Potential Antifibrillatory Agents. N-(ω-Aminoalkoxy)phthalimides[1]

MILTON J. KORNET

College of Pharmacy, University of Kentucky, Lexington, Kentucky 40506

Received September 22, 1965

Our interest in drugs which affect the rate and rhythm of the heart has led us to prepare a series of N-(ω-aminoalkoxy)phthalimides. These compounds are isosteric with the N-(ω-aminoalkyl)phthalimides which are known antifibrillants.[2] One of the latter compounds, N-[4-(3-methylpiperidino)butyl]phthalimide,[2] is reported to be 1.6 times as potent in auricular and 2.5 times as potent in ventricular fibrillation as quinidine, while being only slightly more toxic.

The reaction involved in obtaining the title compounds is shown by the following general equation.

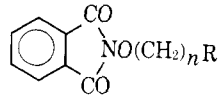
$$o\text{-}C_6H_4(CO)_2NO(CH_2)_nBr + 2HNR_2 \longrightarrow o\text{-}C_6H_4(CO)_2NO(CH_2)_nNR_2 + H_2NR_2{}^+Br^-$$

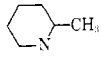
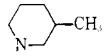
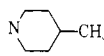
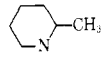
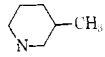
Experimental Section[3]

N-(ω-Bromoalkoxy)phthalimides.—These compounds were prepared by the previously described procedure[4] with the following modifications. The molar ratio of the reactants was changed as follows: N-hydroxyphthalimide (0.1 mole), alkylene bromide (0.25 mole), and triethylamine (0.125 mole). Separation of the N-(ω-bromoalkoxy)phthalimides from the by-product, ω,ω′-bis(phthalimidooxy)alkanes, was achieved by recrystallization from 70% aqueous ethanol. The ω,ω′-bis(phthalimidooxy)-alkanes were insoluble in this solvent system. In this manner, the yields were improved as follows: N-(β-bromoethoxy)phthalimide, 58.1%, mp 97–98°, lit.[4] mp 94–96°; N-(γ-bromopropoxy)phthalimide, 55.7%, mp 72–73°, lit.[4] mp 60–65°; and N-(δ-bromobutoxy)phthalimide, 59.4%, mp 71–72°, lit.[4] mp 70–72°.

TABLE I

N-(ω-AMINOALKOXY)PHTHALIMIDE HYDROCHLORIDES



No.	R	n	Mp, °C[a]	Formula	% nitrogen Calcd	% nitrogen Found
1		2	221–223	$C_{14}H_{16}N_2O_3 \cdot HCl$	9.44	8.86
2		2	208–212	$C_{14}H_{16}N_2O_4 \cdot HCl$	8.96	8.68
3		2	235–236	$C_{15}H_{18}N_2O_3 \cdot HCl$	9.01	8.96
4		2	264–267	$C_{16}H_{20}N_2O_3 \cdot HCl$	8.63	8.64
5		2	222–223.5	$C_{16}H_{20}N_2O_3 \cdot HCl$	8.63	8.33
6		2	249–250	$C_{16}H_{20}N_2O_3 \cdot HCl$	8.63	8.72
7	$CH_3NCH_2C_6H_5$	2	210–212	$C_{18}H_{18}N_2O_3 \cdot HCl$	8.08	8.24
8		3	200–202	$C_{17}H_{22}N_2O_3 \cdot HCl$	8.27	8.15
9	$CH_3NCH_2C_6H_5$	3	179–180	$C_{19}H_{20}N_2O_3 \cdot HCl$	7.76	8.25
10		4	190–192	$C_{16}H_{20}N_2O_4 \cdot HCl$	8.22	8.32
11		4	160–161	$C_{18}H_{24}N_2O_3 \cdot HCl$	7.94	7.68

[a] Compounds **1** through **10** were recrystallized from absolute ethanol, **11** from absolute ethanol–ethyl acetate.

N-(ω-Aminoalkoxy)phthalimide Hydrochlorides.—A typical reaction is described, that for the preparation of N-(δ-morpholinobutoxy)phthalimide hydrochloride. The melting points and analyses are given in Table I. A solution of N-(δ-bromobutoxy)-phthalimide (7.45 g, 0.025 mole) in 50 ml of dry benezene was treated with morpholine (4.35 g, 0.05 mole) and refluxed for 2 hr. The precipitated morpholine hydrobromide was filtered, and the filtrate was evaporated *in vacuo* on a water bath. The residue was dissolved in a mixture of absolute ethanol and ether, and dry HCl was passed in. The precipitated salt was filtered and recrystallized from absolute ethanol and yielded 7.39 g (93.4%) of product, mp 190–192°.

Acknowledgment.—The author wishes to acknowledge the assistance of Mr. Stephen Bower in preparing some of the intermediates.

(1) This investigation was assisted in part by Grant GB-3331 from the National Science Foundation.

(2) (a) K. Hideg and H. O. Hankovszky, *Acta Chim. Acad. Sci. Hung.*, **39**, 391 (1963); (b) K. Hideg, L. Szekeres, H. O. Hankovszky, and J. Papp, *Biochem. Pharmacol., Suppl.*, **12**, 171 (1963); (c) K. Hideg and H. O. Hankovszky, *J. Med. Chem.*, **8**, 257 (1965).

(3) Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. Kurt Eder, Geneva, Switzerland.

(4) L. Bauer and K. S. Suresh, *J. Org. Chem.*, **28**, 1604 (1963).