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Reaction of Aromatic Amines with Epihalohydrins[1]

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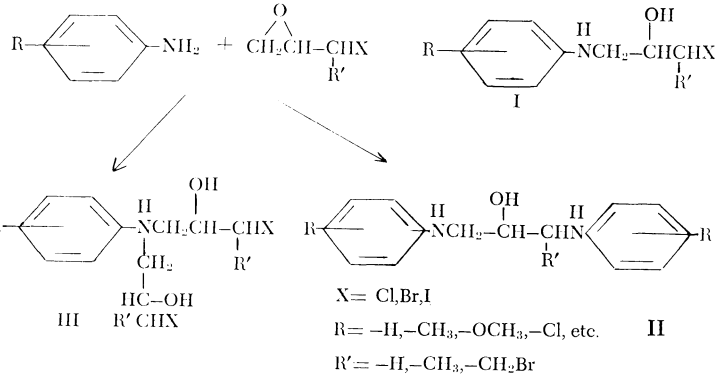
Abstract. Published procedures for the reaction of primary aromatic amines with epihalohydrins to give 1:1 addition compounds are not generally applicable, and we have found that they frequently lead to impure products. The reactions were investigated in water, alcohol and bromobenzene solutions. A number of techniques were used to follow the reaction. Infrared spectroscopy gave qualitative data since significant changes occur in the 2.5 μ — 3.0 μ and the 10 μ — 11 μ regions of the spectrum. Thin layer chromatography made it possible to detect the formation of by-products and to determine the purity of the addition compounds. The best quantitative measure of the rate of the reaction was obtained by means of an oxirane titration with HBr. The reaction of epichlorohydrin with p-anisidine, p-toluidine and aniline in bromobenzene solution exhibited an induction period believed to be due to the catalytic effect of HCl split out from the addition compound by unreacted amine.

The reaction of primary aromatic amines with epihalohydrins may give addition compounds (I, II, III) in which the ratio of amine to halide is 1:1, 2:1, or 1:2. We have been interested in 1:1 addition compounds



(I) since it has been shown that they can be cyclized and the

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resulting 1,2,3,4-tetrahydroquinolin-3-ols can be oxidized with periodate to indoles.(1) During the past few years we have been trying to develop analytical methods that would enable us to determine the purity of 1:1 addition compounds (I) and to examine the kinetics of the addition reaction.

Initially, infrared spectroscopy was employed as an analytical tool since a primary amine doublet at 2.90 μ – 2.98 μ was displaced by a singlet at 2.95 μ as the secondary amine was formed. Also an OH absorption at 2.80 μ was introduced. A characteristic doublet at 10.5 μ and 10.9 μ was found to be reduced as the reaction proceeded. However, infrared spectra proved to give only qualitative data and were not suitable for kinetic studies.

Smith and co-workers (2) have reported that the Volhard method may be used to analyze for Cl^- which can be released from I with IN NaOH. Contrary to their report we found that epichlorohydrin undergoes hydrolysis under these conditions. We attempted to remove the epichlorohydrin from the addition product by solvent extraction or alumina column chromatography prior to analysis, but this failed to give satisfactory results.

Thin layer chromatography (TLC) employing an alumnia base and acetone:hexane developing agents, enabled us to achieve separation of the reactants from I, II, and other reaction products. Rf values for several amines and addition reaction products are shown in Table 1. TLC analysis of addition reactions has shown that a by-product is produced relatively early in the reaction which has Rf values comparable to a known 2:1 addition product (II).

Table 1. Rf Values From Thin Layer Chromatography.

Amine	Rf	Addition Compound	Rf
o-toluidine	.89	o-toluidine-epichlorohydrin	.30
o-anisidine	.88	o-anisidine-epichlorohydrin	.68
aniline	.83	aniline-epichlorohydrin	.60
		aniline-epibromohydrin	.59
p-toluidine	.80	p-toluidine-epichlorohydrin	.58
m-anisidine	.65	m-anisidine-epichlorohydrin	.31
p-anisidine	.58	p-anisidine-epichlorohydrin	.51
		$(p\text{-tolyl}NHCH_2)_2CHOH$	.22

We have repeated many preparations cited in the literature for various addition compounds and their epoxy derivatives (IV). (3,4,5) In each case, TLC has shown that as many as four or five side products are formed during the course of the reaction under the recommended conditions. Many of the addition products were obtained as oils. These oils were purified by column chromatography and picrates were readily prepared and analyzed by means of TLC.

The most successful method of following the rate of the addition reaction has been by means of the Durbetaki titration. (6) We found that HBr in glacial acetic acid quantitatively titrates primary and secondary amines as well as epihalohydrins. Water is a relatively strong base in this system so that its exclusion is necessary.

The reaction of epichlorohydrin with p-anisidine, p-toluidine, and aniline was followed in 1 molar bromobenzene solution. Since the reactant and product amines both titrate quantitatively, their sum is assumed to remain constant, and consequently, the only noticable change is attributed to the consumption of epoxide. A graphic representation of the data (Fig. 1) shows that p-anisidine has reacted to the axtent of about 20% after 120

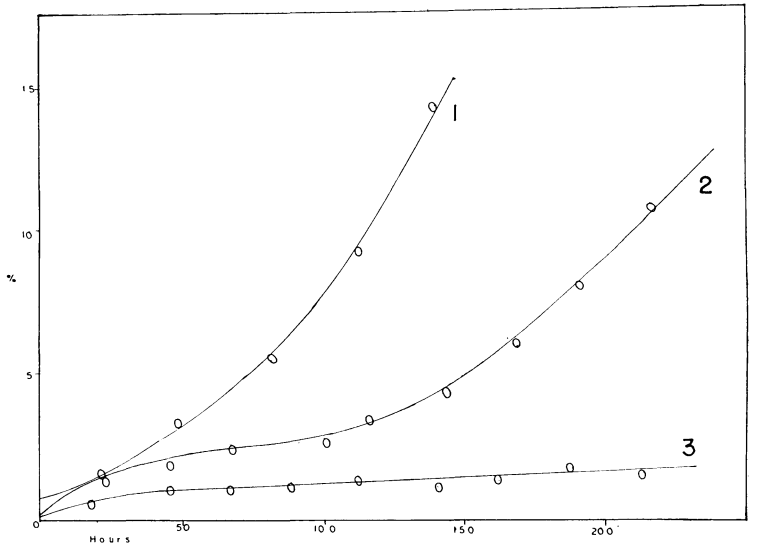


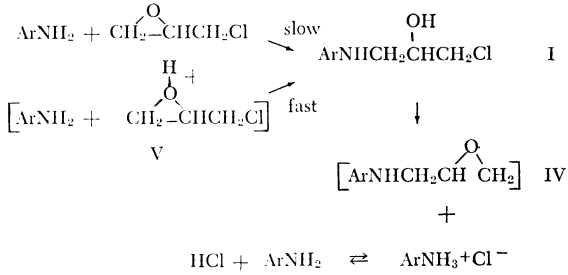
Figure 1. % Epichlorohydrin Reacted Plotted Against Time in Hours. (1) p-anisidine (2) p-toluidine (3) aniline

hours. p-Toluidine has reacted to the extent of about 10% after 210 hours and there is very little reaction with aniline after 215 hours. An induction period accompanies the p-toluidine and p-anisidine reactions.

This induction period in the reaction of various epoxides with nucleophiles appears to be related to acid catalysis which is commonly observed.(7,8) We found that the addition of O.1M amounts of HCl to the p-toluidine-epichlorohydrin reaction in aqueous solution resulted in purer products and greater yields. Also, in the case of the p-anisidine-epichlorohydrin reaction in bromobenzene we observed the formation of small amounts of

crystalline material believed to be the hydrochloride salt of p-anisidine.

A reaction sequence which seems to explain the induction period involves the slow addition of the amine to the primary carbon of the epihalohydrin. The primary amine, acting as a base, serves as an acceptor for the HCl which is split from I with the formation of an epoxy derivative (IV).



The HCl can then protonate the epoxide and lead to a much more rapid nucleophilic addition by the amine. Thus, the reaction proceeds slowly until enough catalyst is released to protonate the epoxide. It should be noted that both the amine and the epoxide compete for the proton, and therefore very little catalyst may be involved in the protonation of the epoxide. Further kinetic studies in other systems may clarify this catalytic effect.

Experimental

Addition Reactions for Rate Determinations. — Equimolar amounts of amine and epoxide were dissolved in bromobenzene without added catalyst. The reaction proceeds much slower in this media than in water or alcohol solutions.

Plates for Thin Layer Chromatography. — Eight plates were prepared, gauged at 0.3 mm. thickness with a Camag Applicator, from a slurry mixture of 27.2g. of alumina (80-200 mesh), 16.0g. of Johns Mansfield Celite Filter Aid, 2.0 g. or $CaSO_4$, and 105 ml. of H_2O. The plates were dried at 120-140°C. for ½ hour and stored over Drierite ($CaSO_4$). The spotted plates were developed for 30 minutes with acetone:hexane mixtures (usually 1:8). The components were made visible by exposure to fuming nitric acid, heating to 130°C., and/or viewing under UV light.

Durbetaki Titration. — The method described by Durbetaki (6) was followed with the following modifications:

(a) Three ml. samples were drawn periodically from reaction vessels held at 25°C. and dissolved in glacial acetic acid before titration.

(b) Primary standard monopotassium acid phthalate was used instead of sodium carbonate.

(c) The titration was followed potentiometrically (glass-calomel), as well as, with crystal violet indicator.

(d) The HBr solution was standardized before and after every titration.

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Synthesis of N-Substituted Diamino-Propanols and their Physiological Effects[1]

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Abstract. The p-toluidine-epichlorohydrin 1:1 addition compound has been reacted with piperidine, pyrrolidine, and morpholine to give disubstituted 2-propanols. 1-(p-Toluidino)-3-pyrrolidino-2-propanol was fed to male rats and organ and body weights measured. The data do not permit us to evaluate adequately the physiological effects of the compound, but differences were observed in the size of the heart, kidneys, and thymus of the test animals.

Reactions of various amines with the addition compounds derived from the condensation of amines with epihalohydrins have led to the synthesis of disubstituted 2-propanols.

Early studies on the physiological properties of I on frogs indicated that it increased the respiratory rate, increased the basal metabolism rate, and increased both the auricular and ventricular rates of the heart beat (1). These results indicated that this compound, or compounds analogous to it, might prove to be useful hypotensive agents. Therefore, we prepared the pyrrolidine and morpholine analogs (II, III).

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