BIOTRANSFORMATION OF (+)-RETICULINE INTO (+)-COREXIMINE WITH RAT LIVER

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The biotransformation of (+)-reticuline (I) into (+)-coreximine (2) in the rat and with homogenised rat liver was demonstrated by tracer experiments with (+)-[N-\(^{14}\)CH\(_3\)]reticuline (1).

In connection with our interest in the biotransformation of isoquinoline alkaloids with animal tissue, we previously reported that (+)-reticuline (I), an important precursor in the biogenesis of opium alkaloids such as berberine, morphine, aporphine, benzophenanthridine and phthalideisoquinoline alkaloids,\(^1,2\) was transformed by rats into coreximine (2), identified by the mass spectrometry and a gas chromatography.\(^3\) We now wish to report, based on tracer studies with (+)-[N-\(^{14}\)CH\(_3\)]reticuline (1), that the enzymes of the rat liver were responsible for the transformation and that interestingly enough the isolated coreximine (2) proved to be the racemate.

(+)-[N-\(^{14}\)CH\(_3\)]Reticuline (1) was prepared by the reductive alkylation of (+)-O,O-dibenzynorreticuline (3)\(^4\) with \(^{14}\)C-formalin and sodium borohydride in methanol followed by debenzylation of (+)-[N-\(^{14}\)CH\(_3\)]O,O-dibenzylreticuline (4) with a mixture of concentrated hydrochloric acid and benzene.\(^5\) By reverse dilution analysis and t.l.c. it was demonstrated that the labelled product was almost free from tetrahydro-
protoberberines such as (±)-coreximine (2). A solution of (±)-[N\textsuperscript{-14}CH\textsubscript{3}] reticuline (1) hydrochloride (about 3 mg) in propylene glycol was administered to a female rat of Wistar strain by intraperitoneal injection. The collected urine was treated with β-glucuronidase, then diluted with (±)-coreximine (2) as a carrier and extracted to give a syrup which was purified by preparative t.l.c. and repeatedly recrystallized to constant activity. This experiment not only proved that (±)-reticuline (1) was transformed into (±)-coreximine (2) in 0.03 % yield but also confirmed our previous finding.

The biotransformation was further examined by incubating a 20 % homogenate of rat liver, prepared in phosphate buffer at pH 7.4 with a Potter-Elvejhem homogenizer, with (±)-[N\textsuperscript{-14}CH\textsubscript{3}] reticuline (1) at 37\textdegree for 2 hr. After dilution with (±)-coreximine (2), the product was worked up as above to give (±)-coreximine (2) which had incorporated 0.083 % of the radioactivity.

The stereochemistry of the coreximine which formed was determined by the comparing the total radioactivities of the pure product after dilution with either of the two optical isomers or the racemate of coreximine (2). Thus, after incubation, the resulting homogenate was equally separated into three fractions, to which (-)-, (+)- and (±)-coreximine (2) were added. After purification to constant activity, the total activity of the product from dilution with (±)-coreximine (0.09 % yield) was nearly twice that obtained from dilution with (-)- and (+)-coreximine (0.044 and 0.05 % yield), respectively.

It is interesting that the above enzymic transformation of reticuline (1) into coreximine was not stereospecific and may involve the imine (7) as an intermediate which could be formed from either the N-oxide (5) or (6) with a suitable leaving group. In order to determine the mechanism and detect other possible products, further experiments are in progress.
REFERENCES

7 The calculated yield = total disintegrations isolated in pure sample x 100
    total disintegration fed

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