[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND PHARMACOLOGY, ST. LOUIS UNIVERSITY]

Monoquaternary Muscle Paralyzing Agents. I. Synthesis of Quaternary N-(ω-Piperidinoalkyl)-phthalimides[1,2]

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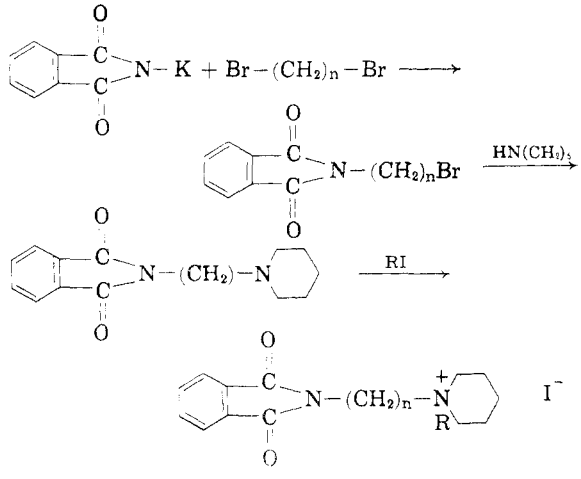
A series of monoquaternary N-(ω-piperidinoalkyl)-phthalimides has been prepared *via* the intermediate N-(ω-bromoalkyl)-phthalimides. The complete homologous series showed oscillation of melting points and a gradual decrease in water solubility with increasing chain length. Maximum biological activity as striated muscle paralyzing agents resulted when the methylene chain between the quaternary nitrogen and the nitrogen of the phthalimide groups was 7 to 9 carbons in length. The most active compound had approximately $^1/_{10}$ the activity of *d*-tubocurarine in frogs.

In recent years, many new synthetic muscle paralyzants have been prepared based on the structure of *d*-tubocurarine. Although the *bis*-quaternary ammonium structure is a usual prerequisite to high curarelike activity, one of the authors[6] observed that monoquaternary N-(dialkylaminoalkyl)-phthalimides were quite active. Since there are few precedent reports in the literature[7,8] concerning highly active monoquaternary curarelike compounds, it was decided to study the effect on biological activity of various structural modifications of such compounds. The effect of varying (1) the distance between the quaternary nitrogen and the nitrogen of the phthalimide group and (2) the size of the quaternary ammonium group is reported in this paper.

With the exception of the monomethylene free base which was prepared *via* the Mannich reaction according to the method of Moore and Rapala,[9] the following reaction scheme was employed.



Most of the preparations proceeded without difficulty and the expected product was isolated in each case. Although the crude yields were good, considerable difficulty was experienced in obtaining analytically pure samples and the yields reported in Tables I and II can be attained only when carefully purified intermediates are used.

The N-(ω-bromoalkyl)-phthalimides were prepared from potassium phthalimide and a three-to fourfold excess of the appropriate dibromoalkane. The addition of a small amount of dimethylformamide to the reaction mixture decreased the time and temperature usually employed in the Gabriel synthesis but did not materially improve the yield. In addition to small amounts of the *bis*-phthalimidoalkane, the desired product was always accompanied by unidentified oily side products which, in the case of the lower melting members of the series, were extremely difficult to remove. Except for the heptamethylene homolog, the products were low melting white solids. The N-(ω-bromononyl)-phthalimide is previously unreported.

The N-(ω-bromoalkyl)-phthalimides reacted smoothly with excess piperidine in benzene to yield the tertiary free base which was then isolated as the hydrochloride salt. The salt of the monomethylene free base decomposed when heated in solution to give back phthalimide, formaldehyde and piperidine and the pure product was therefore obtained in poor yield. Quaternization of the free bases were readily effected and the crude yields were for the most part quantitative.

Each homologous series exhibited an oscillation of melting points which was closely paralleled by the water solubility, the maximum being reached at $n = 4$. In some instances, especially in the cases of

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(6) Kazuo K. Kimura, Ph.D. thesis, University of Illinois, 1949.

(7) Marsh and Herring, *J. Pharmacol. and Exper. Therap.*, **101**, 26 (1951).

(8) Cavallito, Soria, and Hoppe, *J. Am. Chem. Soc.*, **72**, 2661 (1950).

(9) Moore and Rapala, *J. Am. Chem. Soc.*, **68**, 1657 (1946).

TABLE I

N-(ω-PIPERIDINOALKYL)-PHTHALIMIDES AND HYDROCHLORIDES

o-$C_6H_4(CO)_2N$-$(CH_2)_n$-NC_5H_{10}

n	M.P., °C.	Formula	Analyses: Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	HCl M.P., °C.	Yield,[a] %	Analyses: Chlorine Calc'd	Chlorine Found
1	117–118[b]	$C_{14}H_{16}N_2O_2$					185–187[b]	30	12.7	12.4
2	89–90[c]	$C_{15}H_{18}N_2O_2$					241–243	69	12.0	11.9
3	49–50[d]	$C_{16}H_{20}N_2O_2$					232–234	76	11.5	11.5
4	70	$C_{17}H_{22}N_2O_2$	71.29	71.38	7.74	7.93	228	85	11.0	10.9
5	61–62	$C_{18}H_{24}N_2O_2$	71.97	72.20	8.05	7.99	183	79	10.5	10.5
6	69	$C_{19}H_{26}N_2O_2$	72.57	72.80	8.34	8.26	183–184	89	10.1	10.1
7	65	$C_{20}H_{28}N_2O_2$	73.13	73.26	8.59	8.52	170	45	9.72	9.80
8	56	$C_{21}H_{30}N_2O_2$	73.64	74.09	8.83	8.72	161–162	81	9.37	9.43
9	50.5–51.5	$C_{22}H_{32}N_2O_2$	74.12	74.11	9.05	9.24	129–131	80	9.04	9.08
10	59–60	$C_{23}H_{34}N_2O_2$	74.55	74.82	9.25	9.21	116–118	71	8.71[e]	8.37
11	52	$C_{24}H_{36}N_2O_2$	74.96	75.29	9.43	8.99	138	75	8.32	8.32

[a] All yields calculated on basis of hydrochlorides. [b] Reported previously by Moore and Rapala, *J. Am. Chem. Soc.*, **68**, 1657 (1946). [c] Kermack and Smith, *J. Chem. Soc.*, 3096 (1931) report 91°. [d] Braun, *Ber.*, **42**, 2051 (1909) reported 50°. [e] Calc'd for monohydrate: Cl, 8.35.

TABLE II

N-(ω-PIPERIDINOALKYL)-PHTHALIMIDE ALKYL IODIDES

o-$C_6H_4(CO)_2N$-$(CH_2)_n$-NC_5H_{10}.RI

n	M.P., °C	Yield, %	Formula	Analyses: Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Iodine Calc'd	Iodine Found	FROG MPD,[a] Mg./Kg.
(Methiodides, R = CH_3)										
1	199–200	73	$C_{15}H_{19}IN_2O_2$	46.64	46.94	4.96	5.21	32.8	32.7	>400
2	262–263	86	$C_{16}H_{21}IN_2O_2$	48.01	48.04	5.29	5.03	31.7	31.6	>400
3	257–258	64	$C_{17}H_{23}IN_2O_2$	49.28	49.47	5.59	5.84	30.6	30.6	200
4	290–291	93	$C_{18}H_{25}IN_2O_2$	50.49	50.78	5.88	5.70	29.6	29.7	30
5	188	80	$C_{19}H_{27}IN_2O_2$	51.60	51.83	6.15	6.15	28.7	28.7	25
6	167	74	$C_{20}H_{29}IN_2O_2$	52.63	52.52	6.40	6.28	27.9	28.0	20
7	131–132	96	$C_{21}H_{31}IN_2O_2$	53.62	53.76	6.64	6.55	27.0	27.2	25
8	134	99	$C_{22}H_{33}IN_2O_2$	54.55	54.66	6.84	6.82	26.2	26.2	20
9	106–107	71	$C_{23}H_{35}IN_2O_2$	55.41	55.68	7.08	6.90	25.5	25.4	20
10	137.5	56	$C_{24}H_{37}IN_2O_2$	56.24	56.32	7.28	7.44	24.8	25.0	100
11	99	98	$C_{25}H_{39}IN_2O_2$	57.02	57.16	7.47	7.46	24.2	24.1	200
(Ethiodides, R = C_2H_5)										
1	198–199	41	$C_{16}H_{21}IN_2O_2$	48.01	48.02	5.29	5.35	31.7	31.7	>400
2	234–235	80	$C_{17}H_{23}IN_2O_2$					30.6	30.5	200
3	199–200	43	$C_{18}H_{25}IN_2O_2$	50.49	50.40	5.88	6.46	29.6	29.3	60
4	263–264	72	$C_{19}H_{27}IN_2O_2$	51.60	51.68	6.15	5.96	28.7	28.4	40
5	162	73	$C_{20}H_{29}IN_2O_2$					27.9	27.9	20
6	147–148	88	$C_{21}H_{31}IN_2O_2$	53.60	53.17	6.64	6.15	27.0	27.0	20
8	106–107	58	$C_{23}H_{35}IN_2O_2$	55.41	55.68	7.08	7.04	25.5	25.4	40
10	92–93	79	$C_{25}H_{39}IN_2O_2$	57.02	57.03	7.47	7.42	24.2	24.4	120
(Benzyliodides, R = $C_6H_5CH_2$)										
4	262	91	$C_{24}H_{29}IN_2O_2$					25.2	25.4	80
5	196–196.5	72	$C_{25}H_{31}IN_2O_2$					24.5	24.4	60
6	151[b]	70	$C_{26}H_{33}IN_2O_2$					23.8	23.7	>100
d-Tubocurarine chloride (DTC)										2

[a] MPD = minimum paralyzing dose (lymph-sac injection). [b] Forms dihydrate from 95% ethanol, m.p. 90–100°, Calc'd: I, 22.3. Found: I, 22.2.

the five and six carbon compounds, a sintering point accompanied by a color change was observed preliminary to the actual melting point.

PHARMACOLOGIC RESULTS

All quaternary ammonium salts were screened for paralyzing activity in frogs (*Rana pipiens*) by lymph sac injections of 200, 40, and 5 mg./kg. doses. Intermediate dose levels were used to obtain the minimal paralyzing dose. Paralyzed frogs were checked for specificity of muscle paralysis at the neuromyal junction by direct and indirect stimulation of the sciatic nerve. The minimum paralyzing dose (MPD, Table II) of the drugs tested varied from 20 to 400 mg./kg.

A pronounced change in activity resulted when

the number of carbon atoms between the quaternary ammonium group and the phthalimide group was varied. In both series, activity was low until $n = 4$, at which point it abruptly rose until a broad maximum was reached at $n = 7$, 8, and 9. As the chain length was further increased, the activity gradually diminished. It appears, therefore, that there is no critical distance, other than the minimal, between the quaternary ammonium and phthalimide portions of the molecule. Although this does not rule out bond formation between the receptor site and the phthalimide portion of the molecule, the fit must be less specific than that of the *bis*-quaternary ammonium compounds related to *d*-tubocurarine whose nitrogen to nitrogen distance is much more critical.[10]

The "umbrella effect" to which Pfeiffer[11] ascribed the activity of *d*-tubocurarine may also afford a satisfactory explanation for the activity of these monoquaternary salts. The quaternary ammonium portion of the molecule may bond to the receptor sites in a manner similar to *d*-tubocurarine while the large phthalimide nucleus screens the surrounding receptor sites from the approach of the acetylcholine molecules.

Little difference is noted between piperidinomethyl and piperidinoethyl groups on the quaternary nitrogen. Substitution with the bulky benzyl group results in a series with diminished activity. A complete pharmacological report will be presented elsewhere.

(10) Barlow and Ing, *Brit. J. Pharmacol.*, **3**, 298 (1948).
(11) Pfeiffer, *Science*, **107**, 94 (1948).

EXPERIMENTAL[12]

N-(ω-bromononyl)-phthalimide. A mixture of 8.45 g. (0.05 mole) of potassium phthalimide, 57.2 g. (0.2 mole) of 1,9-dibromononane and 3.3 g. (5% by weight) of dimethylformamide was heated at 160° for 1.5 hrs. The solution was filtered to remove precipitated potassium bromide. The filtrate was heated to distill the dimethylformamide and the excess dibromononane removed under reduced pressure. The residue was fractionated under reduced pressure using a free flame and the solid portions of the distillate recrystallized from ethanol. With slight variations in procedure the yield of pure product varied from 40–78%. The analytical sample was first purified on alumina and then recrystallized repeatedly from ethanol, m.p. 37.5°.

Anal. Calc'd for $C_{17}H_{22}BrNO_2$: C, 57.96; H, 6.30. Found: C, 58.08; H, 6.17.

N-(ω-piperidinoalkyl)-phthalimides. A solution of 0.01 mole of the appropriate N-(ω-bromoalkyl)-phthalimide and 3.4 g. (0.04 mole) of piperidine in 30 ml. of benzene was heated on the steam bath for 1 hr. The benzene and excess piperidine were removed under reduced pressure and the residue dissolved in ether. The solution was filtered to remove piperidine hydrobromide and decolorized with charcoal. The dried solution was saturated with hydrogen chloride gas and the white crystalline salt collected on a funnel, washed with ether, and dried.

The free base was liberated from an aqueous solution of the hydrochloride salt with cold sodium carbonate solution. The product was recrystallized from 30–60° petroleum ether.

N-(ω-piperidinoalkyl)-phthalimide alkyl iodides. A solution of 0.005 mole of the N-(ω-piperidinoalkyl)-phthalimide and 0.05 mole of the appropriate alkyl iodide in 100 ml. of dry ether was allowed to stand overnight at room temperature. The precipitated quaternary salt was removed by filtration and the filtrate allowed to stand until no more product was formed. The quaternary salts were recrystallized from either absolute ethanol or isopropanol.

St. Louis, Mo.

(12) Analyses are by Du-Good Chemical Laboratory, St. Louis, Mo., and Clark Microanalytical Laboratory, Urbana, Ill. All melting points are corrected.

[Contribution from the Department of Organic Chemistry, University of Madras]

Synthesis of DL-α-Amino-β-(1-skatyl)propionic Acid

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Skatole has been found to undergo the Mannich reaction with formalin and dimethylamine to give 1-dimethylaminomethylskatole. The methiodide of this base alkylates ethyl acetamidocyanoacetate. The alkylated product after treatment with alkali furnishes DL-α-amino-β-(1-skatyl) propionic acid, a new methyl analog of tryptophan.

Since the elegant synthesis of tryptophan[1] by ethyl acetamidomalonate with gramine, many analogs of tryptophan have been synthesized with a view to studying their antimetabolite properties. Methyl tryptophans and methyl isotryptophans have been of particular interest in this connection and 1,2,4,5,6, and 7 methyl tryptophans[2a] and 6-methyl-2-isotryptophan[2b] have been prepared. It was of interest to synthesize 3-methyl-1-isotryptophan, *viz.*, α-amino-β-(1-skatyl)propionic acid (V) in

(1) Snyder and Smith, *J. Am. Chem. Soc.*, **66**, 350 (1944); Albertson, Archer, and Suter, *J. Am. Chem. Soc.*, **66**, 500 (1944).

(2a) Anderson, *Science*, **101**, 565 (1945); Jackman and Archer, *J. Am. Chem. Soc.*, **68**, 2105 (1946); Rydon, *J. Chem. Soc.*, 705 (1948); Snyder and Pilgrim, *J. Am. Chem. Soc.*, **70**, 3787 (1948); Snyder and Eliel, *J. Am. Chem. Soc.*, **70**, 3855 (1948); Boon, *J. Chem. Soc.*, S 231 (1949); Snyder, Beilfuss, and Williams, *J. Am. Chem. Soc.*, **75**, 1873 (1953); Jones and Kornfield, U.S. Patent 2621187 [*Chem. Abstr.* **47**, 10557 (1953)].

(2b) Snyder and Cook, *J. Am. Chem. Soc.*, **78**, 969 (1956)