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CONFIGURATION OF RETICULINE IN THE OPIUM POPPY

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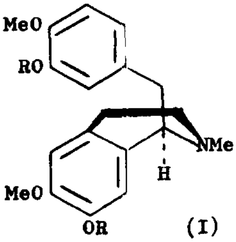
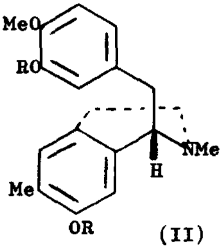
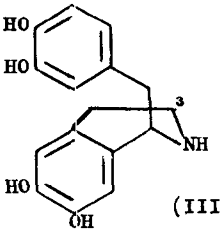
Labelled (±)-reticuline (as I, R=H) has been shown (1,2) to give rise in poppy plants to specifically labelled morphine alkaloids, e.g. thebaine (IV) and, further, (±)-reticuline has been isolated from crude opium (3). These results, when taken with the proof that (-)-reticuline (I, R=H) is the precursor of the morphine alkaloids in the living system (4,5) make it important to determine which epimer of reticuline predominates in opium poppy plants. To this end, (±)-[3-^{14}C]norlaudanosoline (III) was fed over short feeding periods to Papaver somniferum plants (4); it is known that labelled norlaudanosoline gives rise to specifically labelled morphine alkaloids (2). The total alkaloids of the plants were isolated by a method which was proved to extract reticuline, and the further examination of this mixture is outlined below.



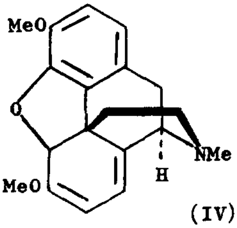
(I)



(II)



(III)



(IV)

(-)-Reticuline (I, R=H) (4) was ethylated with diazoethane to give (-)-*O,O*-diethylreticuline (I, R=Et), $[\alpha]_D^{20}$ -59.3° (c, 1.0 in $CHCl_3$). The (+)-isomer (II, R=H) similarly afforded (+)-*O,O*-diethylreticuline (II, R=Et), $[\alpha]_D^{20}$ +58.7° (c, 1.0 in $CHCl_3$). A small quantity of (-)-*O,O*-diethylreticuline (I, R=Et) multiply labelled with ^{14}C and ^{3}H was prepared by ethylation of the corresponding labelled reticuline (4) and this was mixed with a large excess of radio inactive (-)-*O,O*-diethylreticuline (II, R=Et). The crystalline picrolonate prepared from this mixture was recrystallised several times and a steady fall in the radioactivity of the picrolonate occurred. After three crystallisations, ca. 5% of the original activity was retained. This establishes that dilution analysis is applicable to (+)- and (-)-*O,O*-diethylreticulines in the following way.

The total alkaloids isolated above from the plants were divided into two halves. To one was added a known quantity of radio-inactive (+)-reticuline and the total mixture was O-ethylated with diazoethane. Chromatography of the products give radioactive O,O-diethylreticuline (9 mg.) which was diluted with radio-inactive (+)-O,O-diethylreticuline (60 mg.) and then crystallised several times as the picrolonate. A constant activity of 2.9 x 10^5 dis./100 sec./mmole. was reached after three crystallisation steps. The other half of the total alkaloids was treated in the same way, save that radio-inactive (-)-reticuline and (-)-O,O-diethylreticuline were substituted for the (+)-epimers at the appropriate points Five crystallisations of the picrolonate were necessary to achieve a constant activity of 4.3 x 10^4 dis./100 sec./mmole. The pool of (+)-reticuline thus carries over six times as much activity as the pool of (-)-reticuline. This result is in agreement with the isolation from opium by Brochmann-Hanssen and Nielson of reticuline which has an excess of the (+)-form; their results are reported in the preceding paper (6).

It has recently been shown (5) that five-day old poppy seedlings grown for 2.5 hr. in ^{14}C-carbon dioxide produce highly active reticuline. Some of this material was purified by thin layer chromatography and examined by dilution analysis as above. The total activities of the (+)-, and (-)-O,O-diethylreticulines so obtained were found to be equal within experimental error. This is in clear contrast to the results from opium and from mature poppies fed norlaudanosoline. A possible explanation for this difference might be the rapid conversion of (-)-reticuline into morphine alkaloids in flowering plants, as compared to a slower metabolism of the (+)-isomer. In seedlings, both isomers appear to be metabolized at an equal and rapid rate.

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