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# Toxicity of Nicotinic Acid and Some of Its Derivatives.

FRED G. BRAZDA AND R. A. COULSON.

*From the Department of Biochemistry, Louisiana State University School of Medicine, New Orleans.*

Handler and Dann[1] observed that the incorporation of large amounts of nicotinamide into the diet caused a decreased growth rate in young rats whereas nicotinic acid and trigonelline had little effect. It was concluded that the decreased growth rate was due to the depletion of the stores of methionine (which was deemed essential for the methylation of nicotinamide) since in the process of detoxication nicotinamide was methylated and excreted as what appeared to be trigonelline. Later investigations[2] indicate that the principal detoxication product is more probably nicotinamide methochloride ($N^1$-methylnicotinamide).

The marked toxicity of nicotinamide when administered subcutaneously leads one to suspect that the molecule itself exerts a toxic action which is independent of the effect of the compound on the depletion of the stores of "methyl donors." To determine the influence of molecular configuration on toxicity highly purified preparations of pyridine, nicotinic acid (as the sodium salt), nicotinamide, coramine (N,N-diethylnicotinamide), and the respective methyl derivatives of these compounds were administered subcutaneously to young rats of both sexes weighing between 50 and 100 g. The dose needed to kill one-half of the animals in each group was determined. The results appear in Table I.

TABLE I.
Relative Toxicity of Some Derivatives of Pyridine (Subcutaneous Injection).

| | $LD_{50}$* g/kilo | Relative-order of toxicity |
|---|---|---|
| Pyridine | 1.00 | 5.00 |
| Pyridine methochloride | 0.28 | 17.9 |
| Nicotinic acid | 5.0 | 1.0 |
| Trigonelline | 5.0 | 1.0 |
| Nicotinamide | 1.68 | 3.0 |
| Nicotinamide methochloride | 2.40 | 2.08 |
| Coramine | 0.24 | 20.8 |
| Coramine methochloride | 1.90 | 2.63 |

* $LD_{50}$ = dose needed to kill one-half of the animals.

Methylation decreases the toxicity of coramine and nicotinamide, increases the toxicity of pyridine and has little or no apparent influence on the toxicity of nicotinic acid. It is certain that methylation is not the only factor concerned in the toxicity of these compounds since nicotinamide methochloride is more toxic than nicotinic acid. If pyridine is methylated in the rat as it is in the dog[3] this is an example of the conversion of a toxic compound into one which is even more toxic in the process of "detoxication."

Nicotinamide, coramine and the methyl derivatives of these compounds cause paralysis of the respiratory center when administered in large doses. The injection of pyridine and pyridine methochloride in amounts slightly below the lethal dose produced a deep anesthesia of about 2 hours' duration. These compounds had no apparent effect on respiration. Trigonelline and nicotinic acid have such a low order of toxicity that an accurate estimation is impossible since in the massive doses employed the principal effect may be due to the administration of large amounts of hypertonic solutions.

With regard to the effect of the configura-

[1] Handler, P., and Dann, W. J., *J. Biol. Chem.*, 1942, **146**, 357.

[2] Huff, J. W., and Perlzweig, W. A., *Science*, 1943, **97**, 538; Ellinger, P., and Coulson, R. A., *Nature*, London, 1943, **152**, 383.

[3] His, W., *Arch. exp. Path. u. Pharm.*, 1887, **22**, 253.

tion on the $\beta$ position of pyridine it is evident that the presence of the carboxyl group decreases the toxicity of the molecule. Conversion of this group to the simple amide markedly increases toxicity; the presence of a substituted amide on this position increases the toxicity so that it exceeds that of the unsubstituted pyridine. The high toxicity of coramine suggests the necessity for caution in its administration.

*Summary.* The relative toxicity of subcutaneous injections of nicotinic acid, nicotinamide, coramine, pyridine and their respective methyl derivatives has been determined. Methylation decreases the toxicity of coramine and nicotinamide, increases the toxicity of pyridine and has little or no apparent influence on the toxicity of nicotinic acid. The toxicity of the non-methylated compounds appears to be due directly to the structure of the compounds rather than to the depletion of the body stores of methyl donors in the process of detoxication.

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## Distribution of 2,2 (p-Chlorophenyl) 1,1,1 Trichlorethane (DDT) in Tissues of Rats after Its Ingestion.*

STEPHAN LUDEWIG AND ALFRED CHANUTIN. (Introduced by H. E. Jordan).

*From the Biochemical Laboratory, University of Virginia, Charlottesville.*

The data for the distribution of DDT in tissues of experimental animals fed DDT are limited. Smith and Stohlmann[1,2] analyzed blood, kidney, liver, central nervous-system and bile after acute and chronic poisoning in rabbits and cats by determining organic chloride. The highest DDT concentration was observed in the bile. Laug[3] determined the DDT concentration in tissues of rats fed on diets containing small amounts of DDT for periods varying from 6 months to 2 years. By far, the greatest amount of DDT was found in perirenal fat. In spleen, liver and kidney, the amount of DDT stored appeared to be roughly proportionate to the amount of total ether extractable-material in these organs. Woodward[4] studied the DDT concentrations in tissues of a chronically poisoned dog, monkey, pig and turkey. The highest concentration of DDT was found in fat; the adrenals of the dog and the monkey contained appreciably larger amounts of DDT than the liver, kidney and brain.

The distribution of DDT in the brain, liver, kidney and adrenals of rats fed diets containing 0.1 and 0.2% DDT was determined at frequent intervals.

*Methods.* Inbred male rats of Wistar stock, 60 to 70 days old, and weighing 150-200 g were used as experimental animals. They were maintained on a stock diet until the experimental diet was fed. The diet contained 20% casein (Labco), 8% crisco, 4% inorganic salt,[5] 65% sucrose, 2% agar, vitamin supplements and 0.1 or 0.2% DDT (M.P. 108.6-109.5°). The animals were fed *ad libitum* and were sacrificed at frequent intervals. After nembutal injection, the animals were exsanguinated and the tissues immediately removed for the DDT determination.

The tissues were prepared for analysis according to Ofner's[6] recommendation and the

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1 Smith, M. I., and Stohlman, E. F., *Pub. Health Rep.*, 1944, **59**, 984.

2 Smith, M. I., and Stohlman, E. F., *Pub. Health Rep.*, 1945, **60**, 289.

3 Laug, E. P., personal communication.

4 Woodward, G., personal communication.

5 Osborne, T. B., and Mendel, L. B., *J. Biol. Chem.*, 1913, **15**, 317.

6 OSRD Insect Control Committee, Report No. 65.