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THE SYNTHESIS OF SOME TERTIARY NAPHTHOXYETHYLAMINES[1]

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In view of the pharmacological actions exhibited by many alkyl-substituted phenoxyethylamines it was of interest to prepare a number of naphthoxyethylamines to that their properties might be investigated more extensively. Several compounds of this type have been known for many years. Einhorn and Rothlauf (1) have described β-naphthoxytriethylamine and Clemo and Perkin (2) synthesized the analogous N,N-dimethyl-β-naphthoxyethylamine. Although the latter authors remarked that their product exhibited local anesthetic action, this observation does not appear to have stimulated much further interest. After recognition of the antihistaminic action associated with many aryloxyethylamines, Bovet and Staub (3) reported that β-naphthoxytriethylamine (939F) had a slight antihistaminic action while α-naphthoxytriethylamine (937F) failed to protect animals from death upon subsequent administration of histamine hydrochloride. No details of the preparation of these compounds were given. Cavallini, *et al.*, (4) have studied the circulatory and antiallergic properties of N,N-dimethyl-α-naphthoxyethylamine, and more recently the synthesis of both α- and β-naphthoxytriethylamine (5) and their action as antitubercular agents has been studied (5, 6).

Our interest has been primarily in the local anesthetic action associated with this structure and for this purpose the synthesis of a series of tertiary aminoethyl ethers of both α- and β-naphthol was undertaken.

Although Einhorn and Rothlauf (1) first prepared β-naphthoxytriethylamine by the thermal elimination of carbon dioxide from diethylaminoethyl β-naphthyl

$$\beta\text{-}C_{10}H_7OCOOCH_2CH_2N(C_2H_5)_2 \longrightarrow \beta\text{-}C_{10}H_7OCH_2CH_2N(C_2H_5)_2 + CO_2$$

carbonate, it appeared more advantageous to prepare compounds of this type by interaction of 2-haloethyl naphthyl ethers and secondary amines, a procedure employed by Clemo and Perkin (2). This procedure seemed more attractive than that based on the interaction of 2-dialkylaminoethyl halides with the sodium naphthoxides (5) since a greater variety of tertiary amines could be prepared from only two key intermediates. Several methods were available for the preparation of the requisite haloethyl napthyl ethers. Clemo and Perkin (2) employed a sequence of reactions involving the interaction of ethylene chlorohydrin and *p*-toluenesulfonyl chloride to form 2-chloroethyl *p*-toluenesulfonate and interaction of the latter with sodium β-naphthoxide in aqueous solution. Kirner and Richter (7) prepared β-naphthoxyethanol by interaction of β-naphthol and

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ethylene chlorohydrin in aqueous alkaline solution followed by treatment of the alcohol with thionyl chloride in the presence of pyridine to form the chloride.

We have employed two procedures for the synthesis of the haloethyl naphthyl ethers. The method of Marvel and Tannenbaum (8) for the preparation of phenoxyethyl bromide was adapted to the preparation of both α- and β-naphthoxyethyl bromide. The interaction of ethylene bromide and the appropriate naphthols in hot, aqueous alkaline solution was involved. The yields of naphthoxyethyl bromides were low (40–50%) due to the formation of the dinaphthoxyethanes. Better over-all yields (75–80%) of the equally useful 2-chloroethyl naphthyl ethers were obtained by an adaptation of the Clemo and Perkin technique (2). 2-Chloroethyl benzenesulfonate was prepared by interaction of ethylene chlorohydrin and benzenesulfonyl chloride in the presence of aqueous sodium hydroxide (9). Subsequent interaction of the chloroethyl ester with the naphthols in aqueous alkaline solution gave the desired 2-chloroethyl naphthyl ethers.

$$C_{10}H_7ONa + (CH_2)_2Br_2 \longrightarrow C_{10}H_7OCH_2CH_2Br + NaBr$$

$$C_6H_5SO_2Cl + HO(CH_2)_2Cl \xrightarrow{(NaOH)} C_6H_5SO_3CH_2CH_2Cl + HCl$$

$$C_6H_5SO_3CH_2CH_2Cl + C_{10}H_7OH \xrightarrow{(NaOH)} C_{10}H_7OCH_2CH_2Cl + C_6H_5SO_3H$$

Although Clemo and Perkin were able to prepare 2-chloroethyl *p*-toluenesulfonate in excellent yield (87%) by simply heating *p*-toluenesulfonyl chloride with a large excess of ethylene chlorohydrin, application of the same technique to benzenesulfonyl chloride gave the corresponding chloroethyl ester in yields of only 55–65%. When the reaction was carried out by addition of aqueous sodium hydroxide to a cold mixture of ethylene chlorohydrin and benzenesulfonyl chloride, a greatly improved yield (85–90%) of a more easily purified product resulted. Excellent yields of the chloroethyl naphthyl ethers were obtained upon interaction of the chloroethyl benzenesulfonate and the sodium naphthoxides.

The tertiary amines were prepared by the interaction of the haloethyl naphthyl ethers with appropriate secondary amines in boiling toluene or benzene solution at atmospheric pressure or in benzene solution in a steel bomb at about 120°. The choice of conditions was determined by the volatility of the secondary amine. The products were characterized as free bases, hydrochlorides and methiodides.

Pharmacological studies were carried out by the Parke, Davis Research Laboratories and we are indebted to them for the following results. Local anesthetic action comparable to that of cocaine for mucous surface anesthesia or to that of procaine for injection anesthesia was associated with all the compounds of this group. Solutions of the hydrochlorides (1%) were distinctly irritating to the rabbit's eye. Antihistaminic action was only very slight and a very mild analgesic action complicated by stimulatory effects was observed with certain compounds of this group.

EXPERIMENTAL

2-Chloroethyl benzenesulfonate. Method A. Analogous to the procedure of Clemo and Perkin (2) a mixture of 176 g. (1 mole) of benzenesulfonyl chloride and 200 g. (2.5 moles) of ethylene chlorohydrin was boiled under reflux for six hours. After removal of the excess

ethylene chlorohydrin under diminished pressure, the mixture was diluted with 150 ml. of benzene and washed with 5% sodium hydroxide (cooling by addition of ice is desirable). The benzene solution was dried over potassium carbonate before removal of the solvent by distillation and fractionation of the residue under reduced pressure. The material distilling at 186–189° at 16.5 mm. was collected, yield 132 g. (60%). The product prepared in this manner always had a brownish-green cast which gradually intensified on storage.

Method B. Using a modification of the Földi procedure (9) a solution of 100 g. (2.5 moles) of sodium hydroxide in 600 ml. of water was added during five hours with continuous stirring to a cooled (10–15°) mixture of 176 g. (1 mole) of benzenesulfonyl chloride and 161 g. (2 moles) of ethylene chlorohydrin. The reaction mixture should be kept slightly alkaline to litmus a all times. After completion of the reaction, the mixture was diluted with 250 ml. of benzene and the layers separated. The benzene solution was washed once with water, dried over potassium carbonate and fractionated under diminished pressure after removal of the solvent by distillation. The product was collected at 187–190° at 17.5 mm. (155–157° at 2 mm.) as a clear, colorless liquid, yield 203 g. (91%), n_D^{15} 1.5283, d^{25} 1.3422. Földi (9a) reported b.p. 184° at 9 mm. and d^{15} 1.353; Bert (9b) reported b.p. 192° at 15 mm.

2-Chloroethyl 1-naphthyl ether. A solution of 20 g. (0.5 mole) of sodium hydroxide in 35 ml. of water was added to a mixture of 110 g. (0.5 mole) of 2-chloroethyl benzenesulfonate and 72 g. (0.5 mole) of α-naphthol. The mixture was stirred for an hour on a boiling-water bath, diluted with 250 ml. of hot water, and with continued stirring allowed to cool slowly to room temperature. The product was taken up in benzene, washed with 10% sodium hydroxide, and dried over sodium sulfate. After evaporation of the solvent, the product was distilled under reduced pressure, b.p. 184–185° at 16.5 mm., yield 90 g. (88%), as a colorless, viscous liquid. Clemo and Perkin (2) reported b.p. 202° at 16 mm.; Kirner and Richter (7) reported b.p. 145–147° at 2 mm.

2-Chloroethyl 2-naphthyl ether. A mixture of 30 g. (0.2 mole) of β-naphthol and 44 g. (0.2 mole) of 2-chloroethyl benzenesulfonate was treated with 8 g. (0.2 mole) of sodium hydroxide in 14 ml. of water as in the preceding example. On cooling the reaction mixture 43 g. of crude 2-chloroethyl 2-naphthyl ether separated as a solid. The crude product was extracted with hot petroleum ether to remove unreacted β-naphthol and then recrystallized from 95% ethanol. Yield 36.5 g. (88%); m.p. 81–82°. Clemo and Perkin (2) observed the same melting point.

2-Bromoethyl 1-naphthyl ether. A mixture of 200 g. (1.39 moles) of α-naphthol, 395 g. (2.1 moles) of ethylene bromide, and 600 ml. of water was boiled gently under reflux while 56 g. (1.4 moles) of sodium hydroxide in 200 ml. of water was added slowly during 2.5 hours. Heating was continued for 4.5 hours after complete addition of the sodium hydroxide. After cooling the mixture, the heavy layer of crude product was separated, washed twice with water, and distilled under reduced pressure. Ethylene bromide (120 g.) and 85 g. of α-naphthol were recovered before the product distilled at 168–170° at 5 mm., yield 155 g. (45%). The product solidified on standing and could be recrystallized from methanol, m.p. 33–34° Jacobs and Heidelberger (10) reported b.p. 154–156° at 0.8 mm., m.p. 25°.

2-Bromoethyl 2-naphthyl ether. The reaction between β-naphthol and ethylene bromide was carried out essentially as described for the *alpha*-isomer. Since a substantial part of the product solidified when the reaction mixture was cooled, it was diluted with sufficient benzene to dissolve the product. The benzene solution was washed repeatedly with 5% sodium hydroxide to remove unreacted β-naphthol. On evaporation of the benzene and excess ethylene bromide under reduced pressure the product remained as an oil that solidified slowly on cooling. The solid was recrystallized from 95% ethanol. From 230 g. (1.6 moles) of β-naphthol and 451 g. (2.4 moles) of ethylene bromide, 206 g. (51%) of 2-bromoethyl 2-naphthyl ether, m.p. 92°, was obtained. Previously m.p. 96° (11) and 92° (12) had been reported. β-Naphthol (70 g.) was recovered from the alkaline washings.

TERTIARY NAPHTHOXYETHYLAMINES

Analytical data for the naphthoxyethylamines and their derivatives are summarized. in Table I.

1-[2-(1-Naphthoxy)ethyl]piperidine. A solution of 34.9 g. (0.14 mole) of 2-bromoethyl-1-naphthyl ether and 25 g. (0.29 mole) of piperidine in 150 ml. of toluene was boiled under reflux for four hours. After complete precipitation of the piperidine hydrobromide by addition of ether, the filtrate was evaporated to dryness under reduced pressure. The residual tertiary amine was taken up in ether, treated with dry hydrogen chloride, and the tertiary amine *hydrochloride* recrystallized from a methanol-ether mixture, yield 38.2 g. (94%); m.p. 180–180.5°. The *base* was obtained as a colorless liquid, b.p. 185–186° at 5 mm.; *methiodide*, m.p. 133.5–134.5°.

Under similar conditions the tertiary amine hydrochloride was prepared from 2-chloroethyl 1-naphthyl ether and piperidine in 76% yield.

1-[2-(2-Naphthoxy)ethyl]piperidine. The hydrochloride was isolated in 91% yield from the reaction of 25.9 g. (0.1 mole) of 2-bromoethyl 2-naphthyl ether with 18.5 g. (0.22 mole) of piperidine as described in the preceding examples. The *hydrochloride* was recrystallized

TABLE I

TERTIARY NAPHTHOXYETHYLAMINES AND THEIR DERIVATIVES $C_{10}H_7OCH_2CH_2R$

R	BASE			HYDROCHLORIDE			METHIODIDE		
	Formula	N		Formula	N		Formula	N	
		Calc'd	Found		Calc'd	Found		Calc'd	Found
1-NAPHTHOXY									
Dimethylamino	$C_{14}H_{17}NO$	6.5	6.7	$C_{14}H_{18}ClNO$	5.6	5.7	$C_{15}H_{20}INO$	3.9	3.9
Diethylamino	$C_{16}H_{21}NO$	5.8	5.7	$C_{16}H_{22}ClNO$	5.0	5.0	$C_{17}H_{24}INO$	3.6	3.7
1-Piperidyl[a]	$C_{17}H_{21}NO$	5.5	5.2	$C_{17}H_{22}ClNO$	4.8	4.6	$C_{18}H_{24}INO$	3.5	3.7
4-Morpholinyl	$C_{16}H_{19}NO_2$	5.4	5.3	$C_{16}H_{20}ClNO_2$	4.8	4.9	$C_{17}H_{22}INO_2$	3.5	3.5
2-NAPHTHOXY									
Dimethylamino	$C_{14}H_{17}NO$	6.5	6.4	$C_{14}H_{18}ClNO$	5.6	5.7	$C_{15}H_{20}INO$	3.9	3.9
Diethylamino	$C_{16}H_{21}NO$	5.8	5.7	$C_{16}H_{22}ClNO$	5.0	5.0	$C_{17}H_{24}INO$	3.6	3.7
1-Piperidyl[a]	$C_{17}H_{21}NO$	5.5	5.1	$C_{17}H_{22}ClNO$	4.8	5.0	$C_{18}H_{24}INO$	3.5	3.8
4-Morpholinyl	$C_{16}H_{19}NO_2$	5.4	5.5	$C_{16}H_{20}ClNO_2$	4.8	4.8	$C_{17}H_{22}INO_2$	3.5	3.5

[a] Nitrogen analyses on piperidine derivatives by micro-Dumas, all other by Kjeldahl method.

from methanol-ether mixture, m.p. 209–210°. The *free base* was obtained as a solid, m.p. 48–49° from aqueous ethanol; *methiodide*, m.p. 151–153°.

By interaction of 2-chloroethyl 2-naphthyl ether and piperidine the same hydrochloride was obtained in 88% yield.

4-[2-(1-Naphthoxy)ethyl]morpholine was prepared from 34.9 g. (0.14 mole) of 2-bromoethyl 1-naphthyl ether and 25.4 g. (0.29 mole) of morpholine in toluene solution by boiling under reflux for four hours. The *hydrochloride* was isolated as described in the preceding examples, yield 36 g. (88%); m.p. 199–200° after recrystallization from methanol-ether mixture. The *free base*, b.p. 199–201° at 3 mm., crystallized on chilling, m.p. 37° after crystallization from aqueous methanol. *Methiodide*, m.p. 158–159°.

The same hydrochloride was obtained in 78% yield by interaction of 2-chloroethyl 1-naphthyl ether and morpholine in boiling toluene solution.

4-[2-(2-Naphthoxy)ethyl]morpholine. A solution of 20.5 g. (0.08 mole) of 2-bromoethyl 2-naphthyl ether and 15 g. (0.17 mole) of morpholine in 75 ml. of benzene was boiled under reflux for eight hours. The *hydrochloride* of the tertiary amine was isolated as described in the preceding examples, yield 20.4 g. (85%), m.p. 212–213° after recrystallization from

methanol-ether mixture. The *free base* crystallized from aqueous ethanol, m.p. 79°; *methiodide*, m.p. 163.5–164.5°.

After interaction of 2-chloroethyl 2-naphthyl ether and morpholine in boiling toluene solution, the same hydrochloride was isolated in 81% yield.

N,N-Dimethyl-2-(1-napthoxy)ethylamine. The base, b.p. 145–147° at 2 mm., was obtained in 84% yield by interaction of 2-bromoethyl 1-naphthyl ether and dimethylamine in a 1:1 ether-benzene solution at 120°. *Hydrochloride*, m.p. 218–218.5°; *methiodide*, m.p. 178.5–179.5°. Previously reported (4) b.p. 149° at 2 mm. for the base and m.p. 218° for the hydrochloride.

N,N-Dimethyl-2-(2-naphthoxy)ethylamine was obtained in 86% yield as the *base*, b.p. 153° at 2 mm., m.p. 23–24°, by interaction of 2-bromoethyl 2-naphthyl ether and dimethylamine at 120° in a 1:1 ether-benzene solution. *Hydrochloride*, m.p. 192–193°; *methiodide*, m.p. 235°. Clemo and Perkin (2) reported b.p. 200° at 17 mm. for the base and m.p. 185° for the hydrochloride.

N,N-Diethyl-2-(1-naphthoxy)ethylamine was prepared from diethylamine and 2-bromoethyl 1-naphthyl ether in boiling toluene. The *hydrochloride*, m.p. 162.5–163.5°, was isolated in 84% yield. *Base*, b.p. 175° at 9 mm.; *methiodide*, m.p. 126–127°. Recently, m.p. 159–160° for the hydrochloride and b.p. 157–160° at 2 mm. for the base were reported (5).

N,N-Diethyl-2-(2-naphthoxy)ethylamine was isolated in 82% yield as the *hydrochloride*, m.p. 136–138°, after interaction of 2-bromoethyl 2-naphthyl ether and diethylamine in benzene solution at 110°. *Base*, b.p. 195° at 12 mm.; *methiodide*, m.p. 109–111°. Einhorn and Rothlauf (1) reported b.p. 202° at 18 mm. for the base and m.p. 138–139° for the hydrochloride; b.p. 171° at 3 mm. and m.p. 138° for base and hydrochloride, respectively, have been reported more recently (5).

SUMMARY

1. Several alternative procedures for the preparation of 2-haloethyl naphthyl ethers have been studied.

2. A group of tertiary naphthoxyethylamines was prepared by interaction of the haloethyl naphthyl ethers and various secondary amines. The products were characterized as the free base, hydrochloride, and methiodide in each instance.

3. A brief statement of some of the pharmacological actions of the compounds is given.

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