Biosynthesis of the *Securinega* Alkaloids. Stereospecificity of Hydrogen Loss from C-3 of Tyrosine

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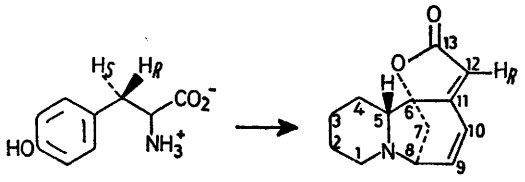
Summary Specimens of (3*RS*)-[3-^{3}H, 3-^{14}C]-, (3*R*)-[3-^{3}H, 3-^{14}C]-, and (3*S*)-[3-^{3}H, 3-^{14}C]-DL-tyrosine have been administered to *Securinega suffruticosa* to demonstrate that the *pro-S* hydrogen at C-3 of tyrosine is lost during the biosynthesis of securinine from this amino-acid.

PLANTS of the genus *Securinega* (*Euphorbiaceae*) contain a group of unusual tetracyclic alkaloids of which securinine (**1**) is the most abundant.[1] Recent evidence[2] has shown that L-tyrosine is incorporated into securinine in a unique manner, providing carbon atoms 6–13 of the securinine skeleton. The formation of securinine from tyrosine results in the loss of one hydrogen atom from the prochiral centre present at C-3 of the amino-acid. Because of the current interest in the stereochemistry of reactions involved in alkaloid biosynthesis,[3,4] we now report the results of experiments which establish the stereospecificity of this hydrogen loss.

p-Anisaldehyde was reduced with potassium borotritiide to [α-^{3}H]-*p*-methoxybenzyl alcohol which was converted to [α-^{3}H]-*p*-methoxybenzyl bromide with gaseous hydrogen bromide.[5] Alkylation[5] of the sodium salt of ethyl acetamidocyanoacetate with the tritiated benzyl bromide followed by acid hydrolysis[5] yielded (3*RS*)-[3-^{3}H]-DL-tyrosine. The tritiated amino-acid was mixed with [3-^{14}C]-DL-tyrosine and the doubly-labelled amino-acid (^{3}H:^{14}C, 4·08) was administered to young *Securinega suffruticosa* plants by the cotton-wick method. After 14 days, radioactive securinine was isolated (0·007% incorporation). The purified, radiolabelled securinine had a

$^3H:^{14}C$ ratio of 1·74 corresponding to a 57% loss of tritium; this indicates that the removal of a hydrogen atom from C-3 of tyrosine is a stereospecific process (expected loss is 50%). Additional experiments define the stereospecificity



(1)

of this hydrogen loss. Samples of (3*R*)-[3-^{3}H]- and (3*S*)-[3-^{3}H]-DL-tyrosine were synthesized by the method of Kirby and Michael.[4] The two specimens of chirally tritiated tyrosine were each mixed with [3-^{14}C]-DL-tyrosine and administered to *S. suffruticosa* plants. The radioactive securinine produced from (3*S*)-[3-^{3}H, 3-^{14}C]-DL-tyrosine ($^3H:^{14}C$, 4·76) had a $^3H:^{14}C$ ratio of 0·30 corresponding to a 94% loss of tritium. The radioactive securinine biosynthesized from (3*R*)-[3-^{3}H, 3-^{14}C]-DL-tyrosine ($^3H:^{14}C$, 4·94) had a $^3H:^{14}C$ ratio of 3·54 indicating a 28% loss of tritium. These results clearly demonstrate that the conversion of tyrosine into securinine proceeds with loss of the *pro-S* hydrogen at C-3 of the amino-acid. The lack of complete loss or retention of tritium during the conversion of tyrosine into (**1**) is probably due to two factors. The first of these is that the specimens of chirally tritiated tyrosine prepared using Kirby and Michael's procedure are only *ca.* 85% stereochemically pure.[4] On this basis, one would expect to see tritium loss or retention figures of approximately 85%. However, a second factor appears to be operating. The conversion of tyrosine to securinine results in the oxidation of C-2 of the amino-acid to a carbonyl group. The biosynthetic sequence leading to (**1**) may therefore involve one or more intermediates in which exchange of the C-3 hydrogens with the medium is possible. Such exchange would account for the fact that the figures for tritium loss obtained in each of the three experiments are slightly higher than would otherwise be expected.

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