65	55	A.Æ	130-131	57.3	57.5	10.3	9.8
13	4		19	150	100	Æ	123-124	32.4	32.6	6.1	6.0
14	4	CH ₃	2	65	100	M.Æ	202-203	34.9	34.9	6.5	6.5
15	6		4	100	95	Viscous oil		I, 43.4	I, 43.1		
16	6	CH ₃	2	65	100	M.Æ	165-166	58.7	58.7	10.5	10.3
								33.7	33.9	6.4	6.0
								36.2	36.0	6.7	6.6
								I, 42.5	I, 42.3		

(1) Paper I of this series: A. P. Phillips, *Science*, **112**, 536 (1950).(2) A. P. Phillips, *This Journal*, **71**, 3264 (1949).

refluxing for some hours, and yields in general approached the theoretical. The quaternary am-

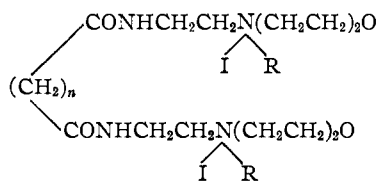
TABLE I (Continued)

(B) AMIDES AND QUATERNARY AMMONIUM SALTS FROM DIETHYLETHYLENEDIAMINE AND ALIPHATIC DICARBOXYLIC ACIDS



Comp. no.	n	R	Reaction conditions ^a		Yield, ^b %	Crystn. solvent ^c	M.p., ^d °C.	Analyses, %			
			Time, hr.	Temp., °C.				Carbon		Hydrogen	
17	0		7	160	100	M.Æ ^d	242-243	Calcd. 46.7	Found 46.5	Calcd. 9.0	Found 8.8
18	0	CH ₃	15	65	90	M.Æ	268-269	33.7	33.9	6.4	6.4
19	0	C ₂ H ₅	17	65	42	Aq.M.Ac	270-271	36.1	36.3	6.7	6.6
20	2		21	160	100	E	64-65	61.0	61.1	10.9	10.4
21	2	CH ₃	24	65	100	M.Æ	147-148	N, 17.8	N, 18.0		
22	2	C ₂ H ₅	24	65	100	M.Æ	190-191	36.1	36.5	6.7	6.6
23	4		20	160	100	M.Æ	147-148	I, 42.5	I, 42.6	N, 9.4	N, 9.5
24	4	CH ₃	3	65	75	M.Æ	134-135	38.3	38.3	7.1	7.1
25	4	C ₂ H ₅	20	65	80	M.Æ	181-182	I, 40.6	I, 40.4	N, 9.0	N, 9.2
						Æ.H	75-76 ^f				
						M.Æ.E	148-149 ^g	45.0	45.1	5.5	5.6
						M.Æ	134-135	38.4	38.9	7.1	6.8
						M.Æ	181-182	40.3	40.0	7.4	7.5
								I, 38.8	I, 38.8		

(C) AMIDES AND QUATERNARY AMMONIUM SALTS FROM MORPHOLINOETHYLAMINE AND ALIPHATIC DICARBOXYLIC ACIDS



26	0		0.5	100	100	M	172-173	53.5	53.8	8.3	7.9
27	0	CH ₃	6	65	100	Aq.M	277-278	32.1	32.2	5.4	5.4
28	1		5	190	80	Æ	127-128	54.8	54.8	8.6	8.4
29	1	CH ₃	5	65	100	M	153-154	33.3	33.7	5.6	5.4
30	2		7	200	100	M.Æ	175-176	56.1	56.4	8.8	8.9
31	2	CH ₃	1	65	90	M.Aq.Æ	221-222	34.5	34.8	5.8	6.1
32	3		2	200	100	M.Æ	154-155	57.3	57.3	9.0	9.2
33	3	CH ₃	4	65	80	M	100-110 dec.	35.6	36.0	6.0	5.9
34	4		2	200	100	M.Æ	164-165	58.3	58.6	9.3	9.4
35	4	CH ₃	2	65	100	Aq.A.Æ	214-215	36.7	37.1	6.2	6.5
36	8		2	200	100	A.Æ.H	149-150	61.9	62.0	9.9	9.6
37	8	CH ₃	18	65	100	Viscous oil					

^a The reaction conditions were arbitrarily chosen and some of the long reaction periods (such as 18-24 hours) were used only because of the convenience of overnight refluxing, even though most of the reactions probably were complete in less than an hour. ^b Yields of less than 100% probably are due to losses incurred during purification. ^c A = ethanol; Ac = acetone; Æ = ethyl acetate; Aq = water; E = diethyl ether; H = Skellysolve B; M = methanol. ^d These data are for the dihydrochloride salt. ^e This compound is the bis-benzyl chloride. ^f This is a known compound: see L. C. Behr and R. S. Schreiber, U. S. Patent 2,438,200. ^g These data are for the dipicrate. ^h All melting points are uncorrected.

monium salts were made by refluxing the bis-tertiaryamino amide in methanol with an excess of the proper alkyl halide, usually methyl or ethyl iodide. Results are summarized in Table I.

The basic amides from dimethylethylenediamine and morpholinoethylamine were surprisingly readily crystallizing solids with melting points between 100-200° and were easily purified by recrystallization from organic solvents. The amides derived from diethylethylenediamine were much lower melting (all below 100°) and were much more difficult to purify by recrystallization, while traces of impurities tended to prevent practical recoveries in crystallization.

The bis-amides from the even numbered series of dicarboxylic acids usually were higher melting and were obtained crystalline more readily than the corresponding derivatives of the adjacent dicarboxylic acids containing an odd number of carbons in their chains.

The bis- β -dimethylaminoethyl amides (see Table IA) were made from all the simple aliphatic dicarboxylic acids, oxalic through adipic and suberic. In this series both the bis-methiodides and the bis-ethiodides were readily obtained pure and crystalline.

Because the diethylaminoethyl amides (Table IB) were more difficult to purify and handle only the

oxalic, succinic and adipic derivatives were synthesized. Here, too, bis-methyl and ethyl iodides were easily prepared.

In the morpholinoethyl series (see Table IC), amides were made from all the simple aliphatic dicarboxylic acids, oxalic through adipic, and sebacic. The bis-methiodides were also prepared but attempts to obtain bis-ethiodides gave as products viscous oils in some cases and there seemed to be some difficulty in attaining satisfactory carbon and hydrogen analyses with these higher alkyl quaternary ammonium salts.

These amides and their quaternary ammonium salts showed no curare-like activity at the dose levels at which many of them showed powerful activity in prolonging the duration of neuromuscular block produced by diacetylcholine in the cat. In the dimethylaminoethyl amide series this latter activity persisted in all members of the group above oxalic regardless of chain length. The bis-methiodide of the succinic amide derivative was about 1.5 times as active in its potentiating action as the tertiary base while both the tertiary base and bis-methiodide of the adipic amide were of nearly equal activity. Both the bis-morpholinoethyl amides and their bis-methiodides were inactive as potentiators of diacetylcholine.

At very much higher dose levels some of the bis-methiodides of the bis-amides exhibited weak curare-like activity.

A detailed report on the pharmacology of these compounds will be made later from these laboratories.

Acknowledgment.—The author is indebted to Messrs. Samuel W. Blackman and N. Martinez, Jr., for the microanalyses included. The dimethylethylenediamine, diethylethylenediamine and morpholinoethylamine were supplied through the courtesy of Mr. J. Conway of the Fine Chemicals Division, Carbide and Carbon Chemical Corporation.

Experimental

The general method of preparation of the bis-tertiary-aminoethyl amides and of their bis-quaternary ammonium salts is illustrated below by an example of each.

N,N'-Bis-(β -dimethylaminoethyl)-succinamide.—A mixture of 18 g. (0.1 mole) of ethyl succinate and 35 cc. (28 g., 0.32 mole) of dimethylethylenediamine was refluxed for four hours in a metal-bath at 150°. After removal of excess amine and alcohol 26 g. (100%) of white crystalline product remained. Recrystallized from ethyl acetate the pure product melted at 134–135°.

N,N'-Bis-(β -dimethylaminoethyl)-succinamide Bis-methiodide.—A solution of 5.2 g. (0.02 mole) of the bis-aminoamide just described in 50 cc. of methanol was treated with 6 cc. of methyl iodide and the mixture was refluxed for one hour. A solid crystalline cake resulted in two minutes. Upon cooling 10.8 g. (100%) of product was obtained and after recrystallization from methanol this melted at 251–252°.

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[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES, BROWN UNIVERSITY]

The Reduction of Cholestanone by Lithium Aluminum Hydride and Aluminum Alkoxides¹

BY HAROLD R. NACE AND GEORGE L. O'CONNOR

Reduction of cholestanone by lithium aluminum hydride or a Meerwein-Ponndorf reaction is shown to give a mixture of α - and β -cholestanol. The ratio of isomeric stanols produced is a function of the size of the reducing agent and the temperature of reaction. With sterically larger aluminum alkoxides the production of α -cholestanol is favored.

Catalytic hydrogenation² of cholestanone for preparing α -(*epi*)-cholestanol is inconvenient and not entirely satisfactory. The purpose of this investigation was to determine whether the reduction of cholestanone by aluminum alkoxides would provide a new and more convenient route to α -cholestanol. Shoppee and Summers³ reported that lithium aluminum hydride reduction of cholestanone gave 4% α -cholestanol, the remainder of the reduction product being the β -isomer. Noyce and Denney have pointed out⁴ that the Meerwein-Ponndorf reduction of sterically hindered ketones with aluminum isopropoxide or reduction with lithium aluminum hydride yields a mixture of epimeric carbinols, and that aluminum isopropoxide

yields more of the *cis*-carbinol than lithium aluminum hydride. They concluded that aluminum isopropoxide reduction produced more *cis*-alcohol because the bulky alkoxide group was more sensitive to steric requirements than an incipient AlH_4^- ion. The Meerwein-Ponndorf reduction has been pictured^{5,6,7} as proceeding through a pseudo-six membered ring transition state. Ring formation would be favored on the less hindered side leading to a *cis*-carbinol, with the hydroxyl being formed on the hindered side.

The reduction of keto-steroids with aluminum isopropoxide has been reported in a few instances to give mixtures of the isomeric stanols,^{8,9} but in-

(1) This paper is based on a portion of the thesis to be submitted by George L. O'Connor in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Brown University.

(2) (a) G. Vavon and B. Jakubowicz, *Bull. soc. chim.*, **53**, 584 (1933); (b) L. Ruzicka, H. Brüngger, E. Eichenberger and J. Meyer, *Helv. Chim. Acta*, **17**, 1407 (1934).

(3) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 687 (1950).

(4) D. S. Noyce and D. B. Denney, *THIS JOURNAL*, **72**, 5743 (1950).

(5) R. Woodward, N. Wendler and F. Brutschy, *ibid.*, **67**, 1425 (1945).

(6) M. Dewar, "Electronic Theory of Organic Chemistry," Oxford at the Clarendon Press, 1949, p. 136.

(7) W. von E. Doering and R. W. Young, *THIS JOURNAL*, **72**, 630 (1950).

(8) (a) R. Marker, D. Turner and E. Wittbecker, *ibid.*, **64**, 221 (1942); (b) R. Marker, H. Crooks, R. Wagner and E. Wittbecker, *ibid.*, **64**, 2089 (1942).

(9) "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 142.