seedlings several series were grown simultaneously containing insulin, Abel's insulin, synthalin, Glukhorment and myrtillin, respectively.

Table VII records the results of this comparative study:

TABLE VII.

| Substance. | Concentration. | Percentage growth. |
|---|---|---|
| Insulin | 8.5 U per 100 cc. | 64.9 |
| | 17 U per 100 cc. | 58.5 |
| Abel's Crystalline Insulin | 0.3 mg. per 100 cc. | 87.0 |
| Synthalin | 0.3 mg. per 100 cc. | 76.8 |
| Glukhorment | 0.3 mg. per 100 cc. | 78.5 |
| Myrtillin | 0.3 mg. per 100 cc. | 93.5 |

In the concentrations employed myrtillin is the least toxic to the seedlings, whereas the guanidine compounds are exceedingly toxic. The commercial insulin 8.5 U per 100 cc. contained (on the basis of Abel's crystalline insulin) approximately 0.2 mg. This would seem to indicate that the extractive material in the insulin preparation, other than insulin, was quite toxic to the seedlings.

## CONCLUSIONS.

*1.* The action of certain hypoglycemic drugs upon the seedlings of lupinus albus has been studied.

*2.* Certain comparisons of toxicity of these drugs to plant protoplasm have been pointed out.

## REFERENCES.


*1.* M. M. Ellis and W. H. Eyster, *Science*, 58 (1923), 541.
*2.* M. M. Ellis and W. H. Eyster, *J. Gen. Phys.*, 6 (1924), 653.
*3.* D. I. Macht and M. B. Livingston, *Ibid.*, 4 (1922), 573.
*4.* D. J. Macht and J. C. Krantz, Jr., JOUR. A. PH. A., 16 (1927), 211.
*5.* J. W. Shive, *Physiol. Researches*, 1 (1915), 327.
*6.* J. J. Abel, *et al.*, *J. Pharm. and Exptl. Therap.*, 31 (1927), 65.
*7.* Frank, Nothmann and Wagner, *Klin. Wochsch.* (1925), No. 45.
*8.* H. Staub and O. King, *Ibid.*, 7 (1928), 1365.
*9.* Nothmann and Wagner, *Ibid.*, 7 (1928), 1996; through *Am. J. Med. Sciences*, 177 (1929), 730.
*10.* E. B. Salem and T. Nyren, *Acta. Med. Scand. Bd.*, 69 (1928), 69.
*11.* F. M. Allen, *Am. J. Physiol.*, 81 (1927), 462.



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# AMINO ALCOHOLS IV.

## POTENIOMETRIC MEASUREMENTS OF CERTAIN HOMOLOGUES OF EPHEDRINE.


BY JOHN C. KRANTZ, JR., AND WALTER H. HARTUNG.


## INTRODUCTION.

Since the introduction of ephedrine into the practice of medicine by Chen and his associates (1 and 2) and the synthesis of this alkaloid by Fourneau and Kanao (3) many of its homologues and analogues have been studied chemically, pharmacologically and clinically. (Adams, *et al.* (4) and others have prepared several of the homologues of ephedrine and studied their action upon blood-sugar

and also their pressor activity.) Miller and Piness (5) have studied phenylethanolamine clinically, and recommended it as a substitute for ephedrine.

One of us (W. H.) (6) has prepared several of the homologues of ephedrine in these laboratories and some of these exhibit definite pharmacological reactions. The availability of this series of homologous amino alcohols offered itself as an opportunity to compare the dissociation constants of these bases, and to initiate a study of physical characteristics as related to pharmacological behavior.

## EXPERIMENTAL.

The hydrochlorides of several of the amino alcohols were prepared and purified as described elsewhere. Tenth molar solutions of these compounds were prepared and their hydrogen-ion concentrations determined by the Wilson (7) hydrogen electrode.

Table I records the results of these determinations.

TABLE I.

| Amino alcohol salt. | $[H^+]$ in 0.1 *M.* sol. | $P_H$ in 0.1 *M.* sol. |
|---|---|---|
| Phenylethanolamine hydrochloride | $1.03 \times 10^{-4}$ | 3.99 |
| Phenylpropanolamine hydrochloride | $2.51 \times 10^{-5}$ | 4.60 |
| Phenylbutanolamine hydrochloride | $2.56 \times 10^{-5}$ | 4.59 |
| Phenylpentanolamine hydrochloride | $2.95 \times 10^{-5}$ | 4.53 |
| Diphenylethanolamine hydrochloride | $1.34 \times 10^{-4}$ | 3.87 |
| *p*-Tolylpropanolamine hydrochloride | $2.68 \times 10^{-5}$ | 4.57 |
| *p*-Tolylbutanolamine hydrochloride | $2.26 \times 10^{-5}$ | 4.64 |
| *p*-Hydroxylphenylpropanolamine hydrochloride | $2.04 \times 10^{-5}$ | 4.69 |
| Phenylpropanolmethylamine hydrochloride | $7.76 \times 10^{-6}$ | 5.11 |

From these data the degree of hydrolysis of the hydrochlorides of the amino alcohols were calculated by the following formula.

$$\frac{[H^+] \times 100}{A \times C} = \text{per cent hydrolysis.}$$

A = the degree of ionization of the strong acid in 0.1 *M.* solution or 0.92.
C = the molar concentration of the salt.

These data are recorded in Table II.

TABLE II.

| Amino alcohol salt. | Percentage hydrolyzed in 0.1 *M.* sol. |
|---|---|
| Phenylethanolamine hydrochloride | $11.2 \times 10^{-2}$ |
| Phenylpropanolamine hydrochloride | $2.72 \times 10^{-2}$ |
| Phenylbutanolamine hydrochloride | $2.78 \times 10^{-2}$ |
| Phenylpentanolamine hydrochloride | $3.20 \times 10^{-2}$ |
| Diphenylethanolamine hydrochloride | $14.5 \times 10^{-2}$ |
| *p*-Tolylpropanolamine hydrochloride | $2.91 \times 10^{-2}$ |
| *p*-Tolylbutanolamine hydrochloride | $2.45 \times 10^{-2}$ |
| *p*-Hydroxylphenylpropanolamine hydrochloride | $2.21 \times 10^{-2}$ |
| Phenylpropanolmethylamine hydrochloride | $8.43 \times 10^{-2}$ |

Some of the free base phenylpropanolamine and also phenylpropanolmethylamine, or ephedrine base, were prepared and dissolved in water preparing 0.1 *M.* solutions, respectively.

The hydrogen-ion concentrations of these solutions were measured.

1. Phenylpropanolamine—0.1 *M.* solution $p_H$ 10.32
2. Phenylpropanolmethylamine—0.1 *M.* solution $p_H$ 10.76

From the hydrogen-ion concentrations of the hydrochlorides of these bases in 0.1 *M.* solution the dissociation constants of the bases were calculated. The following formula (8) was employed.

$$K_b = \frac{[C] \times K_w}{[H^+]^2}$$

The hydrogen-ion concentration of phenylpropanolamine hydrochloride in 0.1 *M.* solution is $2.51 \times 10^{-5}$ and $K_b = 1.6 \times 10^{-6}$. The hydrogen-ion concentration of phenylpropanolmethylamine hydrochloride in 0.1 *M.* solution is $7.76 \times 10^{-6}$ and $K_b = 1.7 \times 10^{-5}$. By colorimetric methods Abildgaard and Rasmussen (9) found the dissociation constant for this compound (*l*-ephedrine) to be $2.3 \times 10^{-5}$.

## CONCLUSIONS.

*1.* The hydrogen-ion concentration of the hydrochlorides of certain homologues of ephedrine has been determined.

*2.* The degrees of hydrolysis have been calculated.

*3.* The hydrochlorides of phenylethanolamine and diphenylethanolamine exhibit a higher hydrogen-ion concentration than the hydrochlorides of those amines having a greater number of carbon atoms in the side chain.

*4.* No marked relationship between the physical measurements determined and the pharmacological behavior was observed.

## BIBLIOGRAPHY.

(1) Chen and Schmidt, *J. A. M. A.*, 87 (1926), 836.
(2) Middleton and Chen, *Arch. Internal Med.*, 34 (1927), 385.
(3) Fourneau and Kanao, *Bull. soc. chim.*, 35 (1924), 614.
(4) R. Adams, *et al.*, *J. Am. Chem. Soc.*, 50 (1928), 2287.
(5) Miller and Piness, *J. A. M. A.*, 91 (1928), 1033.
(6) Hartung and Munch, *J. Am. Chem. Soc.*, 51 (1929), 2262.
(7) Wilson, *Ind. Eng. Chem.*, 17 (1925), 74.
(8) L. Michaelis, "Hydrogen-Ion Concentration," Waverly Press, Baltimore, Md.
(9) J. Abildgaard and H. B. Rasmussen, *Dansk Tids. Farm.*, 4 (1930), 30.

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**The Seventy-Ninth Annual Meeting of the AMERICAN PHARMACEUTICAL ASSOCIATION will be held in Miami, Florida, in 1931. The 1932 Meeting (the 80th) will be held in Canada, jointly with the Canadian Pharmaceutical Association.**