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I. Oxidation of 2,3-Dihydropyran with Potassium Permanganate II. Syntheses of 2-(N-Alkylamino) Tetrahydropyrans

Chien-wei Liao

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I. OXIDATION OF 2,3-DIHYDROPYRAN WITH POTASSIUM PERMANGANATE

II. SYNTHESES OF 2-(N-ALKYLAMINO)TETRAHYDROPYRANS

A Thesis
Submitted to the Graduate Division
of the
University of North Dakota

by
Chien-wei Liao
(B. S., University of Shanghai, 1944)

In Partial Fulfillment of the Requirements
for the
Degree of
Master of Science
in
Chemistry

Grand Forks, North Dakota

May, 1949

This thesis, presented by Chien-wei Liao, in partial fulfillment of the requirements for the degree of Master of Science in Chemistry, is hereby approved by the Committee on Instruction in charge of his work.

COMMITTEE ON INSTRUCTION

Herbert E. Freier
Chairman

E D Coon

Grant W. Smith

Director of the Graduate Division

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Dr. H. E. Freier for his suggestion of the problem and his interest and guidance during the course of these investigations.

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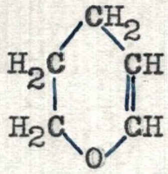
PART ONE

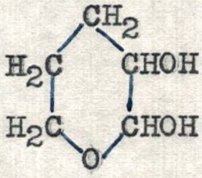
OXIDATION OF 2,3-DIHYDROPYRAN
WITH POTASSIUM PERMANGANATE

I. INTRODUCTION

2,3-Dihydropyran (I), an unsaturated cyclic ether, is a very reactive compound. The present investigation was undertaken to oxidize I with aqueous potassium permanganate solution. It was expected that 2,3-dihydroxytetrahydropyran (II) would be the main product formed by the hydroxylation of I with a theoretical amount of potassium permanganate under controlled conditions. However, it is possible that the dihydroxy compound II may undergo oxidation to yield degrad~~at~~ed products.



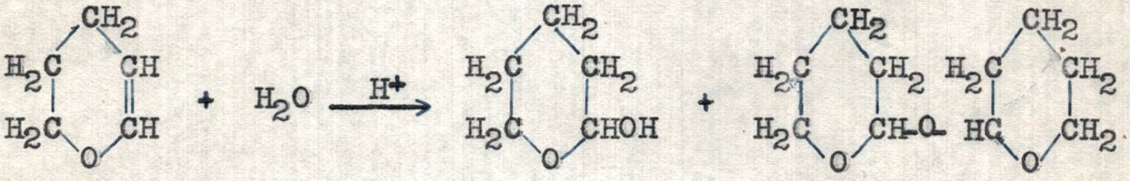
I



II

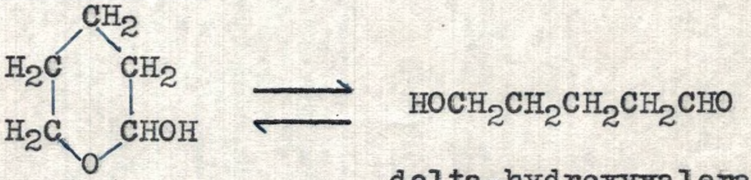
II. HISTORICAL

As can be seen, the presence of a double bond in the dihydropyran molecule makes it very reactive. Many reactions of the addition type verified this prediction. When hydrolyzed with dilute mineral acid solutions, dihydropyran adds a mole of water at the double bond to form 2-hydroxytetrahydropyran and a bicyclic acetal, di-alpha-tetrahydropyryl ether, as a by-product (1). The cyclic hemiacetal exists in equilibrium with the open chain hydroxy aldehyde.



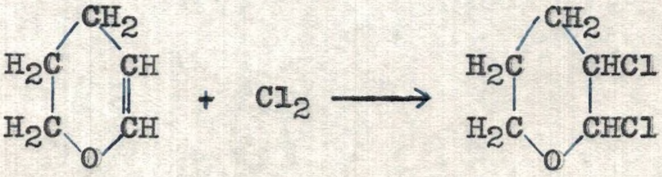
2-hydroxy-
tetrahydropyran

di-alpha-tetra-
hydropyryl ether



delta-hydroxyvaleraldehyde

Dihydropyran is readily halogenated with chlorine to form 2,3-dichlorotetrahydropyran (2), or with bromine to form the corresponding bromo derivative.



2,3-dichloro-
tetrahydropyran

Recently Hurd and Kelso (3) reported the preparation of 2,3-dihydroxytetrahydropyran by the oxidation of 2,3-dihydropyran with hydrogen peroxide in tert-butyl alcohol, using osmium tetroxide as catalyst.

III. THEORETICAL AND DISCUSSION OF RESULTS

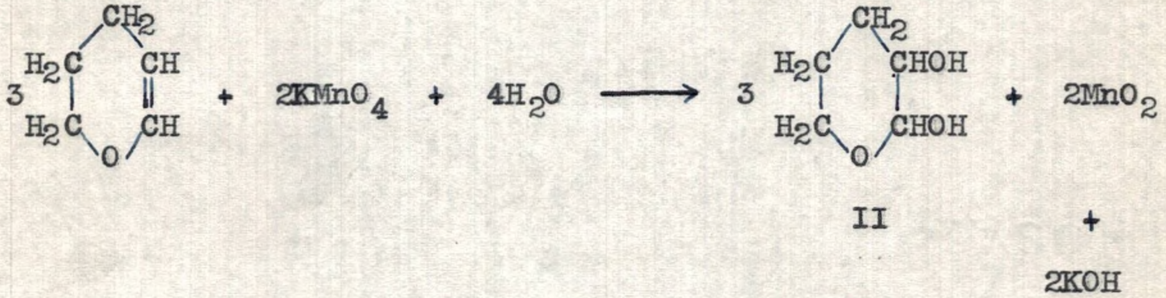
Hydroxylation of a double bond with oxidizing agents such as potassium permanganate and hydrogen peroxide is well known. Under controlled conditions, a glycol is usually the oxidation product. It can be represented by the following general equation:

$$RCH{=}CHR + (O) + H_2O \longrightarrow \underset{\text{a glycol}}{RCHOHCHOHR}$$

Milas and Sussman (4) reported the syntheses of isobutylene glycol from isobutylene, trimethylethylene glycol from trimethylethene, glycerol from allyl alcohol etc., by using hydrogen peroxide in anhydrous tert-butyl alcoholic solutions, with a small amount of osmium tetroxide as catalyst. Because of the stability of this oxidizing agent at room temperature, it is preferred over other oxidizing agents. The same authors later synthesized ethylene glycol from ethylene, propylene glycol from propylene and cetene glycol from cetene (5). They also prepared the dihydroxy compounds from the corresponding unsaturated ones with functional groups attached, e. g. ethyl dihydroxybutyrate from ethyl crotonate (6). According to Böeseken, alpha-glycols were obtained by the oxidation of unsaturated compounds, using potassium permanganate in neutral or slightly alkaline solution, or by using peracids in acid solution (7).

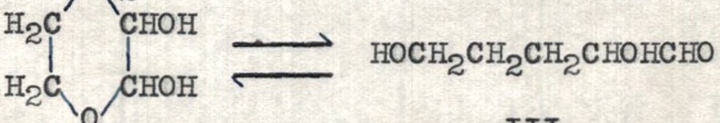
Since 2,3-dihydroxytetrahydropyran could be prepared by the oxidation of 2,3-dihydropyran with hydrogen peroxide, it seemed of interest to try and prepare this same compound by the oxidation of 2,3-dihydropyran with potassium permanganate.

Stoichiometric amounts of dihydropyran and potassium permanganate in neutral aqueous solution were used in the oxidation under various conditions. When the oxidation was performed at 0°C, the expected reaction can be represented by the following equation:



II

Attempts to isolate the dihydroxy compound II were unsuccessful. As was shown previously, 2-hydroxytetrahydropyran can exist in equilibrium with the open chain delta-hydroxyvaleraldehyde. Analogously, it can be reasoned that 2,3-dihydroxytetrahydropyran, which may be formed as an intermediate, may also be in equilibrium with the open chain compound, alpha,delta-dihydroxyvaleraldehyde (III).



III

II

Since the oxidation product was very soluble in water and insoluble in organic solvents, it was impossible to separate the product completely from the aqueous solution. The 2,4-dinitrophenylhydrazone of the crude product was prepared and analyzed. The analysis of the 2,4-dinitro derivative checked well with the postulated formula III. Further evidence to substantiate the postulate that III was the intermediate was obtained by the oxidation of 2,3-dihydropyran with potassium permanganate at room temperature. Under these conditions, if compound III is the intermediate it should be oxidized to alpha-ketoglutaric acid, which on decarboxylation would yield beta-carboxypropionaldehyde. This aldehyde then would be oxidized to succinic acid.

$$HOCH_2CH_2CH_2CHOHCHO \xrightarrow{3(O)} (CHO)CH_2CH_2(CO)COOH + 2H_2O$$

$$(CHO)CH_2CH_2(CO)COOH \xrightarrow{(O)} HOOCCH_2CH_2(CO)COOH$$

alpha-ketoglutaric acid

$$HOOCCH_2CH_2(CO)COOH \longrightarrow HOOCCH_2CH_2CHO + CO_2$$

beta-carboxy-
propionaldehyde

$$HOOCCH_2CH_2CHO \xrightarrow{(O)} HOOCCH_2CH_2COOH$$

succinic acid

The formation of succinic acid by the oxidation of 2,3-dihydropyran at room temperature was actually established experimentally. The mixed melting point of the succinic acid isolated and an authentic sample of succinic acid showed no depression. Since the amount of potassium permanganate used was much less than the theoretical quantity, the reaction might be regarded as a complicated one, giving a mixture of degradated compounds as indicated in the above equations. Extremely poor yields and isolation difficulties prevented further investigation and definite structure proof of these intermediates.

IV. EXPERIMENTAL

TRIAL ONE A Solution of 12.5 grams (0.08 mole) of potassium permanganate (theoretical amount) in 300 ml. of water was added to a mixture of 10 grams (0.12 mole) of 2,3-dihydropyran* and 25 ml. of water in a 500-ml. flask, which was immersed in an ice-bath. This potassium permanganate solution was added dropwise (over a period of three hours) so that the temperature of the reaction mixture was maintained at about 0°C. After the resulting manganese dioxide was removed by filtration, the clear alkaline filtrate was extracted with several portions of ether. The extraction, however, was a failure since no residue remained when the ether was removed by distillation on a steam-bath.

TRIAL TWO A similar reaction was carried out, using 25.2 grams (0.3 mole) of dihydropyran and a stoichiometric amount of potassium permanganate (31.6 grams -0.2 mole- in 850 ml. of water). After the manganese dioxide was removed by filtration, the alkaline filtrate was acidified with the theoretical amount (17 ml.) of concentrated hydrochloric acid. Most of the water was removed by distillation at 55°C and 60-70 mm. The residue was extracted with benzene and the extract was separated from the insoluble substances.

After the benzene was removed by distillation, about 2 grams of a syrupy liquid remained. The 2,4-dinitrophenyl-

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* obtained from the Du Pont Company.

hydrazone of this crude product was prepared according to the procedure by Shriner and Fuson (8). This derivative, a yellow solid, was recrystallized several times from a mixture of dioxane and water. It had a melting point of 228-231°C.

<u>Anal.</u> Calcd. for $C_{11}H_{14}O_6N_4$: C, 44.30; H, 4.73,
Found. C, 44.41; H, 4.43.

<u>TRIAL THREE</u> The previous reaction was repeated with varied adjustments. The quantity of dihydropyran used was 23 grams (0.27 mole). To this was added slowly a solution of 15 grams (0.1 mole) of potassium permanganate in 200 ml. of water. An additional 39 grams (0.25 mole) of solid potassium permanganate were added, in small amounts, to the reaction mixture. Upon further addition of potassium permanganate, the reaction mixture remained violet, showing that the oxidation was completed. The oxidation reaction was carried out over a period of about four hours; no constant temperature control was used. After removal of the manganese dioxide, the solution was acidified with concentrated sulfuric acid. Evolution of a gas was observed; this gas was proved to be carbon dioxide by the lime-water test. The evolution of the carbon dioxide gas was hastened by warming and stirring.

Then the solution was concentrated to 50 ml. by vacuum distillation. After this concentrated solution was saturated with anhydrous sodium sulfate, four ether extractions were made with 50-ml. portions. The combined ether extracts were dried over anhydrous sodium sulfate, filtered to remove the drying agent, and then subjected to distillation to remove the ether. A semisolid was formed when the residue was cooled in an ice-bath. The dry white solid, without recrystallization, had a melting point of 177°C. Pure succinic acid melts at 185°C. The mixed melting point of the white solid isolated and an authentic sample of succinic acid was 184°C.

V. SUMMARY

The oxidation of 2,3-dihydropyran with aqueous potassium permanganate under various conditions was disscussed. At 0°C one of the oxidation products was identified as alpha, delta-dihydroxyvaleraldehyde. Under more vigorous oxidizing conditions, the final product obtained was succinic acid.

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5. Milas and Sussman, ibid., 59, 2345 (1937).
6. Milas , Sussman and Mason, ibid., 61, 1844 (1939).
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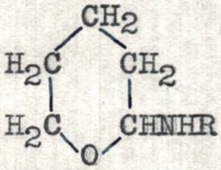
PART TWO

SYNTHESES OF

2-(N-ALKYLAMINO)TETRAHYDROPYRANS

I. INTRODUCTION

Attempts to synthesize 2-(N-alkylamino)tetrahydropyrans were carried out in the present work. Both direct amination and the Hofmann reaction for the preparation of these amines were investigated. The general formulas for the products are represented as I and II.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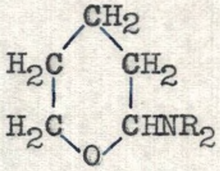
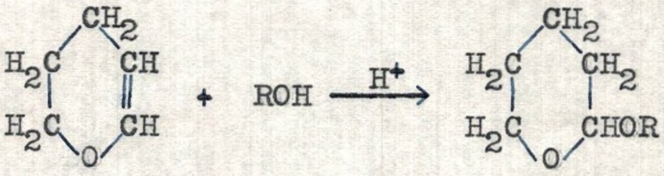

II

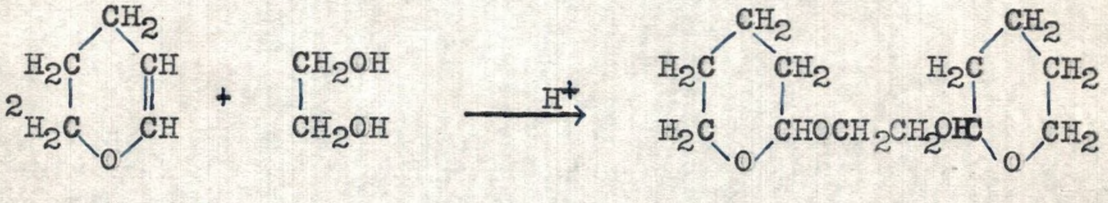
II. HISTORICAL

It has been shown in the first part of this paper that many reactions of 2,3-dihydropyran are due to the presence of the adjacent double bond to the ether group. In addition to those mentioned, there are a few more which are of interest to the present work.

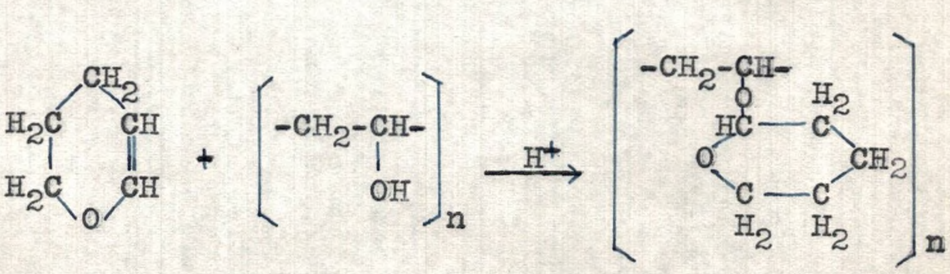
Alcohols (1) and polyhydroxy compounds (2), in the presence of mineral acids or acid salts as catalysts, form addition products as illustrated by the following equations:



alkyl-2-tetra-
hydropyryl ether

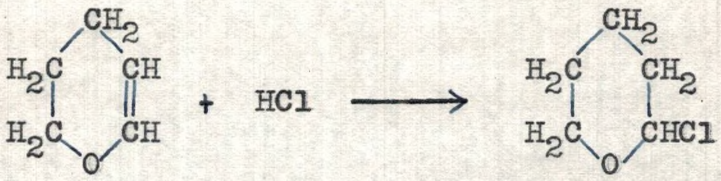


di-(2-tetrahydropyryl)glycol
ether



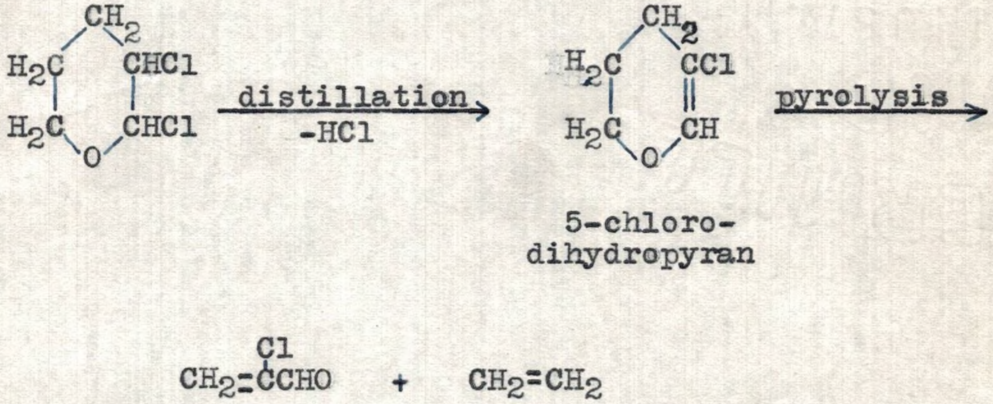
polyvinyl-2-tetra-
hydropyryl ether

Hydrogen bromide and hydrogen chloride react with 2,3-dihydropyran to form 2-bromo and 2-chlorotetrahydropyran (2)(3) respectively.



2-chlorotetrahydropyran

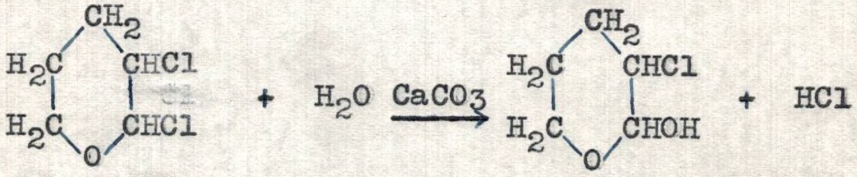
The following reactions show that the halogen in the 2-position is highly reactive (3)(4)(5)(6):



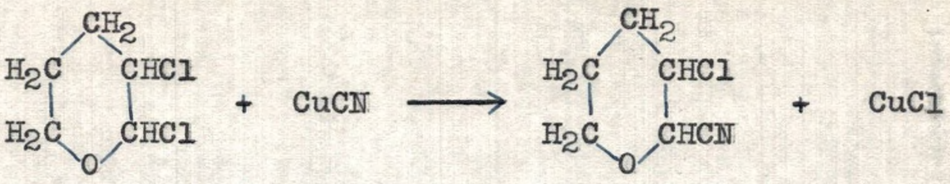
5-chlorodihydropyran

alpha-chloro acrolein

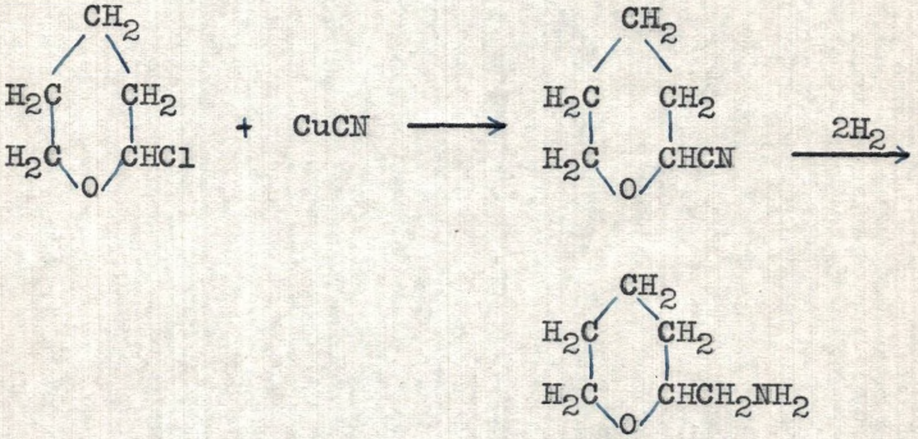
ethylene



2-hydroxy-3-chlorotetrahydropyran

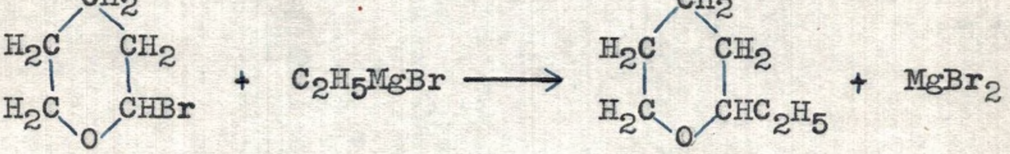


2-cyano-3-chloro-tetrahydropyran



2-aminomethyl-tetrahydropyran

2-Alkyl- and 2-aryltetrahydropyrans, such as ethyl-, propyl- and phenyltetrahydropyran, can be prepared by the Grignard reaction with 2-bromotetrahydropyran (3).



2-ethyltetra-hydropyran

Schulemann, Schönhöfer and Wingler (6) reported the aminoalkylation of amines or their substitution products by treating them with aminoalkylhalides in the form of their salts. They prepared beta-diethylaminoethylaniline from aniline and diethylaminoethylchloride hydrochloride.

$$(C_2H_5)_2NCH_2CH_2Cl.HCl \quad + \quad 3C_6H_5NH_2 \longrightarrow$$

diethylaminoethyl-
chloride hydrochloride

$$(C_2H_5)_2NCH_2CH_2NHC_6H_5 \quad + \quad 2C_6H_5NH_2.HCl$$

beta-diethylamino-
ethylaniline

Secondary cyclohexylarylamines (7) were prepared by Kränzlein and Corell by the alkylation of primary aromatic amines with halocyclohexanes. These secondary amines on further alkylation with ethyl sulfate were converted into tertiary amines.

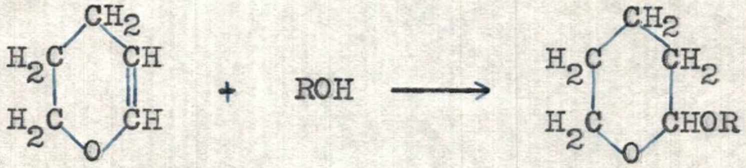
Carleton and Woodward (8) were able to replace the hydrogen of an amino group in a nonphenolic aromatic amine by an alkyl radical, as in the production of mono- and diethyl anilines from aniline. The amine was caused to react with an alkyl alcohol, such as ethyl alcohol, or the corresponding alkyl chloride under super-atmospheric pressure.

According to Hickinbottom (9), when an alkyl bromide was heated with an excess (usually 2.4-4 moles) of a primary aromatic amine, the corresponding secondary amine was the predominating product.

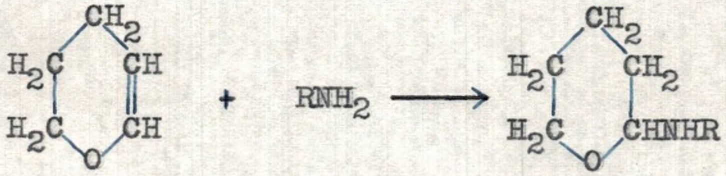
III. THEORETICAL AND DISCUSSION OF RESULTS

A. DIRECT AMINATION

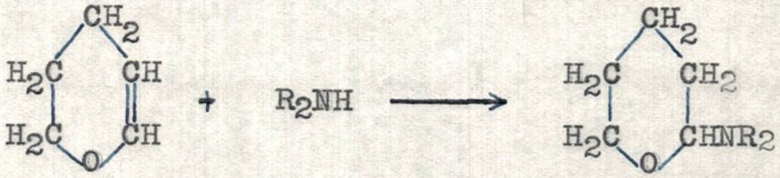
Woods and Kramer (1) have shown that alcohols react by addition with dihydropyran to form cyclic hemiacetals.



Since primary amines contain active hydrogens, it seemed of interest to investigate the possibility of adding amines across the double bond of dihydropyran to form 2-(N-alkylamino)tetrahydropyrans.



In a similar manner, secondary amines should form 2-(N,N-dialkylamino)tetrahydropyrans.



The primary amines that were used in this investigation were ethylamine, benzylamine and aniline. A mixture of dihydropyran and an excess of the amine was refluxed for three to five hours. Under these conditions, no reaction occurred with the above amines since the dihydropyran and the original amines were recovered. A negative nickel chloride test (10) for the detection of secondary amines in the reaction product further substantiated that no reaction had occurred.

Similar reactions were run with the secondary amines diethylamine and piperidine. Piperidine did not react with dihydropyran. It was found that diethylamine did react with dihydropyran to form in poor yield, 2-(N,N-diethylamino)tetrahydropyran. This was proved by the synthesis of the above amine by an alternative method which will be described later.

Since the direct amination reaction was not a general preparative method for these amines, the Hofmann reaction for preparing amines was then investigated.

B. HOFMANN METHOD

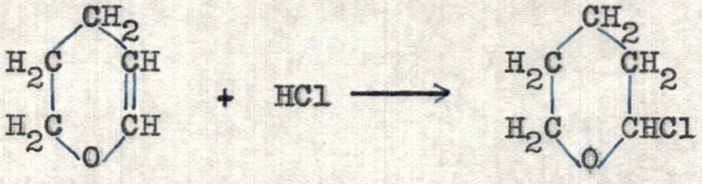
The classical Hofmann method for preparing amines from ammonia or its derivatives and an alky- or arylhalide is well known. It is perhaps the most universal method for preparing amines. In the present work, the alkylation of primary and secondary amines with 2-chlorotetrahydropyran was investigated. The general equations for the Hofmann reactions are as follows:

$$RX + R'NH_2 \longrightarrow RNHR' + HX \quad (a)$$

$$RX + R'_2NH \longrightarrow RNR'_2 + HX \quad (b)$$

Applied to the present work, X stands for chlorine, R' for either alkyl or aryl group and R for the tetrahydropyryl ring. In both cases the formation of by-products, i. e. R_2NR' in reaction (a) and $(R_2NR'_2)^+ X^-$ in reaction (b) was suppressed by the use of excess amounts of the reactant amines.

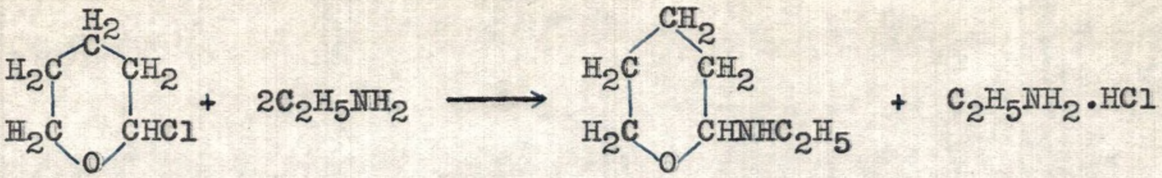
The procedure for the preparation of the alkylating agent, 2-chlorotetrahydropyran (III), was similar to that used by Paul (3).



III

A slow stream of dry hydrogen chloride was passed through dihydropyran until the theoretical amount of hydrogen chloride was absorbed. During the passage of the hydrogen chloride, the reaction mixture was cooled in an ice-bath.

Since the chloro compound would decompose on standing at room temperature, it was immediately added slowly, with vigorous stirring, to an excess amount of amine in absolute ether cooled to 0°C. The reactions of 2-chlorotetrahydropyran with ethylamine, diethylamine, benzylamine and aniline should proceed as follows:



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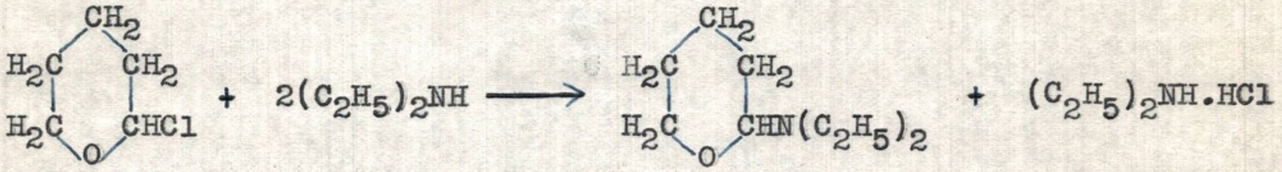
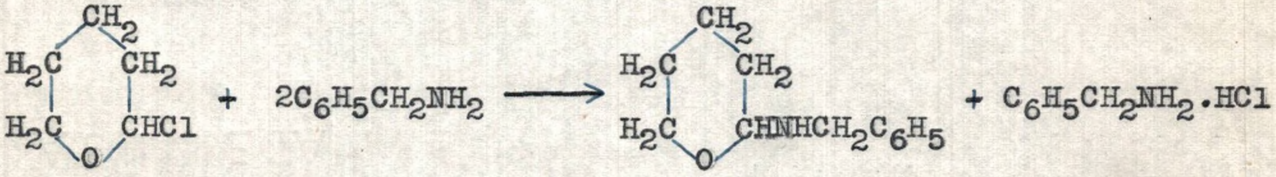
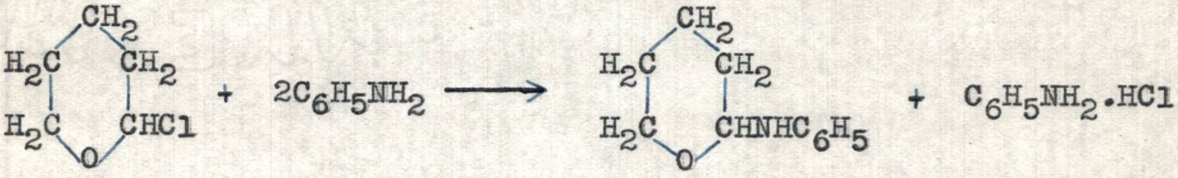


V



VI



VII

The hydrochlorides formed from the different amines used in the syntheses were removed by filtration and identified by their melting points and by their derivatives.

Because of their low boiling points, the excess ethyl- and diethylamine and the solvent were easily removed from the reaction mixture by distillation. The resulting crude aminotetrahydropyrans were purified by vacuum distillation. The yields obtained of the 2-(N-ethylamino)tetrahydropyran (IV), and 2-(N,N-diethylamino)tetrahydropyran (V) were 19.5% and 47% respectively.

An attempt was made to prepare the benzenesulfonamide of IV by causing benzenesulfonyl chloride to react with IV. It was found, from the analyses for carbon and hydrogen, that the product isolated was the benzenesulfonamide of ethylamine. A mixed melting point of the sulfonamide isolated and an authentic sample of the benzenesulfonamide of ethylamine showed no depression.

A mixture of the isolated product V, from the diethylamine reaction, and benzyl chloride was heated under reflux for a short time. The solid thus formed was purified and then analysed for carbon and hydrogen. From the analyses it was concluded that this solid was not the expected quaternary salt of V but rather the benzyl chloride salt of diethylamine, ($[C_6H_5CH_2NH(C_2H_5)_2]^+Cl^-$). A mixed melting point of the product isolated and an authentic sample of the benzyl chloride salt of diethylamine showed no depression.

Since benzylamine is soluble in water and the amine VI is not, the excess benzylamine was removed from the reaction mixture by extraction with water. The liquid residue was dried over anhydrous potassium carbonate and then subjected to vacuum distillation. A 47% yield of 2-(N-benzylamino)tetrahydropyran (VI) was obtained.

An attempt was made to prepare the benzenesulfonamide of VI. The results of the analyses for carbon and hydrogen did not check with the expected sulfonamide. Instead, the analyses agreed well with the dibenzenesulfonamide of benzylamine itself, i. e. $(C_6H_5SO_2)_2NCH_2C_6H_5$. For comparison, the latter compound was made by treating benzylamine with an excess of benzenesulfonyl chloride in the presence of alkali.

$$2C_6H_5SO_2Cl + C_6H_5CH_2NH_2 \xrightarrow{2NaOH} (C_6H_5SO_2)_2NCH_2C_6H_5 + 2NaCl + 2H_2O$$

The melting points of the sulfonamide which was analyzed and that of the dibenzenesulfonamide of benzylamine were identical. A mixed melting point of these two products showed no depression; hence the two sulfonamides were the same.

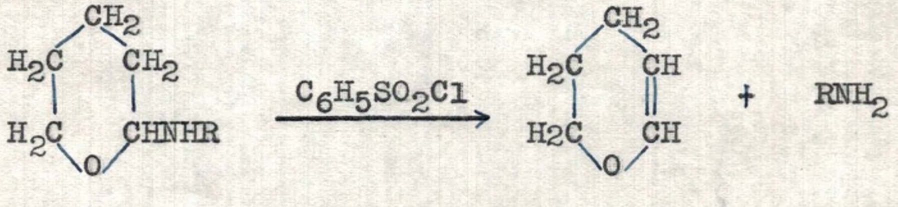
The procedure that was used for the preparation of 2-(N-phenylamino)tetrahydropyran (VII) was similar to that used for the preparation of those amines already mentioned. Since aniline has a rather high boiling point and is insoluble in water, it was impossible to remove the excess aniline from the reaction mixture by distillation or by extraction with water. Therefore, an attempt was made to prepare the benzenesulfonamide of VII directly from the crude product.

From the analyses for carbon and hydrogen, it was found that the expected sulfonamide of VII was not obtained. The analyses, however, checked very well for the dibenzenesulfonamide of aniline, $(C_6H_5SO_2)_2NC_6H_5$. The melting point of the product which was analyzed was the same as that listed in the literature for the dibenzenesulfonamide of aniline.

Because of the abnormal behavior of these 2-(N-alkylamino)tetrahydropyrans, no suitable derivatives could be prepared. That these amines were actually obtained was substantiated in two cases by carbon and hydrogen analyses of the free amines themselves. The results of analyses for amines V and VI were found to check with the postulated formulas. On account of the fact that upon standing, IV turned from colorless to a dark yellow color, suggesting decomposition, and that VII was difficult to purify, these two amines were not analyzed.

Thus it may be concluded that the amines V and VI were prepared by the alkylation of the corresponding amines with 2-chlorotetrahydropyran. It seems permissible to assume that compounds IV and VII were obtained by analogous reactions.

It remains to be explained why the benzenesulfonamides of the original amines were obtained when the 2-(N-alkylamino)-tetrahydropyrans were treated with benzenesulfonyl chloride. All evidence indicated that the aminotetrahydropyrans on long standing or in the presence of benzenesulfonyl chloride or benzyl chloride dissociated into dihydropyran and the corresponding reactant amine.



$$RNH_2 + C_6H_5SO_2Cl \xrightarrow{NaOH} C_6H_5SO_2NHR + NaCl + H_2O$$

$$C_6H_5SO_2NHR + C_6H_5SO_2Cl \xrightarrow{NaOH} (C_6H_5SO_2)_2NR + NaCl + H_2O$$

IV. EXPERIMENTAL

A. DIRECT AMINATION

PREPARATION OF 2-(N,N-DIETHYLAMINO)TETRAHYDROPYRAN (V).

A mixture of 15 grams (0.18 mole) of 2,3-dihydropyran and an excess amount of diethylamine, 17.3 grams (0.24 mole), was refluxed gently for three hours. The reaction mixture was then subjected to distillation. After the unreacted reagents were removed, a brownish liquid, boiling at 180°C was obtained. The yield was 1.5 grams. This product was proved to be 2-(N,N-diethylamino)tetrahydropyran, which was also prepared by the Hofmann method later.

B. PREPARATION OF 2-CHLOROTETRAHYDROPYRAN.

Into 15 grams (0.18 mole) of 2,3-dihydropyran in a 50-ml. flask immersed in an ice-bath, a stream of hydrogen chloride gas was passed (for 25 minutes) until the weight of hydrogen chloride absorbed was 6.6 grams, the stoichiometric amount. The resulting liquid chloro compound, without purification, was used in the subsequent reactions.

C. HOFMANN METHOD

1. PREPARATION OF 2-(N-ETHYLAMINO)TETRAHYDROPYRAN (IV).

Twenty nine grams (0.24 mole) of freshly prepared 2-chlorotetrahydropyran were added slowly, with stirring, to 31 grams (0.69 mole) of ethylamine in 50 ml. absolute ether cooled in an ice-bath. Considerable amount of heat was evolved as the reaction proceeded. A white hygroscopic solid, formed in the reaction, was removed by filtration. This solid melted at 130°C and was proved to be ethylamine hydrochloride. A brown liquid was obtained as filtrate; it gave a positive nickel chloride test. After the excess ethylamine was removed by evaporation, the residual liquid was caused to react with benzenesulfonyl chloride in 10% sodium hydroxide. The sulfonamide, after recrystallization from carbon tetrachloride, had a melting point of 56°C. It was analyzed for carbon and hydrogen.

Anal. Calcd. for $C_{13}H_{19}O_3NS$: C, 57.96; H, 7.11,
Found. C, 51.82; H, 5.96,
Calcd. for $C_8H_{11}O_2NS$: C, 51.80; H, 5.95.

The mixed melting point of the benzenesulfonamide prepared above and that of ethylamine was 54°C.

The product (IV) of a similar run using 21.6 grams (0.17 mole) of freshly prepared 2-chlorotetrahydropyran and 24 grams (0.53 mole) of ethylamine was separated from any unreacted reagents and solvent by fractional distillation. A colorless liquid fraction weighing 3.5 grams, equivalent to a 19.5 percent yield, boiling at 185-190°C, was obtained. It gave a positive nickel chloride test. After standing for two days, the liquid turned dark yellow and gave a negative nickel chloride test, indicating decomposition. Therefore, no attempt was made to analyze the product.

2. PREPARATION OF 2-(N,N-DIETHYLAMINO)TETRAHYDROPYRAN (V).

Twenty nine grams (0.24 mole) of freshly prepared 2-chlorotetrahydropyran were added slowly, with stirring, to 30 grams (0.41 mole) of diethylamine in 50 ml. absolute ether cooled in an ice-bath. Heat was evolved as the reaction proceeded. A white hygroscopic solid, formed in the reaction, was removed by filtration. This solid melted at 215°C and was proved to be diethylamine hydrochloride. The excess unreacted reagents and solvent were removed by distillation from the filtrate. The residual brown liquid thus obtained was refluxed with benzyl chloride in benzene for five minutes. The benzyl chloride salt, after recrystallization from chloroform, had a melting point of 188-189°C. This compound was analyzed for carbon and hydrogen.

<u>Anal.</u> Calcd. for $C_{16}H_{26}ONCl$: C, 67.70; H, 9.23,
Found: C, 66.05; H, 9.12,
Calcd. for $C_{11}H_{18}NCl$: C, 66.15; H, 9.08.

The results of analyses did not check with the postulated composition for the benzyl chloride salt of V but rather checked with that of the original amine, $[C_6H_5CH_2NH(C_2H_5)_2]^+Cl^-$. Therefore the latter was prepared by refluxing diethylamine with benzyl chloride in benzene for 20 minutes. The pure product after recrystallization from chloroform had a melting point of 185°C. The mixed melting point of the benzyl chloride salt of diethylamine and that of V was 188°C.

The amine (V), prepared from a similar run using 21.6 grams (0.18 mole) of freshly prepared 2-chlorotetrhydropyran and 39 grams (0.53 mole) of diethylamine, was isolated by distillation. A colorless liquid, boiling at 180-190°C, weighing 11.2 grams (47% yield), was obtained. It gave a negative nickel chloride test. The sample that was submitted for analysis was purified by vacuum distillation; it had a boiling point of 43-50°C at 1 mm.

Anal. Calcd. for $C_9H_{19}ON$: C, 68.75; H, 12.18,

Found: C, 68.31; H, 12.22.

3. PREPARATION OF 2-(N-BENZYLAMINO)TETRAHYDROPYRAN (VI).

To 36 grams (0.34 mole) of benzylamine, dissolved in 50 ml. of ether and cooled in an ice-bath, was added slowly, with stirring, 14.4 grams (0.12 mole) of freshly prepared 2-chlorotetrahydropyran. Considerable amount of heat was evolved by the reaction. A pale yellow solid which was formed was removed from the reaction mixture by filtration. This solid melted at 245°C and was proved to be benzylamine hydrochloride. The filtrate was then washed with two portions of water (200 ml.) to remove most of the excess benzylamine. After the solvent (ether) was removed by distillation, a slightly brown liquid, giving a positive nickel chloride test, was obtained.

To this brown liquid product, cooled in an ice-bath, was added with stirring, proportional amounts of benzenesulfonyl chloride and 10 percent sodium hydroxide. A yellow semisolid substance, insoluble in alkali, was formed. After it was recrystallized from 95% ethyl alcohol, the solid melted at 128-130°C. The analyses for carbon and hydrogen were as follow:

<u>Anal.</u> Calcd. for $C_{18}H_{21}O_3NS$: C, 65.23; H, 6.38,
Found: C, 58.94; H, 4.36,
Calcd. for $C_{19}H_{17}O_4NS_2$: C, 58.90; H, 4.43.

Because the results of analyses did not check for the benzenesulfonamide of the postulated compound, but did check for the composition of the disulfonamide of benzylamine, the latter was prepared from the original amine, i. e., benzylamine directly. It was prepared by treating benzylamine with an excess amount of benzenesulfonyl chloride in sodium hydroxide solution. The disulfonamide of benzylamine melted at 130°C. A mixed melting point of this sulfonamide and the benzenesulfonamide prepared from the reaction product was 130°C.

The product (VI), obtained from a similar run using 21.6 grams (0.18 mole) of freshly prepared 2-chlorotetrahydropyran and 57 grams (0.53 mole) of benzylamine, was washed with water (300 ml.). After the solvent (ether) was removed, the product was dried with potassium carbonate and then subjected to vacuum distillation. A first fraction of 8 grams boiling at 75-85°C. and 1 mm. was collected. This fraction gave a negative nickel chloride test and was mainly benzylamine. A second fraction of 5 grams boiling at 103-106°C and 1 mm. was obtained. This fraction gave only a faintly positive nickel chloride test. A third fraction of 13 grams boiling at 122-124°C and 1mm.

(bath temperature about 160°C) gave a positive nickel chloride test. Two grams of a syrupy substance were left as residue. A sample of the third fraction was analyzed for carbon and hydrogen.

Anal. Calcd. for $C_{12}H_{17}ON$: C, 75.35; H, 8.96,
Found: C, 75.68; H, 8.77.

4. PREPARATION OF 2-(N-PHENYLAMINO)TETRAHYDROPYRAN (VII).

To 50.7 grams (0.55 mole) of aniline, dissolved in 60 ml. of absolute ether and cooled in an ice-bath, 21.6 grams (0.18 mole) of freshly prepared 2-chlorotetrahydropyran was added slowly, with stirring. Considerable amount of heat was evolved by the reaction. A pale yellow solid melting at 240°C was formed by the reaction and proved to be the aniline hydrochloride. It was removed from the reaction mixture by filtration.

The filtrate, after the solvent was removed by evaporation, was a viscous brown liquid which gave a positive nickel chloride test. An attempt was made to remove the excess aniline from the product by vacuum distillation. After a fraction of 20 ml. was collected by distillation at 50-54°C and 1 mm., the remaining liquid would not distil but formed a viscous polymer-like substance. The distillate gave a negative nickel chloride test and it was proved to be mainly aniline.

Since the attempt to isolate the product by distillation was a failure, the separation of aniline from VII and the preparation of the sulfonamide of VII by Hinsberg's reaction was tried. The product mixture of another similar run was treated with benzenesulfonyl chloride and sodium hydroxide at 15°C. A semisolid substance, insoluble in alkali, was formed. After recrystallization from 95 percent ethyl alcohol, a white solid melting at 140-141°C was obtained. It was analyzed for carbon and hydrogen.

<u>Anal.</u> Calcd. for $C_{17}H_{19}O_3NS$: C, 64.32; H, 6.03,
Found. C, 58.03; H, 4.07,
Calcd. for $C_{18}H_{15}O_4NS_2$: C, 57.80; H, 4.05.

The results of analyses did not check for the benzenesulfonamide of VII, however, the values did check for the composition of the dibenzenesulfonamide of aniline. The melting point of the latter as listed in the literature is 143-144°C; this is in agreement with the melting point of the compound that was analyzed.

V. SUMMARY

The attempted syntheses of 2-aminotetrahydropyrans by direct amination were described. 2-(N,N-Diethylamino)tetrahydropyran (V) was synthesized, in poor yield.

By the Hofmann method, 2-(N-ethylamino)- (IV), 2-(N,N-diethylamino)- (V), 2-(N-benzylamino)- (VI) and 2-(N-phenylamino)tetrahydropyran (VII) were prepared. Of these amines, only V and VI were isolated and analyzed. Since IV decomposed on standing and VII was difficult to isolate, these two compounds were not analyzed. However, it seems permissible to conclude that compounds IV and VII were obtained by analogous reactions. The steps included the reaction of 2-chlorotetrahydropyran, obtained by the addition of dry hydrogen chloride to 2,3-dihydropyran, with an excess amount of the corresponding amine. When attempts were made to prepare derivatives of these aminopyrans, it was found that the latter dissociated into their parent substances.

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