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Inactivity of Coramine (Nikethamide) for *L. arabinosus* and its Conversion to an Active Substance.

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The question of relative activities of various derivatives of nicotinic acid for *L. arabinosus* and for animals has been brought to the front by the discovery of a substance in wheat bran and in certain other materials which is inactive for *L. arabinosus* but is made active by very mild alkali treatment or moderately strong treatment with acid.[1,2] This situation has led to some feeling of unrest in regard to the validity of assay results obtained with *L. arabinosus* using alkali or acid treatment of the samples. Studies to date[3,4] indicate that the animal can utilize derivatives of nicotinic acid more readily than can *L. arabinosus*. The results of the present study support this finding.

Since nikethamide (pyridine β-carboxylic acid diethyl amide) has been found to be quite active for dogs and humans,[5,6,7] we tested it on *L. arabinosus* and obtained 0.03% of the

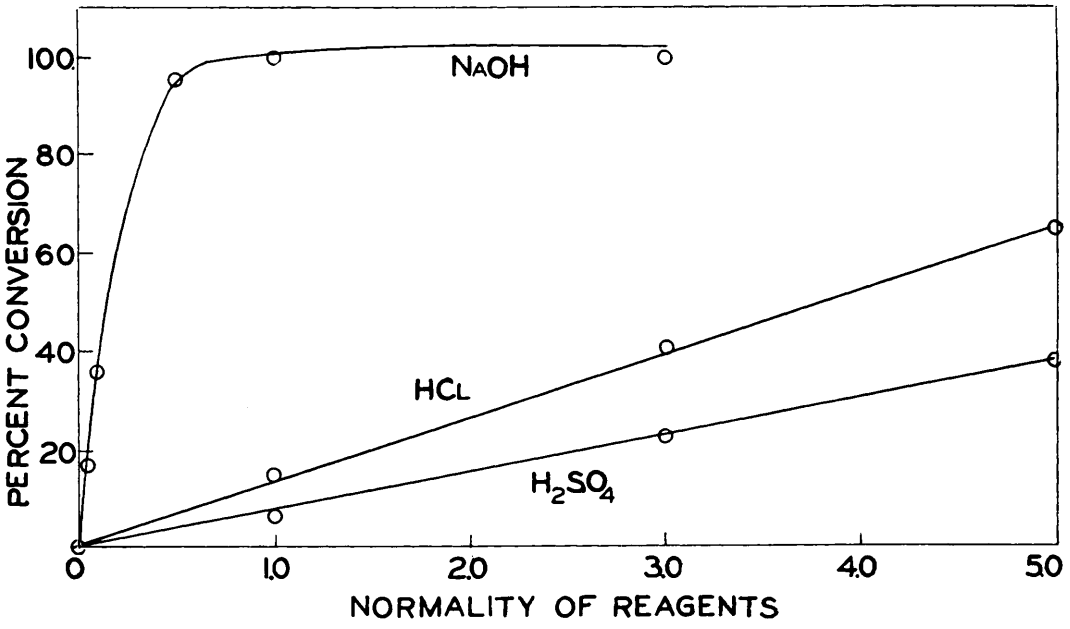

Fig. 1.

Conversion of Coramine to an active substance for *L. arabinosus* by autoclaving 1 hr at 15 lbs with NaOH, HCl, and H_2SO_4.

1 Andrews, J. S., Boyd, H. M., and Gortner, W. A., *Ind. and Eng. Chem., Anal. Ed.*, 1942, **14**, 663.

2 Cheldelin, V. H., and Williams, R. R., *Ind. and Eng. Chem., Anal. Ed.*, 1942, **14**, 671.

3 Elvehjem, C. A., and Teply, L. J., *Chem. Rev.*, in press.

4 Glenn, R. A., Hill, N. C., and Neubeck, V. H., Abs. of papers presented at A. C. S. meeting, Biol. Div., Sept., 1943.

5 Wooley, D. W., Strong, F. M., Madden, R. J., and Elvehjem, C. A., *J. Biol. Chem.*, 1938, **124**, 715.

6 Spies, T. D., Bean, W. B., and Stone, R. E., *J. Am. Med. Assn.*, 1938, **111**, 584.

7 Smith, D. T., Margolis, G., and Margolis, L. H., *J. Pharmacol.*, 1940, **68**, 458.

activity of an equimolar amount of nicotinic acid. This activity may be due to impurities or slight conversion during sterilization. Glenn *et al.*[4] have reported nikethamide to be inactive for this organism. Dorfman *et al.*[8] have found it to be slightly active for *dysentery bacilli*, while Knight[9] and Landy[10] have found it inactive for *Staph. aureus*.

[8] Dorfman, A., Koser, S. A., Reames, H. R., Swingle, K. F., and Saunders, F. J., *J. Inf. Dis.*, 1938, **65**, 163.

[9] Knight, B. C. J. G., *Biochem. J.*, 1938, **32**, 1241.

[10] Landy, M., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 504.

The compound was autoclaved for one hour with various concentrations of NaOH, HCl, and H_2SO_4 at 15 pounds and the resulting mixtures were assayed with *L. arabinosus*. The results summarized in Fig. 1 show that NaOH is most effective, while HCl is somewhat more potent than H_2SO_4 in converting nikethamide to an active compound. Nikethamide is less easily converted to active material than is the "precursor" found in wheat bran, since autoclaving with 0.1 N NaOH, 1 N HCl, or 1 N H_2SO_4 seems to bring about 100% conversion of the latter substance.

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Mechanism of the Diabetogenic Action of Alloxan.*

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Alloxan has been found to produce sustained diabetes mellitus in rats, rabbits, and dogs (Shaw-Dunn and McLetchie,[1] Goldner and Gomori,[2,3] Bailey and Bailey[4]). This diabetes is due to degeneration of the beta cells in the islets of Langerhans (Shaw-Dunn, Sheehan and McLetchie[5]) and consequently to the decrease of insulin production (Goldner and Gomori[6]).

Prior to the establishment of the diabetic syndrome the blood sugar of the rabbit shows a characteristic biphasic reaction, which was first described by Jacobs.[7] An immediate hyperglycemia which reaches its peak within 2 or 3 hours is followed by a severe, often fatal, hypoglycemia, which after a duration of 15 to 20 hours yields to the ultimate hyperglycemia and glycosuria. The hypoglycemic phase is explained by Shaw-Dunn and coworkers[5] as the effect of large amounts of insulin, which are released suddenly from the degenerating beta cells. The phenomenon of the initial hyperglycemia raises the question whether alloxan inhibits insulin before it destroys the site of insulin production. It seemed, therefore, of interest to investigate the question whether insulin is able to prevent the initial rise of the blood sugar after alloxan poisoning and also whether insulin can protect the beta cells against alloxan injury. The latter problem seemed of special interest, since it has been found that insulin treatment and the maintenance of a normal blood sugar level will protect animals against the diabetogenic effect of anterior pituitary

* This work was supported by grants from the Douglas Smith Foundation of the University of Chicago and Eli Lilly and Company, Indianapolis, Indiana.

[1] Shaw-Dunn, J. S., and McLetchie, N. G. B., *Lancet*, 1943, **2**, 384.

[2] Goldner, M. G., and Gomori, G., *Endocrinology*, 1943, **33**, 297.

[3] Gomori, G., and Goldner, M. G., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 287.

[4] Bailey, C. C., and Bailey, O. T., *J. A. M. A.*, 1943, **122**, 1165.

[5] Shaw-Dunn, J. S., Sheehan, H. L., and McLetchie, N. G. B., *Lancet*, 1943, **1**, 484.

[6] Goldner and Gomori, to be published in *Endocrinology*.

[7] Jacobs, H. R., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 407.