

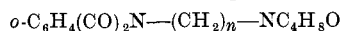
Note

Monoquaternary Muscle Paralyzing Agents—II.¹ Synthesis of *N*-(ω -Phthalimidoalkyl)-*N*-alkyl- morpholinium Iodides*

HUGH B. DONAHOE, ROBERT J. SEIWALD,† SISTER MARY MARGUERITE CHRISTINE NEUMANN, B.V.M.,† and KAZUO K. KIMURA,† *Departments of Chemistry and Pharmacology, St. Louis University, St. Louis, 4, Missouri*

Monoquaternary *N*-(ω -phthalimidoalkyl)-*N*-alkylpiperidinium iodides have been shown to possess activity paralyzing striated muscle.¹ In a continuation of this study, a series of compounds has been prepared in which morpholine has been substituted for piperidine.

Table I. *N*-(ω -Phthalimidoalkyl)-morpholines and hydrochlorides



<i>n</i>	m.p., °C	Formula	HCl m.p.°C	Yield, ^a %	Analyses, % Chlorine	
					Calcd.	Found
1	109–110 ^{b1, e}	C ₁₃ H ₁₄ N ₂ O ₃	198–199 ^{b2}	58	12.5	12.6
2	130–131	C ₁₄ H ₁₆ N ₂ O ₃ ^c	247–249	58	12.0	12.1
3	oil	C ₁₅ H ₁₈ N ₂ O ₃	243 ^{b3}	62	11.4	11.4
4	66.5–67	C ₁₆ H ₂₀ N ₂ O ₃ ^d	232–234	79	10.9	11.0
5	oil	C ₁₇ H ₂₂ N ₂ O ₃	216–218	80	10.5	10.5
6	40 ^{b4}	C ₁₈ H ₂₄ N ₂ O ₃	191–192	77	10.0	10.1

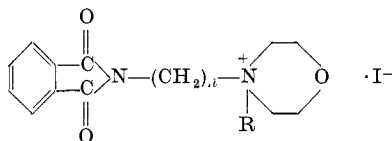
^a All yields calculated on the basis of hydrochlorides. ^b Moore and Rapala² report: (1) 98–103° (as hydrate); (2) 195–196°; (3) 247–248°; (4) 40°. ^c Calcd.: C, 64.59; H, 6.19. Found: C, 64.74; H, 6.15. ^d Calcd.: C, 66.68; H, 6.99. Found: C, 66.92; H, 7.05. ^e Hellmann and Loeschmann report: m.p. 118°.

* This work was supported by a Frederick Gardner Cottrell Grant from Research Corporation and was taken from portions of the Ph.D. dissertations of R. J. Seiwald (1954) and Sr. M. M. C. Neumann, B.V.M. (1954).

† Present addresses: RJS, Department of Chemistry, University of San Francisco, San Francisco, Calif.; Sr. MMCN, Clarke College, Dubuque, Iowa; KKK, Clinical Research Division, Medical Research Directorate, Chemical Research and Development Laboratories, Army Chemical Center, Md.

With the exception of the monomethylene free base, which was prepared *via* the Mannich reaction,^{2, 3} the *N*-(ω -phthalimidoalkyl)-morpholines (Table I) were obtained by reacting *N*-(ω -bromoalkyl)-phthalimides with excess morpholine in benzene to yield the tertiary free bases which were isolated as the hydrochloride salts.

The *N*-(ω -phthalimidoalkyl)-morpholines, as free bases, were reacted with methyl iodide, ethyl iodide or benzyl iodide to prepare the monoquaternary *N*-(ω -phthalimidoalkyl)-*N*-alkylmorpholinium iodides (Table II). Because of reduced activity in the

Table II. *N*-(ω Phthalimidoalkyl)-*N*-alkylmorpholinium iodides

<i>n</i>	m.p., °C	Yield, %	Formula	Analyses, % Iodine		Frog MPD ^a mg/kg
				Calcd.	Found	
Methiodides, R = CH ₃						
1	192-194	45	C ₁₄ H ₁₇ IN ₂ O ₃	32.6	32.7 ^b	^c
2	282-283	40	C ₁₅ H ₁₉ IN ₂ O ₃	31.5	31.4 ^d	^c
3	291	58	C ₁₆ H ₂₁ IN ₂ O ₃	30.4	29.8	^c
4	260 (d.)	92	C ₁₇ H ₂₃ IN ₂ O ₃	29.5	29.6	80
5	193-194	76	C ₁₈ H ₂₅ IN ₂ O ₃	28.6	28.7	60
6	152	84	C ₁₉ H ₂₇ IN ₂ O ₃	27.7	27.8	60
Ethiodides, R = C ₂ H ₅						
2	235-237	39	C ₁₆ H ₂₁ IN ₂ O ₃	30.4	30.5	^c
3	230	26	C ₁₇ H ₂₃ IN ₂ O ₃	29.5	29.4	200
4	260 (d.)	86	C ₁₈ H ₂₅ IN ₂ O ₃	28.6	28.5	150
5	184	88	C ₁₉ H ₂₇ IN ₂ O ₃	27.7	27.4	60
6	154-156	74	C ₂₀ H ₂₉ IN ₂ O ₃	26.9	26.8	60
Benzyl iodides, R = C ₆ H ₅ CH ₂						
4	260 (d.)	71	C ₂₃ H ₂₇ IN ₂ O ₃	25.1	25.4	100
5	201 (d.)	53	C ₂₄ H ₂₉ IN ₂ O ₃	24.4	24.4	40
6	189-191	61	C ₂₅ H ₃₁ IN ₂ O ₃	23.8	24.0	40
<i>d</i> -Tubocurarine Chloride (DTC)						2

^a MPD = Minimum paralyzing dose (lymph-sac injection). ^b Calcd.: C, 43.31; H, 4.41. Found: C, 43.34; H, 4.86. ^c No paralyzing action up to 400 mg/kg. ^d Calcd.: C, 44.78; H, 5.76. Found: C, 45.03; H, 5.94.

lower members of the series, compounds with methylene chains above six carbon atoms in length were not prepared.

Pharmacology

All quaternary ammonium salts were tested for activity in paralyzing striated muscle in frogs (*Rana pipiens*) by lymph sac injection following a previously described procedure.¹

The monoquaternary morpholinium compounds of this type were either devoid of paralyzing activity in the frog or were two to three times less active than the corresponding piperidinium methiodides and ethiodides. Only the five- and six-carbon chain benzyliodides were more active than the *N*-benzylpiperidinium iodides containing the same ω -phthalimidoalkyl groups. In this series, *N*-(5-phthalimidopentyl)-*N*-benzylmorpholinium iodide and *N*-(6-phthalimidohexyl)-*N*-benzylmorpholinium iodide were most active. This activity, however, was only half that of the most active *N*-(ω -phthalimidoalkyl)-*N*-alkylpiperidinium iodide.

Experimental*

N-(ω -Bromoalkyl)-phthalimides. The *N*-(ω -bromoalkyl)-phthalimides were prepared from potassium phthalimide and ω -dibromoalkanes by a previously described method.¹

N-(ω -Phthalimidoalkyl)-morpholines. The tertiary morpholine bases were prepared in one of two ways.

Method A. *N*-Phthalimidomethyl morpholine. The monomethylene derivative was prepared by a Mannich reaction following the procedure of Hellmann and Loeschmann.³

Method B. Morpholine (7.0 g, 0.08 mole) and the appropriate *N*-(ω -bromoalkyl)-phthalimide (0.02 mole) in benzene (60 ml) were heated on the steam bath for 1 h. Benzene and excess of morpholine were removed under reduced pressure and the residue was dissolved in ether. The solution was filtered to remove morpholine hydrobromide, decolorized with charcoal and dried.

* Carbon and hydrogen analyses are by Du-Good Chemical Laboratory, St. Louis, Missouri, and Clark Microanalytical Laboratory, Urbana, Ill. Ionic halogen was determined potentiometrically in this laboratory. All melting points are corrected.

The dried solution was saturated with hydrogen chloride gas and the salt was filtered, washed with ether, and dried.

The base was liberated from an aqueous solution of the hydrochloride with sodium carbonate solution. If solid, the free base was recrystallized from alcohol or petroleum ether. If an oil, it was taken up in ether, dried, and used directly in the quaternization step.

N-(ω -Phthalimidoalkyl)-*N*-alkylmorpholinium iodides. The *N*-(ω -phthalimidoalkyl)-morpholine (0.005 mole) and the appropriate alkyl iodide (0.05 mole) in dry ether (100 ml) were mixed and allowed to stand overnight at room temperature. The precipitated quaternary salt was removed by filtration and the filtrate set aside until no more product was formed. The quaternary salts were recrystallized from either absolute ethanol or 2-propanol.

(Received 14 November, 1960)

References

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- ² Moore, M. B. and Rapala, R. T. *J. Amer. chem. Soc.*, **68**, 1657 (1946)
- ³ Hellmann, H. and Loeschmann, I. *Chem. Ber.*, **87**, 1687 (1954)