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(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]

KATHREN MORTENSON AND
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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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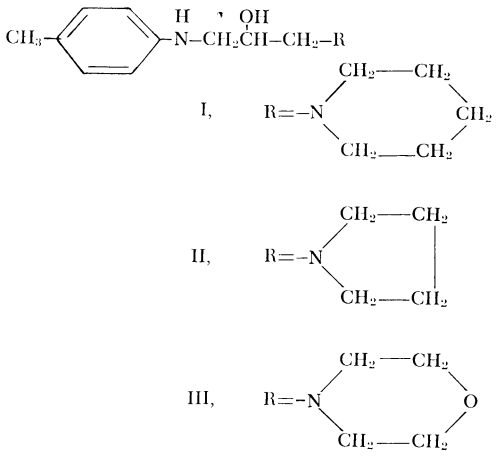

These compounds were prepared by reaction of amines with the addition compound. For example, when piperidine was treated with the p-toluidine-epichlorohydrin 1:1 addition compound in 1,2,4-trichlorobenzene at 200°, the product formed was 1-(p-toluidino)-3-piperidino-2-propanol (I). When other amines, such as pyrrolidine and morpholine, were treated in the same way, analogous compounds (II, III) were obtained. The structures of these compounds were established by elemental analyses and by determination of equivalent weights by titration. Infrared spectra were consistent with the proposed structures. A strong, broad absorption at 2.94 μ appeared in all of the compounds.

It was felt that further studies on the physiological effects of these compounds would be best carried out using male rats.

Methods

Twenty male rats of the Holtzman strain were used. They were ten to twelve weeks old at the beginning of each experiment, and they were kept in individual cages in a thermoregulated room maintained at 25 ± 1° C. and illuminated from approximately 8:00 A.M. to 5:00 P.M. Control animals were fed finely ground Purina laboratory chow. The two sets of experimental animals were given 0.1% and 0.2% of compound II, respectively, mixed thoroughly in the ground laboratory chow by means of a mix-master. All animals were given tap water to drink. Daily body weights were recorded as well as daily food and water consumption measurements for five to seven weeks. The animals were then sacrificed by ether inhalation and autopsied. Testes, prostate, seminal vesicles (drained of fluid), adrenals, kidneys, heart (drained of blood), thyroids, and thymus

were trimmed of fat and connective tissue and weighed. Organ weight/body weight ratios were calulated.

Results

The body weight measurements for the control and the experimental rats in both experiments are shown in Table 1. There was a slight difference in the increase of the body weights of the experimental animals as compared with the controls. It was noticed that during the first week of each experiment, the test rats did not consume as much food and they lost weight. However, by the middle of the second week, they began to gain weight at the normal rate and ate the same amount of food as the controls. Compound II may have produced an undesirable odor or taste to the food, but the rats soon became adjusted to it.

Table 1. Effects of 0.1% and 0.2% Compound II Diet on Body Weights.

Experimental Conditions	No. of Rats	Initial Mean Body Weight (Grams)	Final Mean Body Weight (Grams)	Percent Increase in Body Weight
Normal Diet	5	317.9	412.1	22.8%
0.1% II Diet	5	315.2	389.7	19.1%
Normal Diet	5	250.1	420.4	39.4%
0.2% II Diet	5	247.9	373.4	33.6%

Table 2. Effects of 0.1% and 0.2% Compound II Diet on Organ Weights.

	(Organ Weight in mg./Body Weight in g. x 100)			
Experimental Condition	Testes	Prostate	Seminal Vesicle	Adrenals
Normal Diet	875.3	133.9	204.9	18.1
0.1% II Diet	871.7	139.9	194.7	17.1
Normal Diet	865.5	146.7	214.2	11.9
0.2% II Diet	869.3	133.6	204.2	13.6

Experimental Condition	Kidneys	Heart	Thymus	Thyroid
Normal Diet	787.3	327.1	107.4	5.97
0.1% II Diet	838.1	300.4	90.1	6.13
Normal Diet	754.3	271.5	88.7	4.48
0.2% II Diet	829.5	284.7	116.7	4.49

The organ weight measurements for the control and the experimental animals in both experiments are shown in Table 2. There was a definite increase in the kidney size in both experiments and a decrease in the heart size in one experiment. The results as to the size of the thymus gland were inconsistent in each experiment, and very little is known about this gland. None of the data from the other organs revealed anything significant. The data we have obtained do not permit us to evaluate adequately the physiological effects of II, but further work with all three compounds (I, II, and III) seems desirable.

Experimental

Reaction of 1-(p-toluidino)-3-chloro-2-propanol with amines.— The halide (20 g., 0.1 mole) and the amine (0.4 mole) were dissolved in 1,2,4-trichlorobenzene (200 ml.) and heated for four hours at 200°. Upon cooling most of the product precipitated together with some hydrochloride salt of the amine. The mother liquor was extracted with 10% HCl, and neutralization of the acidic extract gave additional product. The initial precipitate was stirred with water and neutralized. The product from both fractions was recrystallized from ethanol. (I, m.p. 114.5-115.5°; II, m.p. 136-137°; III, m.p. 111-112°.)

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A New Synthesis of N-Substituted Pyrroles[1]

Richard Watts and F. C. Pennington[2]

Abstract. The reaction of 1,2-dibromo-3,4-epoxybutane with p-toluidine and p-benzyloxyaniline led to the synthesis of p-tolylpyrrole and p-benzyloxyphenylpyrrole. We have studied the synthesis involving p-toluidine by means of infrared spectroscopy and colorimetrically by reaction of the pyrrole with acidic dimethylaminobenzaldehyde. The reaction is best carried out by using three moles of amine to one mole of epoxide. This method of synthesizing N-substituted pyrroles compares favorably with other published methods.

It was found that when 1,2-dibromo-3,4-epoxybutane(I) was treated with p-benzyloxyaniline in bromobenzene at room temperature for four days, followed by 36 hours of reflux in bromobenzene in the presence of diethylaniline, a small yield of N-p-benzyloxy phenylpyrrole was recovered. This led to a closer study of the reaction using p-toluidine as the amine.

When a 1:1 molar ratio of p-toluidine to the epoxide was used, trace amounts of a product believed to be the N-p-tolylpyrrole (II) was recovered. In order to establish its structure, authentic II was prepared by condensing p-toluidine with mucic acid (III). Isolation in this experiment and in other experiments was accomplished by means of alumina chromatography. This was aided by a convenient analytical method using acidic dimethylaminobenzaldehyde. Mixed melting point determination and

[1] This work was supported by an NSF-URP grant.

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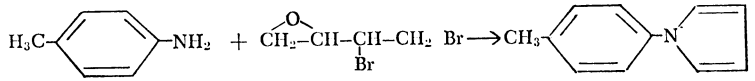
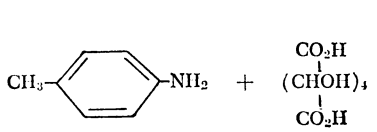
identical infrared spectra established the structure of our product as II.



I II



III

Additional study showed that the reactants could be mixed and heated directly without allowing for a presumed slow addition of the amine to the epoxide to take place before cyclization was initiated. Furthermore, better results could be obtained by using a 3:1 molar ratio of amine to epoxide.

This reaction resembles the synthesis of N-substituted pyrroles formed by condensing amines with 1,2,3,4-tetrabromobutane. (1) Our preliminary results indicate that this new method of synthesizing N-substituted pyrroles is at least as convenient as other published methods.(1,2) We are still evaluating the relative yields and general applicability of the new synthesis.

Experimental

N-p-Tolylpyrrole.—p-Toluidine (8g, 00.75 moles) was melted in a 90° oil bath. 1,2-Dibromo-3-4-epoxybutane (5.74g, 0.025 moles) was added dropwise to the molten amine. When the reaction subsided, the mixture was diluted with 100 ml. of benzene and refluxed for 2 hours. The mixture was washed with 5% HCl, 5% $NaHCO_3$, and water, and dried over anhydrous sodium sulfate. The benzene extract was passed over an alumina column and eluted with benzene. The product was recrystallized from dilute ethanol to yield 0.4 g of the product, m.p. 77-81°.

A recrystallized sample of this product was compared directly to N-p-tolylpyrrole which was obtained by distilling a mixture of mucic acid and p-toluidine and chromatographing the distillate over alumina using benzene as the eluant. A mixed melting point gave no depression. Both samples gave identical infrared spectra and revealed no absorptions in the 2.5μ-3.0μ region.

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