Investigation of the Role of Chrysanthemyl, Lavandulyl, and Artimisyl Alcohols in the Biosynthesis of Chrysanthemic Acid

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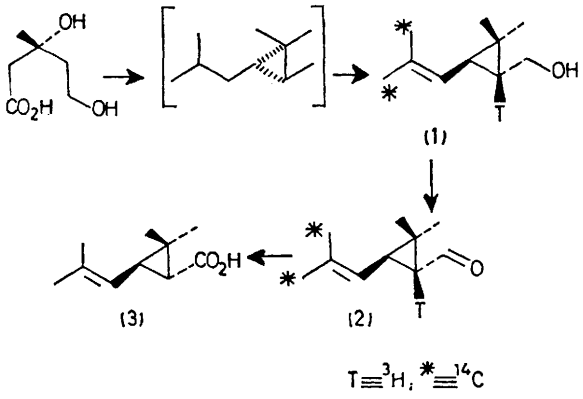
Summary Feeding and trapping experiments in *Chrysanthemum cinerariaefolium* have established that chrysanthemyl alcohol (**1**) is an intermediate in the biosynthesis of chrysanthemic acid (CA) (**3**), whereas lavandulol (**6**) and artimisyl alcohol (**7**) were not incorporated.

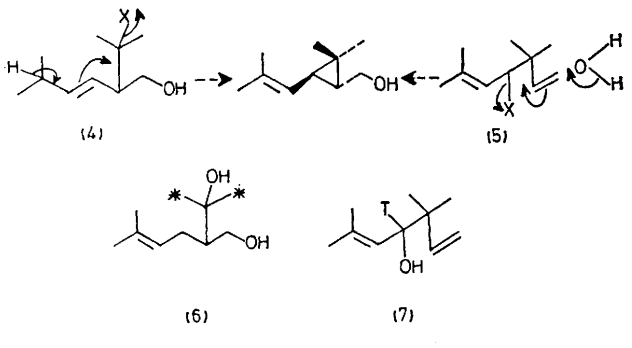
THE monoterpene chrysanthemic acid (CA) (**3**) which is found as esters in *Chrysanthemum cinerariaefolium*, bears a close structural similarity to presqualene and prephytoene, probable biogenetic intermediates in the biosynthesis of squalene and phytoene respectively. Interest in the biosynthesis of these natural cyclopropanes centres largely on the irregular 'tail-to-middle' combination of isoprenoid units found in their structures, and in the mechanism whereby this unusual combination is accomplished.[1,2] The biogenetic relationship between CA and the two other cyclopropanes is not without ambiguity however, since neither the C_{10}-analogue of presqualene/prephytoene nor the C_{10}-analogues of squalene or phytoene have yet been found in Nature.† We now report the results of feeding and trapping experiments designed to examine the involvement of chrysanthemyl alcohol (**1**) in CA biosynthesis and also to examine the role of C_{10}-acyclic precursor molecules in the formation of the cyclopropane ring in CA.

† The presence of chrysanthemyl alcohol in *C. cinerariaefolium* has recently been suggested from preliminary g.c.–m.s. analysis of fresh extract.

1*R*,3*R*-Chrysanthemyl alcohol (**1**), specifically labelled with ^3H and ^{14}C was obtained by reduction ($LiAlH_4$) of the corresponding acid. The ^3H-labelled acid is available by an exchange method using 1*S*,3*R*-CA,[3] and the ^{14}C-labelled acid is available by a method described previously.[4] The radioactive alcohol (71 μCi) (^3H:^{14}C 2·1) was emulsified in



water–Tween 20 and fed to dissected achenes from *C. cinerariaefolium*. After elaborating the plant material, radioactive CA was isolated and converted into its crystalline amide. Crystallisation to constant activity produced an amide having ^3H:^{14}C 1·95, and indicating 0·7% incorporation of chrysanthemyl alcohol into CA. Doubly labelled 1*R*, 3*R*-chrysanthemaldehyde (**2**), prepared by oxidation (MnO_2) of the corresponding alcohol, was fed similarly (29·8 μCi; ^3H:^{14}C 2·03) to *C. cinerariaefolium*. The isolated chrysanthemamide, purified to constant activity, showed ^3H:^{14}C 2·07 and 2·2% incorporation of the cyclopropane aldehyde into CA. In parallel experiments, the DBED salt of 2-^{14}C-mevalonic acid (MVA) (100 μCi) was fed to seedlings of *C. cinerariaefolium* during 48 h, and unlabelled 1*R*,3*R*-chrysanthemyl alcohol (70 mg) was added to the plant extract. The chrysanthemyl alcohol was then separated by chromatography and converted into the 3,5-dinitrobenzoate. Crystallisation to constant activity gave the benzoate, m.p. 85—86°, activity 1400 d.p.m. mg^{-1}, showing 0·09% incorporation of MVA into chrysanthemyl alcohol. Thus chrysanthemyl alcohol is an obligatory intermediate in the biosynthesis of CA from MVA.



SCHEME

Several biogenetic schemes have been suggested for the formation of the cyclopropane ring systems in CA and presqualene.[1] Two such schemes,[1a,d] amenable to experimental scrutiny, involve either the lavandulyl (**4**) or the artimisyl skeletons (**5**) as immediate precursors of the chrysanthemyl skeleton (Scheme). In experiments designed to distinguish these possibilities, we synthesised lavandulol (**6**) and artimisyl alcohol (**7**), radiolabelled as shown, and fed them to *C. cinerariaefolium*. Crystalline chrysanthemamide isolated from either feeding was found to be totally inactive, and further experiments are now in progress to examine possible alternative intermediates between MVA and CA.

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