5-Oxo-octanoic Acid and 5-Oxo-octanal, Precursors of Coniine

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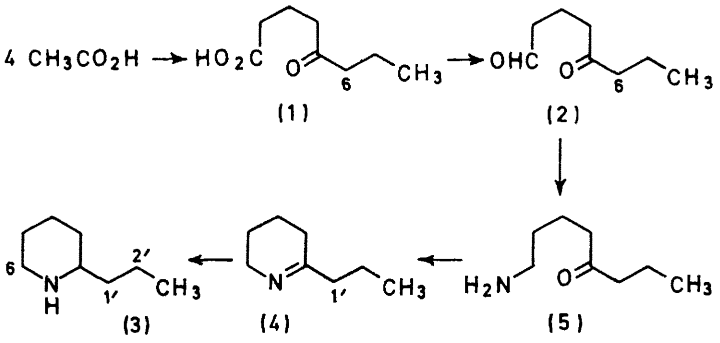
Summary The administration of [6-^{14}C]-5-oxo-octanoic acid or [6-^{14}C]-5-oxo-octanal to hemlock plants (*Conium maculatum*) resulted in the formation of [1′-^{14}C]coniine, with high incorporations of activity as compared with [1-^{14}C]acetate and [1-^{14}C]octanoic acid, suggesting that they are the immediate precursors of coniine.

Recently[1] we discovered that [1-^{14}C]-octanoic acid was a good precursor of coniine (**3**), one of the major alkaloids of hemlock (*Conium maculatum*).[2] We suggested that the octanoic acid was incorporated *via* 5-oxo-octanoic acid (**1**). This compound and 5-oxo-octanal (**2**) have now been prepared labelled with ^{14}C, to test as precursors of coniine, by the following method. Reaction of the Grignard reagent obtained from [1-^{14}C]propyl bromide with cyclopentanone yielded 1-propylcyclopentanol, which on oxidation with potassium dichromate in sulphuric acid afforded [6-^{14}C]-5-oxo-octanoic acid. Dehydration of 1-propylcyclopentanol with phosphorus pentoxide in ether yielded 1-propylcyclopentene,[3] which was converted into 1-propylcyclopentane-1,2-diol with osmium tetroxide. Cleavage of this diol with sodium metaperiodate yielded [6-^{14}C]-5-oxo-octanal.

The specific incorporation of radioactivity into coniine obtained from hemlock plants (6 months old) fed equivalent amounts (0·25 mmole) of sodium [1-^{14}C]acetate, [1-^{14}C]-octanoic acid, [6-^{14}C]-5-oxo-octanoic acid, and [6-^{14}C]-5-oxo-octanal, for 24 h, was 0·009, 0·07, 0·61, and 1·1%, respectively. The total incorporation of activity into the crude alkaloids in these four experiments, which were carried out under identical conditions, was 0·035, 0·45, 3·6, and 6·8%, respectively. The coniine derived from compounds (**1**) and (**2**) was degraded as previously described,[4] and it was established that essentially all the activity was located at C-1′. These results and our earlier observations on the incorporation of acetate[5] are consistent with the biosynthetic scheme illustrated in the Scheme. The condensation of four acetate units yields, after unexceptional reductions, 5-oxo-octanoic acid. 5-Oxo-octanal is obtained by further reduction of this acid, the significantly higher incorporation of this compound suggesting that it is the more immediate precursor of the hemlock alkaloids. A transamination involving the aldehyde group then affords 5-oxo-octylamine (**5**), which would be expected to cyclize spontaneously to γ-coniceine (**4**), an established precursor of coniine.[4,6]

We do not consider that octanoic acid is on the direct route to the hemlock alkaloids, and its observed incorporation into coniine may simply indicate that it can be oxidized in the plant to 5-oxo-octanoic acid. Evidence for this occurring was obtained by adding non-radioactive 5-oxo-octanoic acid to an aqueous alkaline extract of hemlock plants which had been fed [1-^{14}C]octanoic acid for 24 h. On re-isolation of the oxo-acid, and purification by chromatography, distillation, and the formation of a semicarbazone, it was found to be radioactive (0·09% incorporation). Furthermore the re-isolated 5-oxo-octanoic acid was found to have more than 95% of its activity located on the carboxyl group, indicating a direct formation from octanoic acid.



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[1] E. Leete, *J. Amer. Chem. Soc.*, 1970, **92**, 3835.

[2] All the work reported in this communication was carried out with the "Minnesota" variety of hemlock; however analogous results were obtained with the "Chelsea" variety which contains γ-coniceine (**4**) as the major alkaloid (*cf.* S. M. C. Dietrich and R. O. Martin, *Biochemistry*, 1969, **8**, 4163). Thus the administration of [6-^{14}C]-5-oxo-octanoic acid to the Chelsea variety afforded radioactive γ-coniceine which had essentially all its activity located at C-1′.

[3] F. Eisenlohr and G. Gorr, *Fortschr. Chem. Phys. Phys. Chem.*, (*B*), 1925, **18**, 528.

[4] E. Leete and N. Adityachaudhury, *Phytochemistry*, 1967, **6**, 219.

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[6] J. W. Fairbairn and P. N. Suwal, *Phytochemistry*, 1961, **1**, 38.