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SYNTHESIS OF SOME
DIALKYLAMINOPROPYL BETA-NAPHTHYL
ETHERS

Thesis for the Degree of M. S.

MICHIGAN STATE COLLEGE

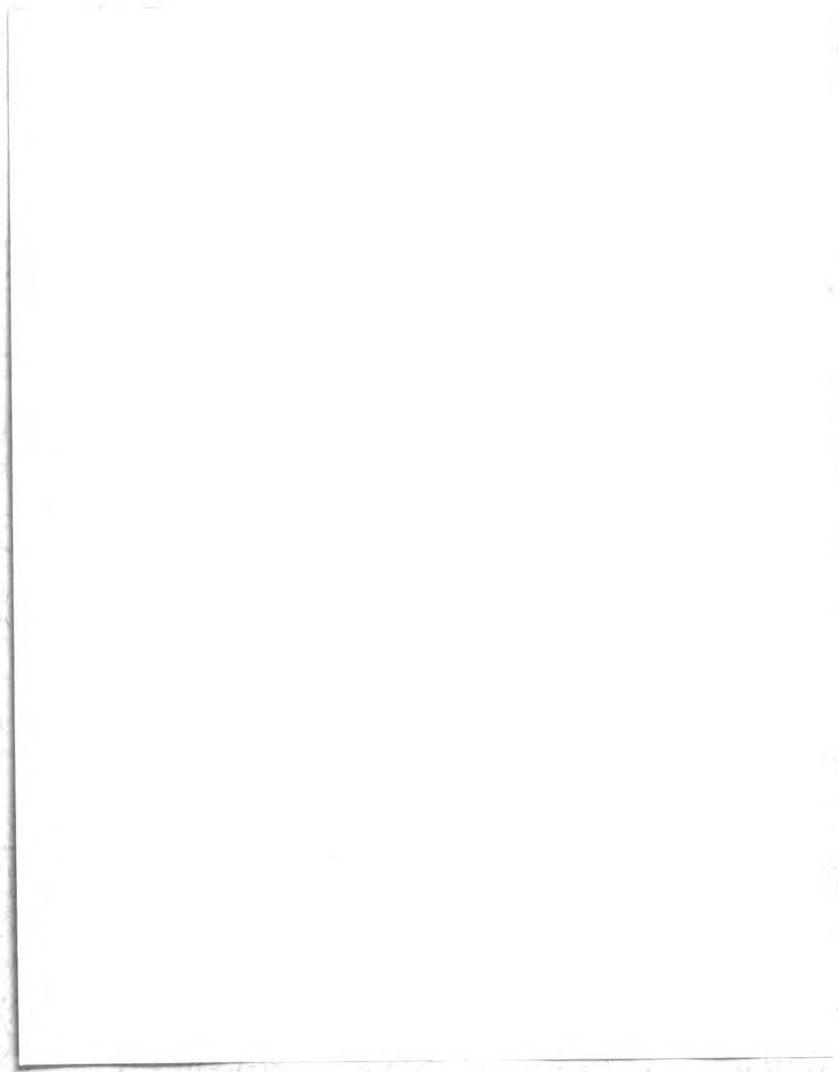
Mildred H. Evans

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**SYNTHESIS OF SOME DIALKYLAMINOPROPYL
BETA-NAPHTHYL ETHERS**

By

Mildred H. Evans

A THESIS

**Submitted to the School of Graduate Studies of Michigan
State College of Agriculture and Applied Science
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for the degree of**

MASTER OF SCIENCE

Department of Chemistry

1953

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INTRODUCTION

INTRODUCTION

Many biologically active compounds have been found to have the general structure (I) in which X represents a hetero atom (1).



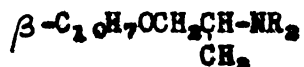
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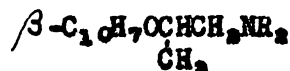
(II)

Herbst and Johnson (2) prepared several dialkylaminoethyl naphthyl ethers (II) which were found to possess marked local anesthetic action.

This thesis describes the preparation of two groups of isomeric dialkylaminopropyl β -naphthyl ethers (III,IV). Both groups of isomers possess the dialkylaminoethyl ether structure but differ in that a methyl group is attached to one or the other of the carbons of the ethyl residue.



(III)



(IV)

Tests have not yet been carried out to determine whether these compounds have local anesthetic or other pharmacological actions or to compare their activity, if any, with that of the compounds prepared by Herbst and Johnson.

HISTORICAL

HISTORICAL

As mentioned in the introduction, the object of this work was the preparation of dialkylaminopropyl β -naphthyl ethers having the formulae $C_{10}H_7OCH_2CH(CH_3)NR_2$ and $C_{10}H_7OCH(CH_3)CH_2NR_2$ in which the group $-NR_2$ was (a) morpholinyl, (b) piperidyl, (c) pyrrolidyl, (d) diethylamino, or (e) dimethylamino.

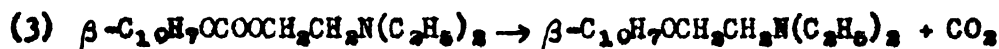
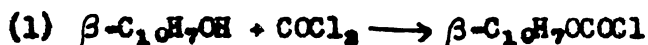
Knorr (3) has prepared dimethylaminoethyl phenyl ether by reaction of phenol and the hydrochloride of dimethylaminoethyl chloride in sodium ethylate. Application of this



procedure to the present problem would have required the preparation of ten different dialkylaminopropyl chlorides ($R_2N-CH(CH_3)CH_2Cl$ and $R_2N-CH_2CH(CH_3)Cl$). A procedure which would require fewer different intermediates would be preferable.

Wright and Moore (4) have prepared α -naphthyl alkamine ethers by refluxing diethylaminopropyl chloride with naphthol in alcoholic potassium hydroxide. This method is an application of Knorr's procedure and would likewise entail the preparation of many different aminopropyl chlorides as intermediates.

Einhorn and Rotlauf (5) prepared dimethylaminoethyl β -naphthyl ether by the thermal elimination of carbon dioxide from β -naphthyl diethylaminoethyl carbonate. The latter was prepared by interaction of β -naphthyl chlorocarbonate and diethylaminoethanol:

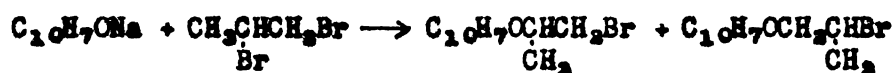


Here again a large group of different aminoalcohols ($\text{R}_2\text{NCH}(\text{CH}_3)\text{CH}_2\text{OH}$ and $\text{R}_2\text{NCH}_2\text{CH}(\text{CH}_3)\text{OH}$) would be required as intermediates if this method were applied to the problem described in this thesis.

Herbst and Johnson (2) prepared a number of α - and β -naphthyl ethers of the type $\text{C}_{10}\text{H}_7\text{OCH}_2\text{CH}_2\text{NR}_2$ in which the group -NR_2 was (a) morpholinyl, (b) piperidyl, (c) diethylamino, or (d) dimethylamino. Their procedure involved the formation of α - and β -naphthyl bromoethyl ethers by the interaction of ethylene dibromide and the naphthol in the presence of sodium hydroxide. Subsequent treatment of the bromoethyl ether with various secondary amines in benzene or toluene solution gave the desired dialkylaminoethyl ethers.

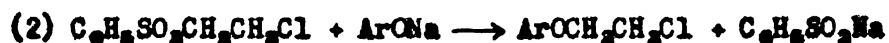
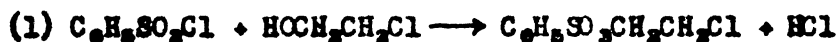


Application of an analogous procedure to the preparation of the isomeric bromopropyl naphthyl ethers was not practical. Although propylene dibromide is readily available, its reaction with β -naphthol would lead to a mixture of isomeric bromopropyl ethers whose separation would be difficult and time consuming at best.

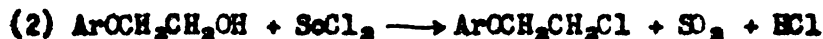
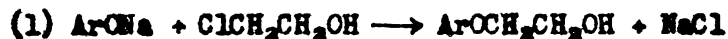


Two alternative procedures were available for the preparation of chloroalkylethers, each of which could be expected to give only one of the anticipated isomers.

Clemons and Perkin (6) had described the synthesis of chloroethyl p-toluenesulfonate from ethylene chlorohydrin and p-toluenesulfonyl chloride. They further showed that interaction of β -naphthol and the chloroethyl p-toluenesulfonate led to the formation of β -naphthyl chloroethyl ether. Földi (7,8) had shown that a similar sequence of reactions could be carried out starting with benzenesulfonyl chloride and ethylene chlorohydrin.



The second alternative, studied by Kirner and Richter (9), involved the treatment of a phenol in alkaline medium with ethylene chlorohydrin. The resulting hydroxyethyl ether on treatment with thionyl chloride was converted into the chloroethyl ether.



None of these methods have been applied to the synthesis of chloro- or bromo,propyl naphthyl ethers.

A number of techniques have been described for the preparation of aryl dialkylaminoalkyl ethers from the corresponding haloalkyl ethers.



Clemons and Perkin (5) and Knorr and Roth (10) both described methods for carrying out the reaction of the halide with a secondary amine in sealed tubes. This technique appeared to be particularly applicable to reactions involving dimethylamine and diethylamine. Cromwell and Fitzgibbon (11), Herbst and Simonian (12), and Herbst and Johnson (2)

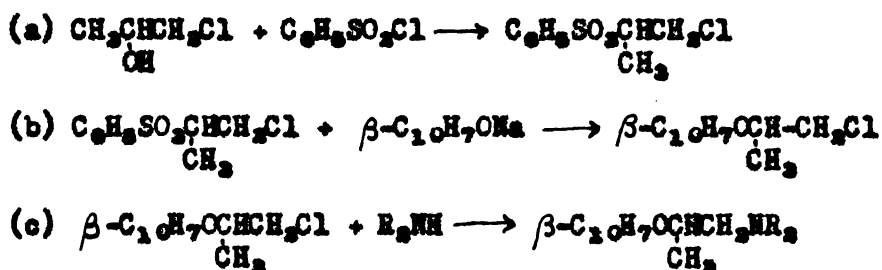
used methods in which the secondary amine and the halide were refluxed in a suitable solvent. This procedure was employed primarily with the less volatile secondary amines.

DISCUSSION

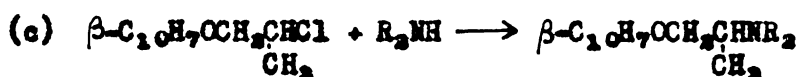
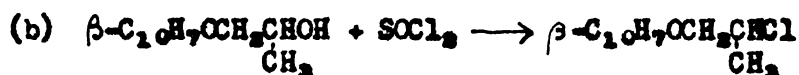
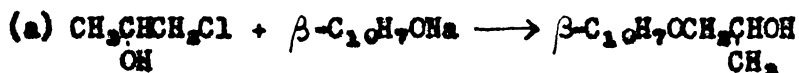
DISCUSSION

Both groups of isomeric dialkylaminopropyl β -naphthyl ethers can be prepared from β -naphthol and propylene chlorohydrin. The use of these readily available chemicals, however, necessitates two different sets of reactions to obtain the two different sets of isomeric products.

An adaptation of the Cleme and Perkin (6) technique should lead to a chloroisopropyl naphthyl ether in which the carbon atom carrying the hydroxyl group in the propylene chlorohydrin was involved in the ether linkage. This technique would require the preparation of a chloroisopropyl benzenesulfonate and its subsequent interaction with β -naphthol as outlined in Scheme I.

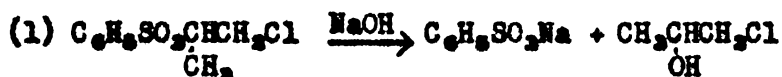
Scheme I

An isomeric chloropropyl naphthyl ether would result by application of the sequence of reactions described by Kirner and Richter (9). By interaction of propylene chlorohydrin and β -naphthol an ether linkage would be formed involving the carbon atom carrying the halogen in the chlorohydrin. The resulting hydroxyalkyl ether would be converted into the chloroalkyl ether on treatment with thionyl chloride as outlined in Scheme II.

Scheme II

A modification of the procedure used for the preparation of n-butyl p-toluenesulfonate (13) was applied to the synthesis of the chloroisopropyl benzenesulfonate (reaction I-a). Very slow addition of aqueous sodium hydroxide solution to the reactants and 100% excess of propylene chlorohydrin were found to be essential to obtain a maximum yield. As low a pressure as possible was needed to distill the chloroisopropyl benzenesulfonate without decomposition. Using greatest care, however, only approximately 40% yields were obtainable.

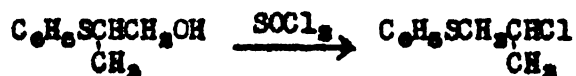
Numerous difficulties were encountered in the reaction of the chloroisopropyl benzenesulfonate with β -naphthol (reaction I-b). A solid, which was later found to be 1-(2-naphthoxy)-2-propanol ($\text{C}_{10}\text{H}_7\text{OCH}_2\text{CH}(\text{OH})\text{CH}_3$), gradually precipitated from the chloroisopropyl naphthyl ether ($\text{C}_{10}\text{H}_7\text{OCH}(\text{CH}_3)\text{CH}_2\text{Cl}$). This alcohol could arise in either of two ways. It could be the product of a side reaction of the β -naphthol with propylene chlorohydrin formed by hydrolysis of the chloroisopropyl benzenesulfonate in the alkaline reaction medium.



It could also be a product of hydrolysis and rearrangement (or vice versa) of the chloroether.



Fuson and Koehnke (14) had observed an analogous rearrangement when 1-hydroxy-(2-propyl) phenyl sulfide was treated with thionyl chloride. The product was 2-chloro-(1-propyl)phenyl sulfide. Whether such a rearrangement



of hydroxy ethers would occur has not been determined, nor has the hydrolysis of similar chloroalkyl sulfides or ethers been studied. However, it is not inconceivable that such rearrangement could take place during the hydrolysis of the chloroalkyl sulfides and ethers.

Hydrolysis of a sample of the chloroisopropyl β -naphthyl ether showed no concrete evidence of a rearrangement. Consequently, it would appear that the alcohol present in the product was formed by the first of the two possible routes.

Repeated distillation of this chloroether may have caused some dehydrohalogenation. A sample which was thought to be free of the alcohol gave low halogen and high carbon and hydrogen analyses. The same sample decolorized bromine in chloroform, indicating that it was unsaturated.

These various side reactions, of course, lower the yield of the desired product. This is shown from the fact that approximately 45% of somewhat contaminated chloroether was about the best yield obtainable.

Powell (15) made γ -hydroxy-n-propyl phenyl ether by dissolving phenol in dilute alkali, adding trimethylene chlorohydrin, and refluxing for one-half hour. A technique essentially the same as his was found to proceed very smoothly for the preparation of the hydroxypropyl β -naphthyl ether (reaction II-a). Yields of approximately 80% were obtained when 100% excess propylene chlorohydrin was used.

For the Darzens reaction (reaction II-b) the procedure of Herbst and Simonian (12) in which a chloroform solution of thionyl chloride is added to a chloroform solution of the alcohol in the absence of pyridine was found to produce the best results.

Gerrard (16) and Carré (17) have independently concluded that the mechanism of the Darzens reaction involves the formation of an intermediate sulfinyl chloride which decomposes thermally to produce the chloride and a molecule of sulfur dioxide.



The existence of the intermediate sulfinyl chloride is verified by the work described in this thesis. On attempting to decompose the excess thionyl chloride in the reaction mixture with methanol a white solid was obtained which melted at 54-55°C. after recrystallization from benzene and ligroin. Carbon, hydrogen, and sulfur analyses agreed reasonably well with the theoretical amounts of these elements present in the methyl ester of the sulfinic acid related to the intermediate sulfinyl chloride (VI).

involving very volatile amines such as diethyl- and dimethylamine were carried out in sealed tubes. In the case of the dimethylamine, which is a gas at room temperature, an aqueous-dioxane solution of the amine was used.

The hydrochlorides were prepared by passing hydrogen chloride through an isopropyl ether solution of the amine.

EXPERIMENTAL

EXPERIMENTAL

Reagents

Propylene chlorohydrin: Obtained from the Dow Chemical Company and Distillation Products Industries, division of Eastman Kodak Company.

Pyrrolidine: Obtained from Electrochemicals Department of E. I. duPont de Nemours and Company.

Hydrogen chloride: Prepared by adding concentrated hydrochloric acid to concentrated sulfuric acid through a capillary tube.

The following reagents were obtained from Distillation Products Industries, division of Eastman Kodak Company:

Benzenesulfonyl chloride

β -Naphthol

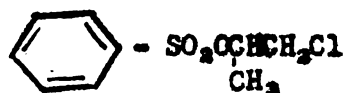
Thionyl chloride

Dimethylamine as a 33% aqueous solution

Morpholine

Pyridine

Diethylamine

Preparation of 1-chloro-2-benzenesulfonyloxypropane

Into a three necked flask fitted with stirrer, thermometer, and separatory funnel was placed 95 g. (86 ml., 1 mole) of propylene

chlorohydrin and 44 g. (32 ml., 0.25 mole) of benzenesulfonyl chloride. While cooling in an ice-water bath 80 ml. of 5 N sodium hydroxide were added dropwise with stirring at such a rate as to maintain the temperature at 10-15°C.

When the sodium hydroxide solution had all been added a second portion of 32 ml. (0.25 mole) of benzenesulfonyl chloride was added to the reaction mixture and another 80 ml. portion of 5 N sodium hydroxide was added dropwise with stirring as before. The total addition time required for both portions of sodium hydroxide was 15-20 hours. Stirring was continued for several hours after the addition was complete.

At the end of the reaction the layers were separated and benzene was added to the organic layer until it would float on water. This benzene solution was washed with 10% sodium hydroxide solution and with water. After drying over potassium carbonate the solvent was removed and the product was distilled under reduced pressure. A total of 47 g. (40%) of material boiling at 149-155° C. (uncorr.) under 3.5 mm. pressure and having a refractive index of 1.5210 at 18°C. was obtained.

Analysis.* Calc'd. for $C_9H_{11}ClO_2S$: Cl, 15.1; S, 13.6.

Found: Cl, 15.2, 15.4; S, 13.5, 13.5.

A series of experiments was done to determine the optimum proportions of propylene chlorohydrin and benzenesulfonyl chloride. The reactions were all carried out as described above. The results are summarized in Table I.

*Analyses except for the nitrogen and chlorine analyses of the tertiary amine hydrochlorides were done by Micro-Tech Laboratories at Skokie, Illinois.

TABLE I

THE DETERMINATION OF THE EXCESS CHLOROHYDRIN NECESSARY FOR THE
PREPARATION OF 1-CHLORO-2-BENZENESULFONOPROPANE

Percentage Excess Chlorohydrin	Propylene Chlorohydrin Grams	Propylene Chlorohydrin Moles	Benzenesulfonyl Chloride Grams	Benzenesulfonyl Chloride Moles	Yield Grams	Yield Per Cent
50	71	0.75	88	0.5	36	32
100	95	1.0	88	0.5	47	40
200	142	1.5	88	0.5	49	42
250	165	1.75	88	0.5	50	43
300	189	2.0	88	0.5	49	42

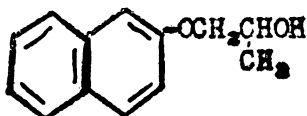
Preparation of 1-chloro-2-(2-naphthoxy)propane



To 42 g. (0.3 mole) of β -naphthol in a three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel was added a solution of 50 g. of sodium hydroxide in 100 ml. water. This mixture was heated on a steam bath and stirred until the naphthol dissolved. With continued heating and stirring 59 g. (0.25 mole) of 1-chloro-2-benzene-sulfonoxypropane was added dropwise from the dropping funnel. Heating and stirring were continued for one hour after the addition was complete. The reaction mixture was poured into ice water and stirred until the ice dissolved. A yellowish oil separated. The oil was taken up in benzene. After drying the benzene solution over potassium carbonate the solvent was removed by distillation. Upon vacuum distillation of the produce two fractions were obtained. The first boiled at 158-66°C. (uncorr.) under 6-8 mm. pressure and had a refractive index of 1.5966 at 19°C. The second boiled at 166-170°C. (uncorr.) under 6 mm. pressure and had a refractive index of 1.5953 at 19°C. The combined yield was 25 g. (45%).

It was found to be impossible to obtain a sample which was completely free of contaminants and which would give satisfactory analytical results. However, since the tertiary amine derivatives gave satisfactory analyses it is probable that this compound was correctly formulated.

Preparation of 1-(2-naphthoxy)-2-propanol



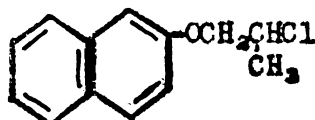
To a solution of 72 g. (0.5 mole) of β -naphthol in 500 ml. 10% aqueous sodium hydroxide was added 95 g. (86 ml., 1 mole) of propylene chlorohydrin. This solution was heated to boiling under a reflux condenser. In a few minutes an oil began to separate from the solution. Refluxing was continued for about 45 minutes. At the end of this time the reaction mixture was allowed to cool, whereupon the oil solidified. Stirring while cooling in an ice bath was found to be helpful to keep the oil from solidifying as a hard coating on the sides of the flask. The white solid was filtered, washed twice with water, and then dissolved in benzene. After the small amount of residual water in the solid was separated from the benzene solution, ligroin was added until the solution was just cloudy. The solution was then allowed to stand until crystallization was complete. A yield of 82 g. (81%) of product melting at 83-84°C. was obtained.

No analysis was carried out on this compound since an entirely independent synthesis by catalytic reduction of β -naphthoxyacetone was reported by Hurd and Perletz (18). They observed a melting point of 82-83°C.

Since it was anticipated that part of the propylene chlorohydrin might be hydrolyzed in the alkaline reaction medium, experiments were done with different proportions of β -naphthol and propylene chlorohydrin

to determine the optimum conditions. The results are summarized in Table II.

Preparation of 2-chloro-1-(2-naphthoxy)propane



Into a three necked flask fitted with stirrer, reflux condenser, and dropping funnel were placed 51 g. (0.25 mole) of 1-(2-naphthoxy)-2-propanol and 100 ml. chloroform. The mixture was stirred until the alcohol was completely or nearly completely dissolved. While stirring 43 g. (26 ml., 0.4 mole) of thionyl chloride dissolved in 50 ml. chloroform was added dropwise at room temperature over a period of about two hours. Stirring was continued overnight. The solvent and excess thionyl chloride were removed by distillation while applying suction from the aspirator, after which heating was continued for four hours at 125-145°C. to liberate the sulfur dioxide from the intermediate sulfinyl chloride. The product was then vacuum distilled to yield 36 g. (66%) of chloroether which boiled at 138-149.5°C. (uncorr.) under 3 mm. pressure and had a refractive index of 1.6059 at 20.5°C. This slightly yellow oil slowly solidified on standing. After two recrystallizations from ethanol a white solid melting at 39-40°C. was obtained.

Analysis. Calc'd. for $C_{13}H_{13}ClO$: C, 70.8; H, 5.9; Cl, 16.1.

Found: C, 71.1, 70.9; H, 6.0, 6.1; Cl, 16.2, 16.1.

TABLE II
THE DETERMINATION OF THE EXCESS CHLOROCHYDRIN NECESSARY FOR THE PREPARATION OF
1-(2-NAPHTHOXY)-2-PROPANOL

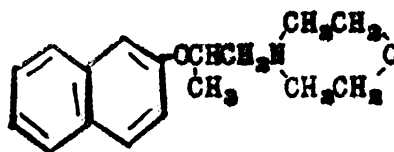
Percentage Excess Chlorochydrin	Propylene Chlorochydrin Grams	Moles	β -Naphthol Grams	Moles	Yield Grams	Per Cent
0	48	0.5	72	0.5	41	41
50	71	0.75	72	0.5	65	65
100	95	1.0	72	0.5	82	81
200	142	1.5	72	0.5	78	78

In several experiments an attempt was made to destroy the excess thienyl chloride in the reaction mixture by addition of methanol. A crude product with a wide melting point range was obtained. On fractional crystallization from benzene and ligroin some 2-chloro-1-(2-naphthoxy)propane and some white solid melting at 54-55°C. were obtained. The carbon, hydrogen, and chlorine analyses for the compound melting at 54-55°C. corresponded reasonably with the theoretical amounts of these elements present in the methyl ester of the sulfinic acid related to the intermediate sulfinyl chloride.

Analysis. Calc'd. for $C_{14}H_{16}O_4S$: C, 60.0; H, 5.7; S, 11.4.

Found: C, 60.5; H, 5.9; S, 11.2.

Preparation of 1-morpholinyl-2-(2-naphthoxy)propane



A mixture of 0.1 mole (22 g.) of 1-chloro-2-(2-naphthoxy)propane and 0.3 mole (26 g., 26 ml.) of morpholine was refluxed for 24 hours. The reaction mixture was transferred to a larger flask and diluted with isopropyl ether. Gaseous hydrogen chloride was bubbled into the solution to precipitate the hydrochlorides of the secondary and tertiary amines. The supernatant liquid was decanted and the isopropyl ether was removed by distillation, leaving a residue of 5 g. of unreacted chloroether. The maximum yield of product, therefore, would be 77%.

The hydrochlorides were dissolved in water. The water solution was made basic with sodium carbonate to liberate the amines, which were extracted with three portions of benzene. After drying over "drierite" the benzene was removed by distillation and the residue was vacuum distilled to give 16 g. (60%) of product boiling at 184-192°C. (uncorr.) under 3 mm. pressure and having a refractive index of 1.5878 at 20.5°C.

The distilled amine was dissolved in dry isopropyl ether. Anhydrous hydrogen chloride was bubbled into the solution to precipitate the hydrochloride, which was recrystallized from acetone, isopropyl alcohol, and isopropyl ether. Crystals melting at 160.5-161.5°C., 139-141°C., and 131-132.5°C. were isolated.

Analysis. Calc'd. for $C_{17}H_{22}ClNO_2$: Cl, 11.9; N, 4.6.

Crystals melting at 160.5-161.5°C.:

Found: Cl, * 12.0; N, ** 4.9.

Crystals melting at 139-141°C.:

Found: Cl, 11.9.

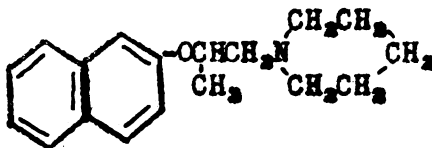
Crystals melting at 131-132.5°C.:

Found: Cl, 11.9.

* Chlorine analyses for this and for subsequent compounds were done by the Fajans method in a 75% ethanol solution using dichlorofluorescein as indicator (19).

** Nitrogen analyses for this and for subsequent compounds were done by the Kjeldahl-Gunning Method with the exception of piperidyl derivatives, for which the Kjeldahl-Gunning-Arnold Method was used (20).

Preparation of 2-(2-naphthoxy)-1-piperidylpropane



A mixture of 0.1 mole (22 g.) of 1-chloro-2-(2-naphthoxy)propane and 0.3 mole (25.5 g., 30 ml.) of piperidine was refluxed for 2½ hours. The reaction mixture was transferred to a larger flask, diluted with isopropyl ether, and the hydrochlorides of the amines were precipitated with gaseous hydrogen chloride. The isopropyl ether solution was decanted and evaporated to give a residue of 5.7 g. of unreacted chloro-ether. The maximum extent of reaction was therefore 74%.

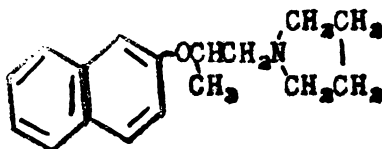
The hydrochlorides were dissolved in water and sodium carbonate was added to liberate the free amines. The amines were extracted with three portions of benzene. After drying over "drierite" the solvent and excess piperidine were removed by distillation. The product was distilled under vacuum. A yield of 16.4 g. (61%) of amine boiling at 140-148°C. (uncorr.) under 3.5 mm. pressure and having a refractive index of 1.5800 at 19.5°C. was obtained.

The amine was dissolved in dry isopropyl ether and the hydrochloride was precipitated with anhydrous hydrogen chloride. The hydrochloride was recrystallized from acetone, isopropyl alcohol, and isopropyl ether. The yield of hydrochloride was 90%. The melting point was 182-183°C.

Analysis. Calc'd. for $C_{18}H_{24}ClNO$: Cl, 11.9; N, 4.6.

Found: Cl, 11.9; N, 4.5.

Preparation of 2-(2-naphthoxy)-1-pyrrolidylpropane



A mixture of 0.1 mole (22 g.) of 1-chloro-2-(2-naphthoxy)propane and 0.3 mole (21 g., 25 ml.) of pyrrolidine was refluxed for 24 hours. The reaction mixture was diluted with isopropyl ether and hydrogen chloride gas was bubbled through the solution to precipitate the hydrochlorides of the amines. The isopropyl ether solution was decanted from the sticky precipitate and evaporated to leave 3.5 g. of unreacted chloroether, indicating a maximum reaction to the extent of 84%.

The hydrochlorides were dissolved in water and sodium carbonate was added to liberate the free amines. The amines were extracted with three portions of benzene. The benzene solution was dried over "drierite." The drying agent was filtered off, the solvent and excess pyrrolidine were removed by distillation, and the product was distilled under vacuum. A total of 18.5 g. (73%) of product boiling at 154-164°C. (uncorr.) under 2.5 mm. pressure and having a refractive index of 1.5900 at 19°C. was obtained.

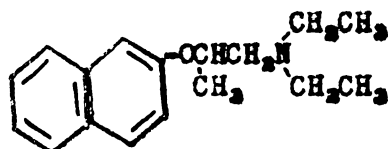
The amine was dissolved in anhydrous isopropyl ether and the hydrochloride was precipitated with gaseous hydrogen chloride. The hydrochloride was recrystallized by dissolving it in acetone and isopropyl alcohol and adding isopropyl ether until the solution was slightly cloudy. A 98% yield of hydrochloride, which melted at 153.5-157.5°C., was obtained. This product was apparently a mixture of crystal forms,

since on further recrystallization it yielded crystals melting at 139-140°C., 163-165°C., and 178.5-179°C. The analyses were carried out on the product melting at 153.5-157.5°C.

Analysis. Calc'd. for $C_{17}H_{22}ClNO$: Cl, 12.5; N, 4.8.

Found: Cl, 12.3; N, 5.0.

Preparation of 1-diethylamino-2-(2-naphthoxy)propane



A mixture of 0.1 mole (22 g.) of 1-chloro-2-(2-naphthoxy)propane and 0.3 mole (22 g., 31 ml.) of diethylamine was heated in a sealed tube at 100-105°C. for 48 hours. The contents of the tube were washed out with isopropyl ether and the hydrochlorides were precipitated with gaseous hydrogen chloride. After dissolving the hydrochlorides in water, the layers were separated. The aqueous layer was washed once with isopropyl ether. The combined isopropyl ether layers were dried over "drierite." Removal of the solvent and distillation gave 11.5 g. of unreacted chloroether, indicating a maximum reaction to the extent of 48%.

The water solution was made basic with sodium carbonate to liberate the amines, which were extracted with four portions of benzene. After the benzene solution was dried over "drierite," the solvent and excess diethylamine were removed, and the product was vacuum distilled. A total of 9.7 g. (38%) of material boiling at 150-155°C. (uncorr.) at 3.5 mm. pressure and having a refractive index of 1.5635 at 19.5°C. was obtained.

The hydrochloride was produced by passing dry hydrogen chloride gas through an isopropyl ether solution of the amine. Two recrystallizations from acetone, isopropyl alcohol, and isopropyl ether gave a hydrochloride which melted at 129.5-131°C.

Analysis. Calc'd. for $C_{17}H_{24}ClNO$: Cl, 12.4; N, 4.8.

Found: Cl, 12.4; N, 5.1, 4.9.

Preparation of 1-dimethylamino-2-(2-naphthoxy)propane



A mixture of 0.05 mole (11 g.) of 1-chloro-2-(2-naphthoxy)propane and 0.2 mole (33 ml.) of 33% aqueous solution of dimethylamine and 20 ml. dioxane was heated in a sealed tube at 100-105°C. for 48 hours. After the contents of the tube were washed out with isopropyl ether, the hydrochlorides were formed with gaseous hydrogen chloride, whereupon they dissolved in the aqueous layer. More water was added to dissolve the hydrochlorides completely. The layers were separated. The aqueous layer was washed once with isopropyl ether. The combined isopropyl ether layers were dried over "drierite," then evaporated to leave 2.7 g. of unreacted chloroether, indicating a maximum reaction to the extent of 75%.

The amines were liberated by making the aqueous solution of the hydrochlorides basic with sodium carbonate. The product was extracted with four portions of benzene. After drying over "drierite" the solvent was removed and the product was distilled under reduced pressure to give

6.5 g. (57%) of amine boiling at 149-152°C. (uncorr.) at 3.5 mm. and having a refractive index of 1.5752 at 19°C.

The hydrochloride was prepared by dissolving the amine in dry isopropyl ether and passing in anhydrous hydrogen chloride. After recrystallisation from acetone and ethyl acetate a 92% yield of hydrochloride was obtained. Crystals melting at 118-120°C. and 160-161°C. were isolated. Recrystallisation of the product melting at 118-120°C. from the same solvents yielded crystals melting at 135.5-136.5°C. Apparently the compound can exist in three different crystal forms.

Analysis. Calc'd. for $C_{18}H_{20}ClNO$: Cl, 13.8; N, 5.3.

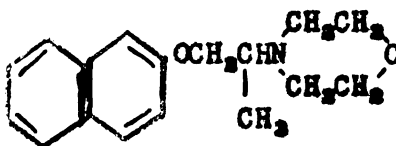
Crystals melting at 160-161°C.:

Found: Cl, 13.6; N, 5.5, 5.3.

Crystals melting at 135.5-136.5°C.:

Found: N, 5.3.

Preparation of 2-morpholinyl-1-(2-naphthoxy)propane



A mixture of 0.1 mole (22 g.) of 2-chlore-1-(2-naphthoxy)propane and 0.3 mole (26 g., 26 ml.) of morpholine was refluxed for 24 hours. The reaction mixture was then transferred to a larger flask and diluted with isopropyl ether. Hydrogen chloride gas was bubbled into this solution to precipitate the hydrochlorides. The hydrochlorides were dissolved in water to facilitate their separation from the isopropyl

ether solution of the starting material. After separation of the layers the aqueous layer was washed once with isopropyl ether. This washing was added to the isopropyl ether layer, which was then dried over "drierite." After removal of the solvent 2.3 g. of unreacted chloroether were recovered. The maximum percentage reaction was therefore 90.

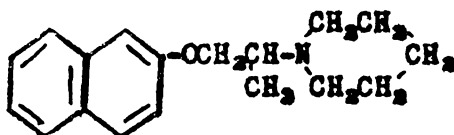
The water layer was made basic with sodium carbonate to liberate the amines, which were separated by three extractions with benzene. After drying over "drierite" the benzene and excess morpholine were removed by distillation and the product was vacuum distilled. A pale yellow oil boiling at 182-185°C. (uncorr.) under 3 mm. pressure and having a refractive index of 1.5877 at 19°C. was obtained. The yield was 21.5 g. (79%).

The amine was dissolved in dry isopropyl ether and the hydrochloride was precipitated with anhydrous hydrogen chloride. The hydrochloride thus obtained was dissolved in acetone and isopropyl alcohol. Isopropyl ether was added to produce a slightly turbid solution from which the hydrochloride crystallized on standing. An 86% yield of hydrochloride, which melted at 163.5-164°C. after a second recrystallization, was obtained.

Analysis. Calc'd. for $C_{17}H_{22}ClNO$: Cl, 11.9; N, 4.6.

Found: Cl, 12.0; N, 4.7.

Preparation of 1-(2-naphthoxy)-2-piperidylpropane



A mixture of 0.1 mole (22 g.) of 2-chloro-1-(2-naphthoxy)propane and 0.3 mole (26 g., 30 ml.) of piperidine was refluxed for 24 hours. The reaction mixture was diluted with isopropyl ether and hydrogen chloride gas was bubbled through the solution to precipitate the hydrochlorides of the amines. The hydrochlorides were dissolved in water and the layers were separated. The aqueous layer was washed once with isopropyl ether. The isopropyl ether layers were combined and dried over "drierite." The solvent was removed from the dried ether solution and 10.5 g. of unreacted chloroether was recovered, indicating that 52% had reacted.

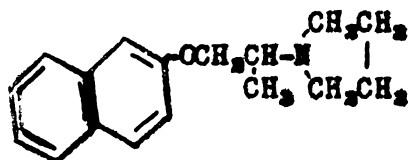
The aqueous layer was made basic with sodium carbonate to liberate the amines, which were then extracted three times with benzene and dried over "drierite." The benzene and excess piperidine were removed from the product by distillation. The tertiary amine was distilled under 3 mm. pressure to give 11 g. (40%) of product boiling at 170-173°C. (uncorr.). The refractive index was 1.5838 at 19.5°C.

To prepare the hydrochloride the amine was dissolved in dry isopropyl ether and dry hydrogen chloride gas was passed through the solution. The hydrochloride was recrystallized from acetone, isopropyl alcohol, and isopropyl ether. A 97% yield of the hydrochloride was obtained. Two crystal forms, melting at 164-165.5°C. and 190-190.5°C. were isolated. The form melting at 164-65.5°C. could be made to resolidify into needles which melted at 190-190.5°C. The analyses were performed on the crystal form melting at 190-190.5°C.

Analysis. Calc'd. for $C_{18}H_{24}ClNO$: Cl, 11.9; N, 4.6.

Found: Cl, 11.8; N, 4.6.

Preparation of 1-(2-naphthoxy)-2-pyrrolidylpropane



A mixture of 0.1 mole (22 g.) of 2-chloro-1-(2-naphthoxy)propane and 0.3 mole (21 g., 25 ml.) of pyrrolidine was refluxed for 24 hours. The reaction mixture was diluted with isopropyl ether and the hydrochlorides of the amines were precipitated with gaseous hydrogen chloride. The hydrochlorides were dissolved in water and the ether layer was separated. The aqueous layer was washed once with isopropyl ether. The combined ether layers were dried over "drierite" and then evaporated to give 3.7 g. of unreacted chloroether, thus indicating 83% reaction.

The aqueous solution of the hydrochlorides was made basic with sodium carbonate to liberate the amines, which were extracted with three portions of benzene. After drying over "drierite" the benzene and excess pyrrolidine were removed by distillation and the tertiary amine was distilled under 3 mm. pressure to give 21 g. (83%) of product which boiled at 167-173°C. (uncorr.) and had a refractive index of 1.5842 at 20°C.

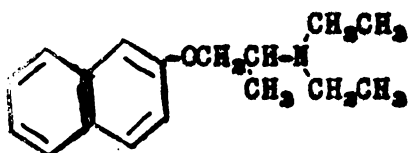
In order to prepare the hydrochloride the amine was dissolved in dry isopropyl ether and anhydrous hydrogen chloride was bubbled through the solution. The hydrochloride was recrystallized from acetone, isopropyl alcohol, and isopropyl ether. An 88% yield of hydrochloride melting at 169-170.5°C. was obtained. On recrystallization of this

product for a second time from the same solvents a melting point of 155-155.5°C. was observed; apparently the product may crystallise in two forms. The analyses were carried out on the crystals melting at 155-155.5°C.

Analysis. Calc'd. for $C_{17}H_{22}ClNO$: Cl, 12.5; N, 4.8.

Found: Cl, 12.2, 12.3; N, 4.9, 4.7.

Preparation of 2-diethylamino-1-(2-naphthoxy)propane



In each of two sealed tubes was placed 0.1 mole (22 g.) of 2-chloro-1-(2-naphthoxy)propane and 0.3 mole (22 g., 31 ml.) of diethylamine. These were then heated at 100-105°C. for 72 hours. The contents of the tubes were washed out with isopropyl ether and combined. Gaseous hydrogen chloride was bubbled through the solution to precipitate the hydrochlorides, which were then dissolved in water. The layers were separated, the aqueous layer was washed with isopropyl ether, and the combined ether layers were dried over "drierite." After the solvent was removed from the dried isopropyl ether solution the residue of unreacted chloroether was distilled. A total of 34 g. of chloroether was recovered, indicating a maximum reaction of 22%.

The aqueous layer was made basic with sodium carbonate to liberate the amines, which were extracted with four portions of benzene. The benzene solution was dried over "drierite," after which the drying agent was filtered off, the solvent and excess diethylamine were removed, and

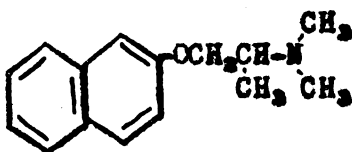
the product was distilled. At a pressure of 3-3.5 mm. the amine boiled at 153-161°C. (uncorr.) and weighed 6 g. (12%). The refractive index was 1.5712 at 20°C.

The amine was dissolved in dry isopropyl ether to precipitate the hydrochloride by the addition of dry hydrogen chloride gas. The oily hydrochloride would not crystallise from any of the solvents or solvent mixtures tried, but always came out as an oil. Attempts to obtain a crystalline sulfamate, benzyl chloride, or ethiodide also failed. Consequently, the amine was regenerated and redistilled. A nitrogen analysis was carried out on this redistilled amine.

Analysis. Calc'd. for $C_{17}H_{23}NO$: N, 5.4.

Found: N, 5.1.

Preparation of 2-dimethylamino-1-(2-naphthoxy)propane



A mixture of 0.05 moles (11 g.) of 2-chloro-1-(2-naphthoxy)propane, 0.2 mole (33 ml.) of 33% aqueous solution of dimethylamine, and 20 ml. dioxane was heated in a sealed tube at 100-105°C. for 48 hours. After the tube was opened, the contents were washed out with isopropyl ether. The hydrochlorides were formed with gaseous hydrogen chloride, whereupon they dissolved in the aqueous layer. More water was added to dissolve the hydrochlorides completely. The layers were separated and the water layer was washed with isopropyl ether. The isopropyl ether

layers were dried over "drierite" and evaporated to give 1.3 g. of unreacted chloroether, indicating 88% reaction.

The aqueous layer was made basic with sodium carbonate to liberate the amines, which were extracted with four portions of benzene. The benzene solution was dried over "drierite." After removal of the benzene by distillation the product was distilled under vacuum to give 9 g. (78%) of product boiling at 180-182°C. (uncorr.) under 4 mm. pressure.

The hydrochloride was prepared by passing anhydrous hydrogen chloride into an isopropyl ether solution of the amine and recrystallizing from acetone, isopropyl alcohol, and isopropyl ether. A 95% yield of hydrochloride was obtained. The white crystals melted sharply at 139-140°C. after a second recrystallisation.

Analysis. Calc'd. for $C_{10}H_{20}ClNO$: Cl, 13.8; N, 5.3.

Found: Cl, 13.7; N, 5.4.

SUMMARY

SUMMARY

1. 1-Chloro-2-(2-naphthoxy)propane was prepared by interaction of 1-chloro-2-benzenesulfonoxypropane and β -naphthol in an aqueous alkaline medium. The 1-chloro-2-benzenesulfonoxypropane was prepared by treating propylene chlorohydrin with benzenesulfonyl chloride in the presence of sodium hydroxide.

2. 2-Chloro-1-(2-naphthoxy)propane was synthesized from 2-hydroxy-1-(2-naphthoxy)propane by treatment with thionyl chloride. The 2-hydroxy-1-(2-naphthoxy)propane was prepared by interaction of propylene chlorohydrin and β -naphthol in an alkaline medium.

3. Tertiary amino derivatives of 1-chloro-2-(2-naphthoxy)propane and 2-chloro-1-(2-naphthoxy)propane were prepared by heating the chloroalkyl ethers with morpholine, piperidine, pyrrolidine, diethylamine, and dimethylamine. All of the tertiary amines appeared as high boiling liquids.

4. The hydrochlorides of the tertiary amines were prepared. Several of the hydrochlorides appeared to exist in more than one crystal form.

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