S. a.c.3. ANNAM CHACKO, P.–Studies on the Synthesis and CNS Activity of Strychnine Derivatives–1987–Dr. P. Madhavan Pillai.

Strychnine, the major alkaloid present in Strychnos nuxvomica seeds has been reported to stimulate the entire central nervous system with preferrence for the spinal cord. It is a powerful convulsant and because of this property, it is an important pharmacological tool as it plays a unique role as an inhibitor of post synaptic inhibitory impulses. It is useful to study inhibitory transmitter and receptor types. However, because of its extremetoxicity, strychnine does not have any therapeutic application in the Western system of medicine.

The present work was undertaken with a view to obtaining strychnine derivatives having CNS stimulating properties but with sufficiently low toxicity so that they may eventually find some application in medicine. As nuxvomica seeds, its possible utilization in therapeutics will have considerable commercial significance.

A number of derivatives of strychnine were prepared. These included products with nitro, amino, acetamido, bromo and sulphonamido groups introduced at the 2 position by electrophilic aromatic substitutions and subsequent chemical conversions as required. Also reduction of the amide carbonyl group at position 10 using lithium aluminium hydride provided strychnine. Treatment of strychnine with benzaldehyde and substituted benzaldehydes yielded derivatives with benzylidene groups attached at 11-position. Similarly an oxime was obtained at this position by reaction with amylnitrite. Catalytic hydrogenation of strychnine in the presence of palladium of carbon provided the known 21-22 dihydrostrychnine which on nitration gave another derivative having nitrogroup at 2-position and with the 21,22 double bond saturated. The structures of all new compounds were established with the help of spectral data and elemental analysis. Finally a reaction of strychnine with chloroform in the presence of benzoyl peroxide yielded a trichloromethyl derivative, but the exact position of this group has not been determined. These reactions have thus yielded structural analogues of strychnine with modifications at the aromatic ring and at position 10,11 and 21-22.

There have been reports that the N-oxides of alkaloids generally modify their pharmacological properties and the N-oxide of strychnine (known as genostrychnine) is less toxic and less convulsive than strychnine itself. However, strychnine N-oxide is not being used as a therapeutic agent now probably because of the threat of convulsions at higher doses. All the derivatives of strychnine which were prepared as mentioned earlier were, therefore, converted into their N-oxides by well established procedures. Brucine N-oxide was also prepared from brucine for the same type of comparative studies.

Pharmacological studies were carried out on the derivatives of strychnine and

their N-oxides. These experiments were conducted systematically on frogs weighing 40-100 g. Each does was given to a number of frogs as uniform suspension and equimolar quantities were administered and strychnine was kept as control.

Generally, the N-oxides of all compounds were less toxic and most of them showed no convulsions in accordance with earlier reports. The nitro, bromo and amino substituents at 2-positions of strychnine did not substantially change the pharmacological activity. 2-amino strychnine, 2-acetamidostrychnine and its N-oxides manifested muscle relaxant properties as well. The acetamido derivative and its N-oxide were less toxic and did not exhibt strychnine type convulsions or toxicity.

The introduction of the biologically important sulphonamido group also reduced the toxicity of the strychnine molecule and the N-oxide further decreased the toxicity as expected. Although the benzaldehyde condensation product at position 11 showed increased toxicity and convulsive property, substituted benzaldehyde condensation products provided compounds with substantially lower toxicity compared to strychnine. Their N-oxides were found to have further decreased toxicity with a similar effect on the convulsant activity. The 11-oximino derivative and its N-oxide also had reduced toxicity. Saturation of the double bond at the 21,22 position made the molecule more toxic and produced stronger convulsions. These effects were demonstrated both by dihydrostrychnine and the 2-nitrodihydro-strychnine. The N-oxides of the saturated derivatives also had correspondingly increased toxicity compared to their unsaturated analogues.

One of the products with lowest toxicity was the trichloromethyl derivative and it produced only very minor convulsions on frogs. The toxicity and convulsive property was further decreased when the trichloromethyl derivative was converted into its N-oxide. A complete pharamacologgical screening of these compounds are required for their further biological evaluation.

This work has provided several new compounds which are significantly less toxic than strychnine and its N-oxide as shown from the pharmacological studies. A they also possessed CNS stimulating properties, they are well suited for further screening to assess their potential as valuable therapeutic agents.