Biosynthesis of Securinine: the Mode of Incorporation of Lysine

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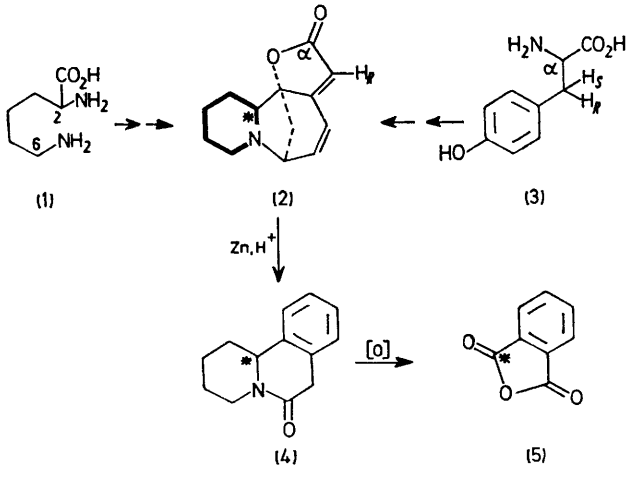
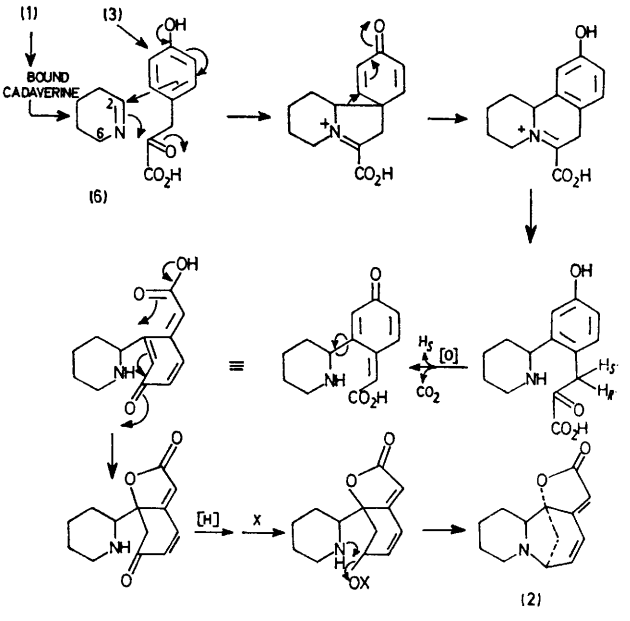
Summary The piperidine ring of securinine is derived from a C_5N unit, Δ^1-piperideine, which originates from lysine in non-symmetrical fashion by loss of the carboxy carbon and the α-amino group.

SECURININE (**2**), the major alkaloid of *Securinega suffruticosa* Rehd., originates from two amino acid fragments.[1] One of these, derived from tyrosine (**3**), yields the C_6–C_2 unit of the alkaloid (light lines).[1–3] All the carbon atoms of tyrosine other than the carboxy group are maintained,[2] the α-carbon supplies the lactone carbon atom of the alkaloid,[1,2] and the *pro-R* proton from the β-carbon of tyrosine is retained in the alkaloid whereas the *pro-S* proton is lost.[3]



SCHEME 1

The second fragment, a C_5N unit (heavy lines), is presumably derived from lysine,[1,2] *via* cadaverine. Specific incorporation of radioactivity from [1-^{14}C]cadaverine into securinine (**2**), in the predicted symmetrical manner (50% of label at *) has been demonstrated,[2] but the mode of incorporation of lysine has not yet been determined. In particular, it is not known whether securinine is one of the piperidine alkaloids whose C_5N units are derived from lysine in non-symmetrical fashion[4] (*cf.*, anabasine, sedamine, *N*-methylpelletierine), or whether it belongs to the group of alkaloids whose C_5N units originate from lysine in a symmetrical manner (*e.g.*, the lupine,[5] decodon,[6] and lycopodium[7] alkaloids).



SCHEME 2

In separate experiments [2-^{14}C]-DL-lysine (100 μCi, 3 mCi mmol^{-1}, New England Nuclear) and [2-^{14}C]-Δ^1-piperideine (30 μCi, 4·7 mCi mmol^{-1}, prepared[8] from [2-^{14}C]-DL-lysine) were administered to *Securinega* plants by the wick method. After 3 days in contact with tracer, the plants were harvested and securinine was extracted. The active sample was diluted with inactive carrier, crystallized to constant specific activity ($1·5 \times 10^5$ dpm mmol^{-1} and

$3{\cdot}1 \times 10^4$ dpm mmol^{-1}, respectively) and degraded[2] to the benzquinolizidine (**4**) and thence to phthalic anhydride (**5**) (Scheme 1). The molar specific activity of the samples of phthalic anhydride obtained ($1{\cdot}4 \times 10^5$ and $3{\cdot}0 \times 10^4$ dpm mmol^{-1}, respectively) indicated that in each case more than 90% of the activity of securinine had been localized at the asterisked carbon atom (*i.e.*, at the only carbon atom of the non-tyrosine derived portion of securinine retained in phthalic anhydride), which is thus derived predominantly if not exclusively from C-2 of lysine and from C-2 of Δ^1- piperideine.

Securinine is thus shown to be one of the piperidine alkaloids whose derivation from lysine avoids a symmetrical intermediate.[4] It is the first amongst this group of alkaloids whose nitrogen atom is common to two rings. All other lysine-derived alkaloids whose nitrogen lies at a ring junction (*e.g.*, lupine,[5] decodon[6] and lycopodium[7] alkaloids) incorporate lysine by way of a symmetrical intermediate.

A further tracer experiment throws light on the origin of the nitrogen atom of securinine. This nitrogen might be supplied by the lysine-derived[9] or by the tyrosine-derived[10] fragment. Administration to *Securinega* plants of a sample of [*RS*-6-^{3}H;6-^{14}C]-DL-lysine (^{3}H:^{14}C = $8{\cdot}1 \pm 0{\cdot}1$, prepared by mixing [*RS*-6-^{3}H]-DL-lysine, 0·8 mCi, 21 Ci mmol^{-1} and [6-^{14}C]-DL-lysine, 0·1 mCi, 48 mCi mmol^{-1}, both Commissariat á l'Ènergie Atomique, France) yielded securinine (^{3}H:^{14}C = $8{\cdot}0 \pm 0{\cdot}5$) which had retained all tritium, relative to ^{14}C. This result indicates that the nitrogen atom of securinine is derived from the ϵ-amino nitrogen of lysine. Derivation of the securinine nitrogen from any other source would require loss of the ϵ-nitrogen of lysine along the route of biosynthesis of the alkaloid. Loss of the ϵ-nitrogen of lysine, in turn, must be accompanied by labilization and loss of at least part of the tritium, relative to ^{14}C, from [*RS*-6-^{3}H]lysine.

The present results, together with the data presented earlier[1-3] are consistent with the route to securinine shown in Scheme 2.

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