Biosynthesis of the Ipecac Alkaloids and of Ipecoside, a Cleaved Cyclopentane Monoterpene

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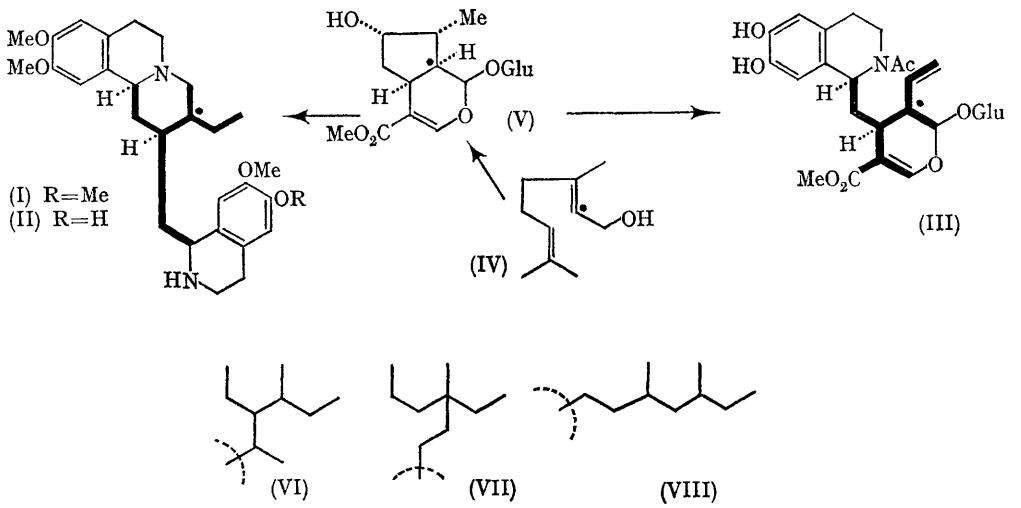
EMETINE (I) and cephaeline (II) differ from most isoquinoline alkaloids by possessing the C_{9-10} unit (thickened bonds) shown dissected in (VI) and there were early indications[1] that mevalonate is involved in the biosynthesis of (I) and (II). The residue (VI) as such or in rearranged state (VII and VIII) also forms the reduced portion of the indole alkaloids and here its monoterpenoid origin has been established.[2,3] Further, loganin (V) was recently proved to be a key intermediate between geraniol (IV) and representative examples from the three major groups of indole alkaloids.[4]

It was important to study the biosynthesis of cephaeline (II) and of a congener, ipecoside[5] (III), in *Cephaelis ipecacuanha* (a) to gain evidence for or against the view that loganin is of general importance as a precursor of the C_{9-10} unit and (b) to establish that ipecoside is formed from loganin by cleavage[6] of the cyclopentane ring.

[2-^{14}C]Geraniol (IV) was administered to *C. ipecacuanha* plants which then afforded radioactive cephaeline (II; 0·015% incorp.) and ipecoside (III; 0·038% incorp.). The former was converted into emetine *N*-phenylurea and oxidised (Kuhn–Roth) as earlier[1] to give propionic acid (98% of total activity) and radio-inactive acetic acid. Dihydroipecoside (as III; vinyl group reduced) was similarly degraded to propionic acid (101% of total activity) and inactive acetic acid. Both substances (II) and (III) are thereby proved to



be specifically labelled at the indicated positions and their monoterpenoid origin is established.

[O-*methyl*-^{3}H]Loganin[4] was incorporated by the plants into ipecoside (1·7% incorp.) and Zeisel determination showed all of the activity (104%) was located at the *O*-methyl group. Rigorous proof that loganin acts as precursor of ipecoside and cephaeline was obtained by feeding [O-*methyl*-^{3}H; 2-^{14}C]loganin to the plants (ratio ^{3}H:^{14}C, 8·99); the [2-^{14}C]loganin was prepared biosynthetically.[4] Radioactive ipecoside (1·9% incorp.) and cephaeline (0·97% incorp.) were isolated which, respectively, showed ^{3}H:^{14}C ratios of 6·8 and 0·93. Thus, most of the labelled *O*-methyl group is retained, relative to the internal ^{14}C standard (76% retention), during the biological conversion of loganin into ipecoside but, as expected, is largely lost (10% retention) when cephaeline is formed. The residual ^{3}H-activity of cephaeline was shown (Zeisel) to be entirely present in the *O*-methyl groups. Kuhn–Roth degradation of dihydroipecoside, prepared from the active ipecoside, gave radio-inactive acetic acid and ^{14}C-active propionic acid which because of the small quantity available could not be entirely freed from radio-inactive impurities. At this stage, its molar activity corresponded to 86% of the molar activity of ipecoside in agreement with specific ^{14}C-labelling at the indicated position (see III).

These results establish that the C_9-unit of the Ipecacuanha alkaloids and the C_{10}-unit of ipecoside are of monoterpenoid origin from geraniol and that loganin (V) acts as a specific precursor of both systems. Ipecoside is thus a seco-cyclopentane monterpene and its ready availability allows the mechanism of the cleavage reaction to be studied. This is postulated[3] to occur by fragmentation of hydroxyloganin. It is probable that many other seco-cyclopentane systems are derived from loganin; *inter alia* gentiopicrin,[7] swertiamarin,[8] sweroside,[8] and bakankosin[9] all warrant study with labelled loganin.

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