Notes

Monoquaternary Muscle Paralyzing Agents. III.[1] Synthesis of N-(ω-Phthalimidoalkyl)trialkylammonium Iodides

Hugh B. Donahoe, Robert J. Seiwald, Sr. M. Marguerite Neumann, Donald E. Heitmeier,

Department of Chemistry, St. Louis University, St. Louis, Missouri 63103

and Kazuo K. Kimura

Bio-Medical Research Laboratories, Atlas Chemical Industries, Inc., Wilmington, Delaware 19899

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It has been shown that certain monoquaternary N-(ω-phthalimidoalkyl)piperidines and -morpholines possess muscle-paralyzing activity which varies with the length of the alkyl chain and the size of the alkyl group attached to the nitrogen.[1,2] To study the effect of change of the alkyl substituents on the quaternary nitrogen, compounds have been prepared in which the groups attached to the nitrogen have been varied from Me_3 to Et_3 by successive replacement of Me by Et. Several compounds have also been prepared which contain more bulky benzyl groups.

Two synthetic routes were employed. Either (1) a secondary amine was condensed with the appropriate N-(ω-bromoalkyl)phthalimide[1,3] and the tertiary base thus formed was quaternized with an alkyl iodide or (2) a tertiary amine was treated directly with an N-(ω-iodoalkyl)phthalimide to form the monoquaternary salt.

N-(ω-Bromoalkyl)phthalimides were converted to the corresponding N-(ω-iodoalkyl)phthalimides (Table I) by halogen exchange with NaI in dry acetone.[4] In this step it was essential that the bromo intermediate be pure, as the iodo compounds were difficult to obtain in analytical condition.

The condensation of the various secondary amines with N-(ω-bromoalkyl)phthalimides proceeded in a satisfactory manner. The tertiary amines thus obtained were all low-melting solids or viscous oils soluble in ether and benzene and sparingly soluble in 30–60° petroleum ether. With the exception of the dibenzylaminobutyl and -hexyl derivatives (Table II), the free bases were not characterized further but were treated directly with an alkyl iodide.

The quaternizations of the dimethyl and diethyl free bases were carried out by treating their ether solutions with a three- or fourfold excess of an alkyl iodide (method A). The dibenzylamine free bases could not be quaternized by this method. They were made to react, however, by refluxing directly with MeI on a steam bath for 2–3 hr (method B). These bases could not be quaternized with EtI by this method even when refluxed on a steam bath for several days. The trimethylammonium and triethylammonium salts were prepared by treating the N-(ω-iodoalkyl)phthalimide with Me_3N in a pressure bottle (method C) or with Et_3N under reflux (method D).

Table I
N-(ω-Iodoalkyl)phthalimides
o-$C_6H_4(CO)_2N(CH_2)_nI$

n	Mp, °C	Yield, %	Formula	Analyses
2	100[a]	68	$C_{10}H_8INO_2$	
3	85–86[b]	95	$C_{11}H_{10}INO_2$	
4	88.5–89[b]	92	$C_{12}H_{12}INO_2$	
5	77.5–78.5[c]	97	$C_{13}H_{14}INO_2$	
6	77.5–78	97	$C_{14}H_{16}INO_2$	I[d]
7	41.5–42	76	$C_{15}H_{18}INO_2$	I
8	63.5–64	90	$C_{16}H_{20}INO_2$	I
9	53–53.3	93	$C_{17}H_{22}INO_2$	I
10	66.5–67.5	91	$C_{18}H_{24}INO_2$	I
11	59–61	97	$C_{19}H_{26}INO_2$	I

[a] S. Gabriel, *Ber.*, **53B**, 1985 (1920), reports 99–100°. [b] Previously reported by M. Fields, D. E. Walz, and S. Rothchild, *J. Am. Chem. Soc.*, **73**, 1000 (1951). [c] S. Gabriel, *Ber.*, **42**, 4050 (1909), reports 75–76°. [d] C: calcd, 47.06; found, 47.54.

Table II
N-(ω-Phthalimidoalkyl)dibenzylamines
o-$C_6H_4(CO)_2N(CH_2)_nN(CH_2C_6H_5)_2$

n	Mp, °C	Yield, %[a]	Formula	Analyses
4	86–87	*a*	$C_{26}H_{26}N_2O_2$	C, H
4	193–194	81	$C_{26}H_{26}N_2O_2$·HCl	Cl
5	Oil	*a*	$C_{27}H_{28}N_2O_2$	
5	157–158	70	$C_{27}H_{28}N_2O_2$·HCl	C, H, Cl
6	41–42	*a*	$C_{28}H_{30}N_2O_2$	C, H
6	222	82	$C_{28}H_{30}N_2O_2$·HCl	Cl

[a] All yields were calculated on the basis of hydrochlorides.

The yields reported for the quaternary salts (Table III) reflect the relative ease of purification rather than the completeness of reaction. A pure product was obtained in good yields only when the intermediates were in a state of high purity. The use of impure intermediates, although resulting in good crude yields, gave products which could be purified only with great difficulty and consequent loss of material.

Biological Results and Discussion.—All quaternary ammonium salts were tested for paralyzing activity in frogs (*Rana pipiens*) by lymph sac injection following a previously described procedure.[2]

In general, activity increased directly with the increase in the methylene chain up to a maximum of eight or nine carbon atoms and decreased thereafter. The greatest departure from the general activity trends was in the case of the increase of activity of the trimethylammonium compounds where the methylene chain contained four and five carbon atoms.

In the frog, except for the compounds containing the dimethylethylammonium groups or those containing benzyl groups on N, there were few differences in

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(2) H. B. Donahoe, R. J. Seiwald, M. C. C. Neumann, and K. K. Kimura, *J. Org. Chem.*, **22**, 68 (1957).

(3) M. B. Moore and R. T. Rapala, *J. Am. Chem. Soc.*, **68**, 1057 (1946).

(4) M. Fields, D. E. Walz, and S. Rothchild, *ibid.*, **73**, 1000 (1951).

TABLE III
N-(ω-PHTHALIMIDOALKYL)TRIALKYLAMMONIUM IODIDES
o-$C_4H_4(CO)_2N(CH_2)_nNR_1R_2R_3I$

n	Mp, °C	Yield, %		Formula[a]	Frog MPD,[b] mg/kg
		$NR_1R_2R_3 = N(CH_3)_3$			
2	293–295	54	C	$C_{13}H_{17}IN_2O_2$	>400
3	240	56	C	$C_{14}H_{19}IN_2O_2$	200
4	287–288	98	C	$C_{15}H_{21}IN_2O_2$	15
5	181–182.5[c]	90	C	$C_{16}H_{23}IN_2O_2$	15
6	214–215	90	C	$C_{17}H_{25}IN_2O_2$	20
7	160–161	95	C	$C_{18}H_{27}IN_2O_2$	20
8	173	86	C	$C_{19}H_{29}IN_2O_2$	20
9	119–121	87	C	$C_{20}H_{31}IN_2O_2$	10
10	172–173	92	C	$C_{21}H_{33}IN_2O_2$	20
11	153–153.5	91	C	$C_{22}H_{35}IN_2O_2$	40
		$NR_1R_2R_3 = NC_2H_5(CH_3)_2$			
4	268	88	A	$C_{16}H_{23}IN_2O$	50
6	118–120	79	A	$C_{18}H_{27}IN_2O$[d]	40
		$NR_1R_2R_3 = NCH_3(C_2H_5)_2$			
2	238–239	46	A	$C_{15}H_{21}IN_2O_2$[e]	300
3	237–238	46	A	$C_{16}H_{23}IN_2O_2$	100
4	280–281	80	A	$C_{17}H_{25}IN_2O_2$	30–40
6	127–128	60	A	$C_{19}H_{29}IN_2O_2$	20–30
8	93–94	53	A	$C_{21}H_{33}IN_2O_2$[f]	20
10	103–105	58	A	$C_{23}H_{37}IN_2O_2$	40
		$NR_1R_2R_3 = N(C_2H_5)_3$			
4	254–255	83	B	$C_{18}H_{27}IN_2O_2$	30
6	164–166	82	B	$C_{20}H_{31}IN_2O_2$	30
8	136–138	78	D	$C_{22}H_{35}IN_2O_2$	20
10	122–124	82	D	$C_{24}H_{39}IN_2O_2$	>50
		$NR_1R_2R_3 = N(C_2H_5)_2CH_2C_6H_5$			
4	192 dec	64	A	$C_{23}H_{29}IN_2O_2$[g]	30–40
5	165–165.5	94	A	$C_{24}H_{31}IN_2O_2$[g]	30–40
6	153	93	A	$C_{25}H_{33}IN_2O_2$[g]	80
		$NR_1R_2R_3 = NCH_3(CH_2C_6H_5)_2$			
4	95–98	88	B	$C_{29}H_{35}IN_2O_2$[h]	*i*
5	169–170	52	B	$C_{28}H_{31}IN_2O_2$	*i*
6	159–160	49	B	$C_{29}H_{33}IN_2O_2$	*j*
d-Tubocurarine chloride (DTC)					2

[a] All compounds showed a correct analysis for C, H, I except where noted. [b] MPD = minimum paralyzing dose (lymph-sac injection). [c] Sinters at 176°. Sample analyzed correctly only after melting and allowing to resolidify. Before melting the compound analyzed for the monohydrate (I: calcd, 30.2; found, 30.2). [d] C: calcd, 50.24; found, 50.65. [e] C: calcd, 46.40; found, 46.88. [f] H: calcd, 7.04; found, 6.62. [g] Analyzed for I only. [h] Calculated for monoethanolate. [i] No paralyzing action. [j] Too insoluble to test.

activities at comparable chain lengths. The dimethylethylammonium compounds possessed lower activity in the four- and six-carbon structures. The longer chain compounds were therefore not prepared. The same was true of the higher members of the diethylammonium compounds. Those compounds with two benzyl groups attached to the quaternary nitrogen showed no muscle-paralyzing activity in the frog. The six-carbon homolog was too water insoluble to be tested.

The most active compound of this series was N-(9-phthalimidononyl)trimethylammonium iodide which had approximately one-fifth the activity of *d*-tubocurarine in the frog. Several of these compounds demonstrated considerable ganglionic blocking action when tested on the nictitating membrane of the cat and varying degrees of depolarizing activity were obtained in anesthetized roosters.

Experimental Section[5]

N-(ω-Bromoalkyl)phthalimides.—The N-(ω-bromoalkyl)phthalimides were prepared from potassium phthalimide and α,ω-dibromoalkanes by a previously reported method.[2]

N-(ω-Iodoalkyl)phthalimides.—A solution of anhydrous NaI (10.6 g, 0.071 mole) and the appropriate N-(ω-bromoalkyl)-phthalimide (0.01 mole) in 100 ml of dry Me_2CO was heated under reflux for 8 hr. Me_2CO was removed under reduced pressure and the residue was triturated with H_2O (50 ml). The solid remaining was filtered and recrystallized from EtOH.

N-(ω-Phthalimidoalkyl)dialkylamines.—A solution of 0.01 mole of the appropriate N-(ω-bromoalkyl)phthalimide and 0.04 mole of a secondary amine in 30 ml of C_6H_6 was heated on a steam bath for several hours. C_6H_6 and excess amine were removed under reduced pressure and the residue was dissolved in Et_2O. The solution was filtered to remove any amine hydrobromide, decolorized with charcoal, and dried. The dry Et_2O solution was used directly to prepare quaternary salts or treated with HCl gas to obtain the hydrochloride. The precipitated hydrochloride was collected, washed (Et_2O), and recrystallized (EtOH).

N-(ω-Phthalimidoalkyl)trialkylammonium Iodides.—The monoquaternary N-(ω-phthalimidoalkyl)trialkylammonium iodides were prepared by one of the following ways.

Method A.—A dry Et_2O solution of the N-(ω-phthalimidoalkyl)-dialkylamine was treated with a three- or fourfold excess of the appropriate alkyl iodide and allowed to stand overnight at room temperature. The precipitated quaternary salt was removed by filtration and the filtrate was allowed to stand until no more product was formed. The quaternary salts were recrystallized from either absolute EtOH or *i*-PrOH.

Method B.—The N-(ω-phthalimidoalkyl)dialkylamine (0.01 mole) and 10 ml of the RI were refluxed on a steam bath for 2–3 hr. The reaction flask was cooled and Et_2O was added to completely precipitate the quaternary salt. The salt was filtered, washed (Et_2O), dried, and recrystallized as in A.

Method C.—A solution of N-(ω-iodoalkyl)phthalimide (0.004 mole) in 50 ml of anhydrous Et_2O was saturated with Me_3N at 0° in a pressure bottle and allowed to stand at 30° for 72 hr. The precipitate was filtered from the reaction mixture, washed (Et_2O), and recrystallized as in A.

Method D.—The appropriate N-(ω-iodoalkyl)phthalimide (0.006 mole) and 10 ml of Et_3N were heated on a steam bath for 3 hr. During the course of the reaction the quaternary salt precipitated from solution. The flask was cooled and dry Et_2O was added to complete precipitation. The salt was filtered, washed (Et_2O), dried, and recrystallized as in A.

(5) C and H analyses are by Du-Good Chemical Laboratory, St. Louis, Mo., and Clark Microanalytical Laboratory, Urbana, Ill. Ionic halogen was determined potentiometrically in this laboratory. All melting points are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

Some Organoboron Compounds Containing a Bis(2-chloroethyl)amino Group Joined to Boron[1]

Y. FULMER SHEALY AND ROBERT F. STRUCK

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

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Boron, having two 2s and one 2p electrons, forms trivalent compounds that do not have a complete shell of valence electrons. These electron-deficient compounds, which are isoelectronic with carbonium ions, can coordinate with electron-donor molecules. Trivalent boron compounds having O, N, or related ele-

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