Biosynthesis of Shihunine, an Alkaloid of the Orchid *Dendrobium pierardii*

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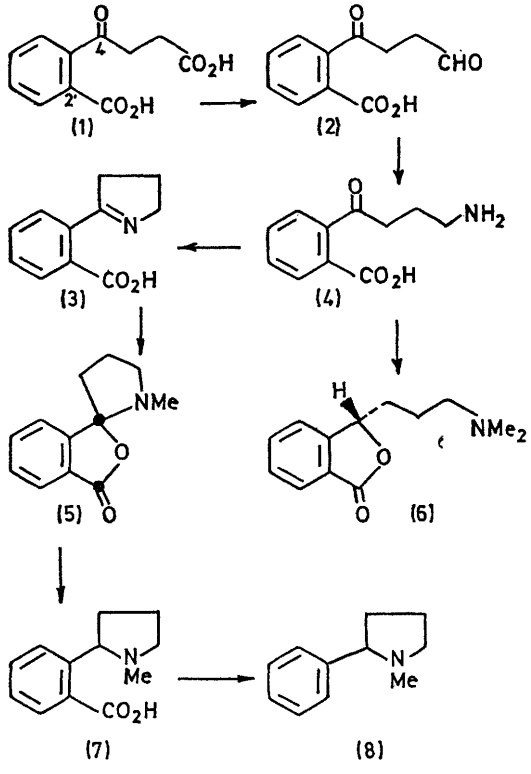
Summary 4-2′-Carboxyphenyl-4-oxobutanoic acid (**1**), the established precursor of several plant and bacterial napthoquinones, has been found to be also an excellent precursor (13·5% incorporation) of shihunine, a phthalide-pyrrolidine alkaloid present in *Dendrobium pierardii*.

SHIHUNINE (**5**) and pierardine (**6**) are found in the orchid, *Dendrobium pierardii* and related species.[1,2] We considered that these alkaloids were derived from 4-2′-carboxyphenyl-4-oxobutanoic acid (**1**) by the route shown in the Scheme. This compound is an important intermediate in the formation of several 1,4-naphthoquinones: lawsone,[3,4] juglone,[4] and the bacterial menaquinones.[4,5] It is suggested that the keto-aldehyde (**2**) obtained from (**1**) by reduction, undergoes transamination affording the keto-amine (**4**). Reduction of the ketone group, lactone formation, and *N*-methylation then yields pierardine. Cyclization of (**4**) to the pyrroline (**3**), followed by *N*-methylation and lactone formation yields shihunine.

This hypothesis was tested by feeding [4,2′-*carboxy*-$^{14}C_2$]-(**1**)[6] (17·1 mg, 1·78 × 10^8 d.p.m.) to a *D. pierardii* plant by means of cotton wicks inserted into the stem of the plant, just before flowering (February). After 12 days the plant (fresh wt. 500 g) was harvested and yielded shihunine (510 mg, 9·6 × 10^6 d.p.m./mM, 13·5% incorporation) and pierardine hydrochloride (121 mg, 4·4 × 10^4 d.p.m./mM, 0·012% incorporation). The radioactive shihunine was degraded.[1] Hydrogenation in the presence of Adams catalyst yielded dihydroshihunine (**7**) (9·3 × 10^6 d.p.m./mM) which was heated with barium oxide affording 1-methyl-2-phenylpyrrolidine (**8**) (4·6 × 10^6 d.p.m./mM). Oxidation of (**8**) with potassium permanganate yielded benzoic acid (4·5 × 10^6 d.p.m./mM), which on subjecting to a Schmidt



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reaction yielded aniline, isolated as benzanilide (inactive) and barium carbonate ($4{\cdot}5 \times 10^6$ d.p.m./mM). These results indicate that the shihunine was labelled equally at the positions indicated with heavy dots in structure (**5**), and establishes (**1**) as a direct precursor of the alkaloid. The much lower incorporation of (**1**) into pierardine may indicate that this alkaloid was not being actively produced at the time of feeding.

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