

## Aspects of the Biosynthesis of the Terpenoid Dendrobine

By ATTILIO CORBELLA, PIERLUIGI GARIBOLDI, and GIANCARLO JOMMI\*

(Laboratorio di Chimica Organica della Facoltà di Scienze, Università di Milano, Via Saldini, 50, Milano, Italy)

**Summary** During the biosynthesis of dendrobine (5), a hydrogen is transferred from C-1 of farnesol (1) to C-8 of (5).

FEEDING experiments on living plants of *Coriaria japonica*<sup>1a</sup> have clarified some aspects of the biosynthesis of tutin and ascertained the role of copaborneol as intermediate.<sup>1b</sup> According to the general scheme reported in the literature,<sup>1a,c-f</sup> one of the key steps leading to the formation of picrotoxane sesquiterpenoids is the cyclization of the germacranol cation (2) to the muurolane (4). The results presented here support this scheme and are consistent with a 1,3-hydride shift, the cation (2) giving rise to the cation (3).<sup>†</sup> Dendrobine is a suitable substrate to obtain direct evidence for this mechanism unlike tutin which has no C-8 hydrogen.

By feeding living plants of *Dendrobium nobile* Lindl. with potassium (3*RS*)-[2-<sup>14</sup>C, 5-<sup>3</sup>H<sub>2</sub>]mevalonate, radioactive dendrobine (5) was obtained (1.4% incorporation yield), the loss of 1:6 tritium label resulting from hydroxylation at C-3 (see Table).

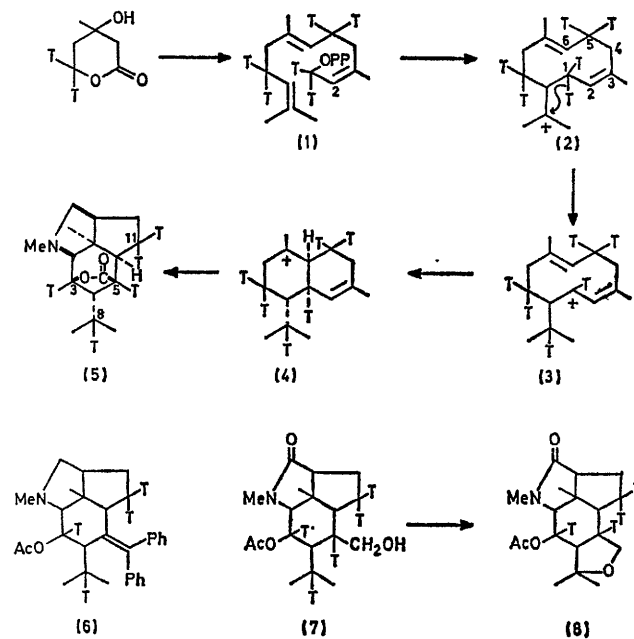
TABLE

	<sup>3</sup> H: <sup>14</sup> C ratio	
	Found	Calc.
(3 <i>RS</i> )-[2- <sup>14</sup> C, 5- <sup>3</sup> H <sub>2</sub> ]Mevalonate	7.22	
(5)	5.98	6.02
(6)	4.78	4.78
(7)	5.85	5.98
(8)	4.77	4.78

According to known procedures,<sup>2</sup> radioactive dendrobine was converted into (6) and (7). Compound (7) showed the same <sup>3</sup>H: <sup>14</sup>C ratio as the starting material, whereas (6)

retained only 4:5 of the tritium label of dendrobine. Irradiation of (7) in benzene, in the presence of Pb(OAc)<sub>4</sub>,<sup>3</sup> gave (8) [m.p. 142–144°; [α]<sub>D</sub><sup>20</sup> + 128.2° (CHCl<sub>3</sub>); <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>) δ 1.24 (3H, s, 9-Me) and 1.28 (3H, s, 10-Me)] with simultaneous loss of 1:5 of the tritium label.

These data demonstrate that of the two tritium atoms at C-1 of farnesol, one is at the expected position in dendrobine



<sup>†</sup> A similar conclusion has been drawn in the biosynthesis of a microbial derivative of  $\gamma$ -cadinene (M. Rohr, A. Hagenbach, and D. Arigoni, personal communication).

(C-5), the other having migrated to the tertiary carbon of the isopropyl group (C-8 of dendrobine). Further experiments, which will be described in the full paper, show that all the remaining tritium in dendrobine is at C-3 and C-11 (one and two tritium atoms, respectively).

These results exclude both the formation of a cyclopropane ring<sup>1e</sup> and the intermediacy of a bisabolane or camphepane<sup>2a,4</sup> during dendrobine biosynthesis.

Consideration of the geometry of (3) and (4) leads to the conclusion that a 2-*cis*,6-*trans* configuration of the double bonds of (3) is necessary for the formation of (4). Recent investigations on the biosynthesis of nerol<sup>5</sup> and of 2-*cis*,6-*trans*-farnesol<sup>6</sup> add support to the hypothesis of the intermediacy of aldehydes for *trans-cis* isomerization of double bonds. The localization of the tritium label at C-5 and C-8

in dendrobine biosynthesised from [5-<sup>3</sup>H<sub>2</sub>]mevalonic acid excludes the intermediate formation of farnesal in this case.

According to this finding, three suggestions can be made to explain the biosynthesis of dendrobine and possibly of the related sesquiterpenoids: (i) C-2 *trans-cis* isomerization of farnesol can take place with a mechanism different from that involving an aldehyde, or (ii) 2-*cis*,6-*trans*-farnesol can be synthesized through an independent biogenetic pathway, or (iii) *trans-cis* isomerization can occur on the allylic cation, the 2-*trans*-isomer of (3), originating from 2-*trans*,6-*trans*-farnesol. Taking into account the latest results, the third hypothesis seems to be the most likely.

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<sup>3</sup> See for example, K. Heusler, *Tetrahedron Letters*, 1964, 3975.

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