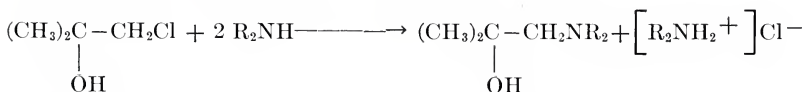# The Preparation of Amino Alcohols

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Introduction

Since amino alcohols and their derivatives are of considerable importance as local anesthetics, their preparation has been the object of much attention. Three more or less general methods of preparation, as well as a host of minor ones, have been developed. In the first of these[1] the amino group is introduced into an ester, aldehyde, or ketone, and this amino compound is converted into an amino alcohol either by reduction or through the Grignard reaction. This method is very satisfactory in those cases where the amino alcohol can be readily isolated from aqueous solution and where the amino ester, aldehyde, or ketone is easily obtained and is stable. In the second method, which applies only to beta amino alcohols, the corresponding ethylene oxide is treated with ammonia or an amine.[2] This method is an excellent one but is limited by the availability of the ethylene oxides.

The third and most generally used reaction consists in treating the corresponding chloro (or bromo) hydrine with the desired amine, either at atmospheric pressure or in a sealed vessel, depending on the volatility of the reactants.[3] Ammonia does not work as well as primary and secondary amines. Since hydrogen halide is formed in the reaction, it is necessary to remove it for the reaction to proceed.

$$(CH_3)_2C-CH_2Cl + 2\ R_2NH \longrightarrow (CH_3)_2C-CH_2NR_2 + \left[R_2NH_2{}^+\right]Cl^-$$
$$\qquad\quad |\qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$\qquad\ OH\qquad\qquad\qquad\qquad\qquad\qquad\ OH$$

Ordinarily, a second equivalent of amine is used for this purpose. This procedure has two main disadvantages. The yield of amino alcohol is apt to be low, especially in the case of the less basic, aromatic amines, and the procedure is an expensive one, particularly where the amine used is one of the higher, less readily available ones.

Since large amounts of amino alcohols were needed for work being conducted in this laboratory, a study was undertaken to determine whether inorganic bases could be substituted for the second equivalent of amine and, if so, to ascertain which inorganic bases were most suitable.[4]

Experimental Procedure

Reactions carried out at atmospheric pressure.—One-fourth of a mole of the chlorohydrine, one-fourth of a mole of the amine, and a

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[1]Mannich and Hof, 1927. *Arch. Pharm.* **265**:589. Paal and Weidenkaff, 1906. Ber., **39**:810.

[2]Krassusky, 1927. *Journ. prakt. Chem.* **115**:322.

[3]Fourneau, 1904. *Compt. rend.* **138**:766.

slight excess of the alkaline binding agent were mixed with the solvent. This usually consisted of 100 cc. of 50% alcohol, except in the cases where excess amine was used as binding agent, when the solvent was benzene. The mixture was heated under a reflux condenser for six to nine hours. It was then allowed to cool to room temperature and was poured into water. The organic layer was separated, the aqueous layer was made *strongly* basic with sodium hydroxide and extracted several times with ether. The combined ether extracts and the main organic layer were dried over anhydrous magnesium sulfate and then distilled through a Vigreux column or a modified Claisen flask, according to circumstances.

Reactions carried out at higher pressures.—One-fourth of a mole of the chlorohydrine, one-fourth of a mole of the amine, and a slight excess of the alkaline binding agent were dissolved or suspended in 150 cc. of dry benzene, and the mixture was heated in a small autoclave at 125-130°C. for eight to ten hours. The cooled mixture was filtered and the benzene solution was distilled.

Discussion of Results

For the first phase of the study, the reaction of isobutylene chlorohydrine with the weakly basic ethylaniline was chosen. As can be seen from the data in Table I, no amino alcohol was obtained when excess amine was used as the binding agent. Pyridine and sodium acetate also proved to be too weakly basic to bring about a reaction.

TABLE I.—Reaction of Isobutylene Chlorohydrine and Ethylaniline at Atmospheric Pressure

Binding Agent	Solvent	Yield of Amino Alcohol
Excess amine	Benzene	0%
Pyridine	Benzene	0%
Pyridine	Aqueous alcohol	0%
Sodium bicarbonate	Aqueous alcohol	48%
Sodium acetate	Aqueous alcohol	0%
Boric oxide	Aqueous alcohol	11%
Magnesium oxide	Aqueous alcohol	28%
Calcium oxide	Aqueous alcohol	36%
Potassium hydroxide	Aqueous alcohol	26%
Trisodium phosphate	Aqueous alcohol	15%

Of the other binding agents tried, sodium bicarbonate was the most satisfactory, and the oxides of calcium and magnesium next. The relatively low yield of amino alcohol, obtained when potassium hydroxide was used, is probably due to the fact that it is too strong a base and caused partial decomposition of the tertiary chlorohydrine to the volatile isobutylene oxide, which escaped from the reaction mixture. From

the above data, it is permissible to conclude that, for a binding agent to be satisfactory, it must be a fairly strong base but that too strong a base causes side reactions which lower the yield of amino alcohol.

The use of sodium bicarbonate and sodium carbonate in the preparation of other amino alcohols from isobutylene chlorohydrine was investigated next. A good yield (47%) of amino alcohol was obtained from methylaniline, using sodium bicarbonate as binding agent and aqueous alcohol as solvent. Dibutylamine gave a 61% yield of the corresponding amino alcohol, and diethylamine a 46% yield. In extending the study to the higher, less basic aromatic amines, it was found that no amino alcohol could be obtained from isobutylene chlorohydrine and diphenylamine or alpha-naphthylamine, either in the presence or the absence of sodium carbonate. This is not especially strange since these amines are so weakly basic that they will not dissolve in dilute hydrochloric acid. For reasons as yet unexplained, dicyclohexylamine yielded no amino alcohol either with or without a binding agent.

Sodium carbonate and sodium bicarbonate proved to be satisfactory binding agents in the preparation of amino alcohols from trimethylene chlorohydrine and diethyl and dibutylamines. In this case also, dicyclohexylamine yielded no amino alcohol. These data are summarized in Table II.

TABLE II.—Preparation of Amino Alcohols from Chlorohydrines at Atmospheric Pressure

Chlorohydrine	Amine	Binding Agent	Yield of Amino Alcohol
Isobutylene...............	Ethylaniline	$NaHCO_3$	48%
Isobutylene...............	Methylaniline	$NaHCO_3$	47%
Isobutylene...............	Di-n-butylamine	Na_2CO_3	61%
Isobutylene...............	Diethylamine	$NaHCO_3$	46%
Trimethylene..............	Di-n-butylamine	Excess amine	33%
Trimethylene..............	Di-n-butylamine	$NaHCO_3$	48%
Trimethylene..............	Di-n-butylamine	Na_2CO_3	47%
Trimethylene..............	Diethylamine	$NaHCO_3$	53%

Since, with the lower-boiling amines, it is desirable to carry the reaction out in a sealed vessel to avoid losses and since, obviously, sodium carbonate or bicarbonate cannot be used under such conditions, it seemed advisable to investigate the use of other binding agents for this purpose. From the data in Table I, it seemed that magnesium oxide would be suitable. This proved to be the case for the reaction of diethylamine with isobutylene chlorohydrine. Using excess amine as binding agent, a 19% yield of amino alcohol was obtained. Under the same conditions of time, temperature, solvent, and pressure but substituting magnesium oxide for the excess amine, the yield of the amino alcohol was increased to 30%.

The physical constants of the amino alcohols prepared in the course of this work are recorded in Table III. Not all of these have been described before.

TABLE III.—Physical Constants of Amino Alcohols

Amino Alcohol	B.pt. °C.	Press. mm.	n_D^{20}	d_4^{20}
Methylanilino-tert-butyl alcohol.....	132-133°	12	1.5479	1.0160
Ethylanilino-tert-butyl alcohol......	137-138°	12	1.5418	1.0029
Dibutylamino-tert-butyl alcohol.....	118-119°	21	1.4379	0.8422
Diethylamino-tert-butyl alcohol.....	78-80°	45	1.4253	0.8382
3-Diethylamino-l-propanol..........	85-86°	20	1.4439	0.8600
3-Dibutylamino-l-propanol.........	121-122°	11	1.4476	0.8617

Summary

1.   The use of alkaline, inorganic binding agents in the preparation of amino alcohols from chlorohydrines and secondary amines has been investigated.

2.   Sodium carbonate and sodium bicarbonate have been shown to be the most satisfactory binding agents for reactions at atmospheric pressure. In many cases, the use of these substances increases the yield of amino alcohol markedly. Magnesium oxide appears to be a satisfactory binding agent for use at higher pressures.