propenes) in the presence of aluminum chloride.

2. There is a marked difference in reactivity between *cis*- and *trans*-dichloroethylene. The former may be condensed in good yield with isopropyl and *t*-butyl chlorides, whereas the latter gives only a fair yield of product with the propyl halide and a very poor yield with the butyl compound.

3. Ethyl chloride could not be condensed with *cis*-dichloroethylene.

4. The reaction of isopropyl chloride with trichloroethylene in the presence of aluminum chloride at 0–20° yields tetrachloropentane (presumably 1,1,1,2-tetrachloro-3-methylbutane) and its dehydrochlorination product, trichloropentene.

RIVERSIDE, ILL. RECEIVED MAY 3, 1946

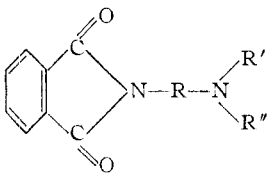
[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

N-Alkamine Substituted Phthalimides[1]

BY M. B. MOORE AND R. T. RAPALA

For a number of years, one of us[1a] has been interested in the synthesis of N-alkamine substituted phthalimides useful as local anesthetics. Some compounds of this type have previously been synthesized[2] but no study of their pharmacologic action has been reported. In many cases they were not carefully purified, but were immediately hydrolyzed to the diamines according to the Gabriel method,[3] or a modification of this.

Table I lists the compounds prepared in this series conforming to the general formula



in which R is an alkylene group, straight or branched; R′ and R″ are alkyl groups or hydrogen or may complete a heterocyclic ring of which the nitrogen is a member. Other modifications which do not conform to the above general type will be reported later.

Experimental

The five methods used are illustrated by the following procedures:

N-γ-Diethylaminopropylphthalimide, Method A.—Phthalic anhydride (74 g., 0.5 mole) and γ-diethylaminopropylamine (65 g., 0.5 mole) were heated in an oil-bath at 160–180° for an hour. After cooling, the viscous liquid product was taken up in water with a slight excess of hydrochloric acid. The aqueous solution was filtered with a little Darco, and the oily base precipitated from the clear aqueous solution of the hydrochloride by addition of excess sodium carbonate. The base was shaken out in petroleum ether, and solvent evaporated. The base was then taken up in a little absolute alcohol, and the crystalline hydrochloride precipitated therefrom by addition of alcoholic hydrochloric acid, with ice cooling; dry ether was added to give more complete precipitation. After filtration and washing with ether, the air-dried crystals weighed 142 g. After drying in a vacuum at boiling acetone temperature with phosphorus pentoxide, the alcohol of crystallization was lost.

Method B.—Phthalimide (14.7 g., 0.1 mole) and γ-diethylaminopropylamine (13.0 g., 0.1 mole) were gently heated together in an oil-bath at 90–110° for four and one-half hours. During the first hour, evolution of ammonia occurred and the mixture became a viscous liquid. The product was taken up in aqueous hydrochloric acid and further purified as described under Method A.

N-β-Di-*n*-butylaminoethylphthalimide, Method C.—β-Di-*n*-butylaminoethyl chloride (19.5 g., 0.1 mole) and potassium phthalimide (19 g., 0.1 mole) were refluxed with 100 cc. of absolute alcohol (12A) for eleven hours. The reaction mixture was filtered from the precipitate of potassium chloride, and the alcohol distilled under vacuum from the filtrate. The residue was taken up in petroleum ether, solution filtered and distilled. The fraction, b. p. 161–177° (2.5 mm.), amounted to 11 g. It was further purified by solution in aqueous hydrochloric acid and filtration with charcoal, followed by liberation of the base and its extraction with ether.

N-ω-Diethylaminohexylphthalimide, Method D.—N-ω-Bromohexylphthalimide (7.8 g., 0.025 mole), diethylamine (7.3 g., 0.1 mole) and 50 cc. of absolute alcohol (12A) were refluxed for eleven hours. The solution was filtered and solvent distilled at atmospheric pressure. The residue was partitioned between water and petroleum ether to remove water-soluble impurities. The dried petroleum ether extracts were evaporated and the residue taken up in absolute alcohol and precipitated by hydrochloric acid, ether being added to aid in complete precipitation. The precipitate was recrystallized from a small volume of 12A absolute alcohol.

N-Morpholinomethylphthalimide, Method E.—Phthalimide (39.4 g., 0.2 mole) in a small round-bottomed flask was covered with dilute alcohol (1:1). The mixture was stirred, and 40 cc. formalin was added, followed by morpholine (17.5 g., 0.2 mole). With continued stirring, the magma was heated to refluxing and refluxed for fifteen minutes, after which nearly all was dissolved. The solution was filtered hot and, after three days in the cold room, the crystalline product was filtered and recrystallized from 3A alcohol.

The pharmacology of these compounds was studied by Dr. R. K. Richards and co-workers and will be reported in detail elsewhere. Most of the compounds possessed local anesthetic properties, γ-diethylaminopropylphthalimide being the best of the series for injection anesthesia from the standpoint of efficiency, toxicity and lack of irritation. Its properties in general are quite similar to those of procaine. Increase in the length of the alkylene chain beyond three carbons tends to increase toxicity without a cor-

(1) Presented on the program of the Division of Medicinal Chemistry at the Atlantic City meeting of the American Chemical Society, April 8–12, 1946.

(1a) Moore, U. S. Patent 2,343,198 (1944).

(2) (a) Sachs, *Ber.*, **31**, 3230 (1898); (b) Walls, *J. Chem. Soc.*, 104 (1934); (c) Shriner and Hickey, THIS JOURNAL, **61**, 888 (1939); (d) Kharasch and Fuchs, *J. Org. Chem.*, **9**, 359 (1944).

(3) (a) Gabriel, *Ber.*, **20**, 2224–2236 (1887); (b) **21**, 566–575 (1888); (c) **22**, 2223–2227 (1889); and many later papers.

TABLE I

R	$NR'R''$	Synthesis	Yield, %	Solvent	M. p., °C. or b. p. (mm.)	Formula	N, % Calcd.	N, % Found
—CH_2—	NC_4H_8O	E	84	H_2O	98–103[f] or 96–98	$C_{13}H_{14}N_2O_3 \cdot H_2O$	10.60	10.59
				Ether–alc.	195–196 (dec.)	$C_{13}H_{14}N_2O_3 \cdot HCl$	9.92	9.53
—CH_2—	NC_5H_{10}	E	35	Alc. 80%	94–95[a]	$C_{14}H_{16}N_2O_2$		
				Ether–alc.	186–187	$C_{14}H_{16}N_2O_2 \cdot HCl$	9.98	9.55
—CH_2CH_2—	$N(CH_3)_2$	A	2.5	Pet. ether	104–105	$C_{12}H_{14}N_2O_2$	12.84	12.93
—CH_2CH_2—	$N(C_2H_5)_2$	C	59	Pet. ether	45–47[b]	$C_{14}H_{18}N_2O_2$		
					235–236	$C_{14}H_{16}N_2O_2 \cdot HCl$		
—CH_2CH_2—	$N(i\text{-}C_3H_7)_2$	C	30	Alc.–ether	207–209	$C_{16}H_{22}N_2O_2 \cdot HCl$	9.01	8.96
—CH_2CH_2—	$N(n\text{-}C_4H_9)_2$	C	36	Pet. ether	161–167 (2.5)	$C_{18}H_{26}N_2O_2$	9.26	9.25
—$(CH_2)_3$—	$N(CH_3)_2$	A	37	Alc. abs.	203–204	$C_{13}H_{16}N_2O_2 \cdot HCl$	10.43	10.37
—$(CH_2)_3$—	$N(C_2H_5)_2$	A or B	83	Alc.–ether	79–80	$C_{15}H_{20}N_2O_2 \cdot HCl \cdot C_2H_6O$	8.17	8.46
			85	Acetone	181–182[c]	$C_{15}H_{20}N_2O_2 \cdot HCl$	9.44	9.41
—$(CH_2)_3$—	$N(i\text{-}C_3H_7)_2$	D	15	Alc.–ether	214–216	$C_{17}H_{24}O_2N_2 \cdot HCl$	8.62	8.55
		C	53					
—$(CH_2)_3$—	$N(n\text{-}C_4H_9)_2$	C	43	Pet. ether	190(3)	$C_{19}H_{28}N_2O_2$	8.85	9.17
			70	Acetone	115–116	$C_{19}H_{28}N_2O_2 \cdot HCl$	7.94	7.52
—$(CH_2)_3$—	$N(n\text{-}C_5H_{11})_2$	A	70	Water	87–88	$C_{21}H_{32}N_2O_2 \cdot HCl \cdot 2H_2O$	6.73	6.75
—$(CH_2)_3$—	N(cyclo-$C_6H_{11})_2$	D	30	Alc.–pet. ether	>265	$C_{23}H_{32}N_2O_2 \cdot HCl$	6.92	6.89
—$(CH_2)_3$—	NC_4H_8O	C		Alc. abs.	247–248 (dec.)	$C_{15}H_{18}N_2O_3 \cdot HCl$[d]	9.01	8.83
—$(CH_2)_3$—	$NCH(CH_3)(CH_2)_4$	C	31	Alc.–ether	190–192	$C_{17}H_{22}O_2N_2 \cdot HCl$	8.68	8.50
—$CH_2CH(CH_3)$—	$N(C_2H_5)_2$	C	40	Acetone	178–179	$C_{16}H_{26}N_2O_2 \cdot HCl$	9.44	9.33
—$CH(CH_3)CH_2$—	$N(C_2H_5)_2$	C	29	Acetone	184–185	$C_{15}H_{20}N_2O_2 \cdot HCl$	9.44	9.36
—$(CH_2)_3$—	$NHCH_3$	A	2.8	Alc.–ether	204–207	$C_{12}H_{14}N_2O_2 \cdot HCl$	11.00	10.75
—$(CH_2)_3$—	$NH(i\text{-}C_3H_7)$	A	28	Ether	58–60	$C_{14}H_{18}N_2O_2$	11.38	11.72
				Pet. ether				
—$(CH_2)_3$—	$NH(n\text{-}C_4H_9)$	A	9.5	Alc. abs.	195–197	$C_{15}H_{20}N_2O_2 \cdot HCl$	9.44	9.50
—$(CH_2)_4$—	$N(C_2H_5)_2$	D	35	Alc. abs.	183–184	$C_{16}H_{22}N_2O_2 \cdot HCl$	9.01	8.73
—$CH_2CH_2CH(CH_3)$—	$N(C_2H_5)_2$	D	4	Acetone	158–159	$C_{16}H_{22}N_2O_2 \cdot HCl$	9.01	8.65
—$(CH_2)_5$—	$N(C_2H_5)_2$	D	62	Alc.–ether	175–176	$C_{17}H_{24}N_2O_2 \cdot HCl$	8.62	8.46
—$CH(CH_3)(CH_2)_3$—	$N(C_2H_5)_2$	A	57	Pet. ether	174–182(5)	$C_{17}H_{24}N_2O_2$[e]	9.72	9.84
—$(CH_2)_6$—	$N(C_2H_5)_2$	D	65	Alc–ether	206–208	$C_{18}H_{26}N_2O_2 \cdot HCl$	8.27	8.07
—$(CH_2)_6$—	NC_4H_8O	D	30	Pet. ether	40–42	$C_{18}H_{24}N_2O_3$	8.85	8.53

[a] Sachs (ref. 2(a)) m. p. 117–118°. [b] Walls (ref. 2(b)) m. p. 46–47°. [c] Shriner and Hickey m. p. 144–145°. [d] Prepared by Dr. M. T. Leffler. [e] Kharasch and Fuchs (ref. 2(d)) obtained this compound as a mixture with its isomer. The preparation from the diamine eliminates the rearrangement which they describe. [f] Hot stage melting point.

responding increase in efficiency, and branching of this chain is unfavorable. Increasing the size of R′ and R″ does not increase the efficiency in wheals to any marked extent, but does increase corneal anesthetic effect. When either R′ or R″ is H, the efficiency is decreased, even for a compound of the same molecular weight. The compounds in which R is methylene were not tested, because the hydrochlorides, soluble in water, rapidly decomposed and deposited a precipitate of phthalimide.

Acknowledgment.—Thanks are due Messrs. E. F. Shelberg and L. F. Reed for the microanalyses herein reported.

Summary

A series of N-alkamine substituted phthalimides is reported, most of whose members are effective local anesthetics, especially for parenteral rather than topical use.

NORTH CHICAGO, ILLINOIS RECEIVED APRIL 29, 1946

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Metalation of Benzotrifluoride

BY JOHN D. ROBERTS[1] AND DAVID Y. CURTIN

Aromatic substituents groups which direct *ortho–para* in electrophilic substitution reactions such as nitration and sulfonation appear to exert a similar influence in the nuclear metalation of substituted benzenes.[2] No studies have been reported of the influence in metalation reactions of groups which lead to *meta* substitution with electrophilic reagents. In general, reaction of such groups with the customary metalating agents occurs more rapidly than nuclear metalation. In the present work the metalation of benzotrifluoride has been investigated since the trifluoromethyl group is known to be resistant to chemical attack[3,4] and strongly *meta*-directing in nitration[4] and in chlorination[5] reactions.

Benzotrifluoride is readily metalated in refluxing ether solution by *n*-butyllithium. Carbonation of the metalation products gave a 48% yield of a

(1) National Research Fellow, 1945–1946.

(2) See Morton *Chem. Rev.*, **35**, 1 (1944), for a summary of work on orientation in nuclear metalation reactions notably by Gilman, Morton and Wittig and their collaborators.

(3) Gilman and Woods, THIS JOURNAL, **66**, 1981 (1944).

(4) Swarts, *Bull. sci. acad. roy. Belg.*, **6**, 389 (1920); *Chem. Zentr.*, **92**, II, 32 (1921).

(5) Wertyporoch, *Ann.*, **493**, 153 (1932).