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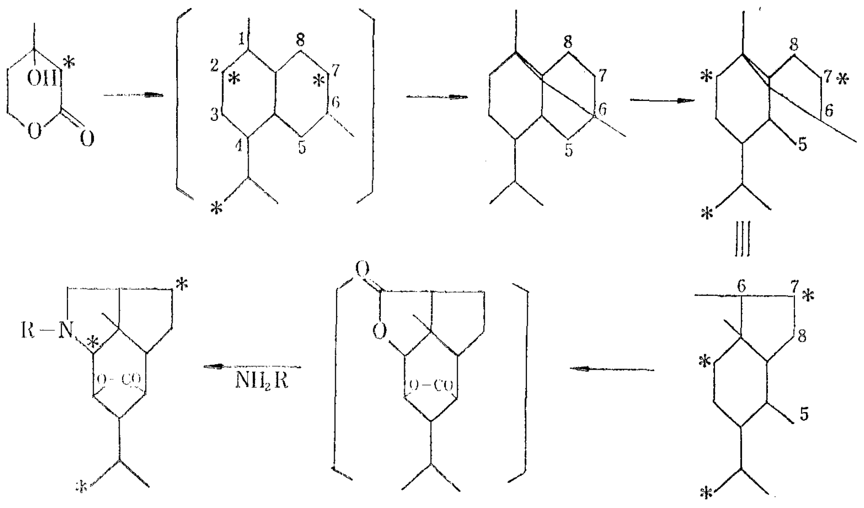
Biosynthesis of Dendrobine

Dendrobine, an alkaloid isolated from the Chinese drug "Chin Shi Hu" by Suzuki, *et al.* in 1932 has recently been studied by Japanese workers1~3) to establish the structure (I). It possesses fifteen carbon skeleton (except N-methyl group) and has an intimate structural correlation with the aglycones of several bitter glucosides, such as coriamyrtin,4) tutin5) or picrotoxinin6) isolated from the toxic Coriaria or Anamirta plants. Biogenetically, these bitter aglycones are seemed to be belonged to the sesquiterpenes and be derived from bisabolane (or cadalane) type precursors by the cleavage of C-C bond between C_5 and C_6. It seems also reasonable to assume that dendrobine would be formed biologically by the addition of ammonia (or methylamine) to this type of sesquiterpenes.



(I : $R=CH_3$)

In recent years, several reports have been published to elucidate the incorporation of mevalonic acid to the biosynthesis of some alkaloids. Benn and May7) have reported the biosynthesis of diterpene alkaloid, browniine from mevalonic acid though Herbert and Kirby8) have found on the other hand, that mevalonic acid was not incorporated into delphenine in *Delphenium elata.* McCapra, *et al.*9) and Goeggel, *et al.*10) have also found the incorporation of mevalonic acid into the indole alkaloids. These facts have led us to communicate the result of our experiment, in which the incorporation of mevalonic acid into dendrobine was observed.

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Sodium mevalonate-2-^{14}C (50 μc., 5.85 mg.) was administered into the stem of *Dendrobium nobile* by the cotton wick method and the plant (91 g., fresh weight) was harvested after 12 days. The radioactive dendrobine obtained (12 mg.) was purified by a silica gel column chromatography using benzene-methanol (25:2) as a solvent.

The radioactivity of dendrobine was measured with a liquid scintillation counter (Tri Carb 314 EX). The specific activity was 3.68×10^5 d.p.m./m*M* and the total incorporation ratio was 0.012%. The radioactive dendrobine was then oxidized with chromium trioxide in diluted sulfuric acid to afford acetic acid. Acetic acid obtained was converted to 1-acetoamidonaphthalene and purified by sublimation and recrystallization to measure the radioactivity. The specific activity of acetic acid was 2.93×10^4 d.p.m./m*M* (95.5% of theoretical).[*1]

A sufficient incorporation of mevalonic acid-2-^{14}C into dendrobine indicates that the biosynthesis of this alkaloid proceeds through the ordinary biosynthetic pathway of sesquiterpenes.

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[*1] The theoretical specific activity of acetic acid should be 3.06×10^4 d.p.m./m*M* on the assumption that acetic acid is equally derived from the methyl and isopropyl groups of dendrobine molecule by Kuhn-Roth oxidation.

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Convenient Synthesis of 6-(1-Acetyl-2-piperidyl)-6-hydroxy-2-cyclohexene-$\Delta^{1,\alpha}$-acetic Acid γ-Lactone, the Key Intermediate in Total Synthesis of Securinine

Recently, the total synthesis[1] of securinine (I)[2] has been accomplished starting from 1,2-cyclohexanedione monoethyleneketal[3] *via* the ketol (II)[4] and the lactone (V).[2] However, in that synthesis the yield from II to V was only ca. 0.5%. From the preparative point of view, another better route was sought for the synthesis of V. We have now found the following new route providing V in 36.7% overall yield from II.

The ketol (II)[4] was brominated with bromine in glacial acetic acid at 55~65° in the presence of hydrobromic acid to give the bromo-ketone (III), m.p. 169~170°, IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3472 (OH), 1718 (CO), 1629 (N-Ac), in 75% yield. Dehydrobromination of III by heating with lithium bromide and lithium carbonate in dimethylformamide at 120° for

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