Stereochemistry of the Hydrogen Introduction at C-25 in the Biosynthesis of Tomatidine

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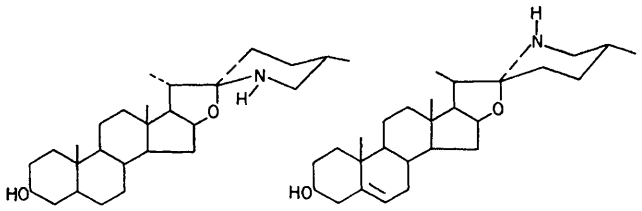
Summary The C-26 atom of tomatidine, bearing the nitrogen atom, derives from the C-2 atom of MVA; from this it is inferred that the introduction of hydrogen at the C-25 atom of the Δ^{24} biosynthetic intermediate occurs from the 24-*si*, 25-*si* face.

IT is generally accepted[1,2,3] that biosynthesis of steroidal alkaloids like tomatidine (I) or solasodine (II) proceeds according to the pathway:

$$(III) \xrightarrow{A} (IV) \xrightarrow{B} (I) \text{ or } (II)$$

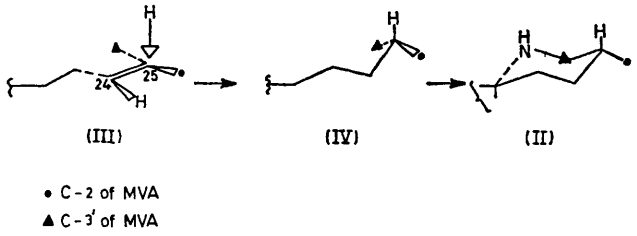
Guseva *et al.*[4] showed that in *Solanum lancinatum* the 27 methyl group of solasodine (II), a 25*R* steroidal alkaloid, derives from C-2 of MVA; this result, and the 25*R* configuration of solasodine, indicate that during the saturation of the Δ^{24} intermediate (III), in which the geometry of the C-24 double bond is that indicated in Scheme 1,[5] the hydrogen atom introduced at C-25 entered from the 24-*si*, 25-*si* face.†



(I) (II)

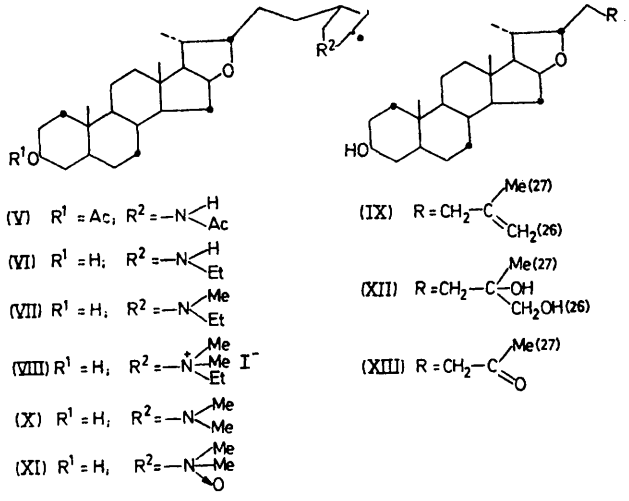
We now report the results of our investigation of tomatidine (I), a steroidal alkaloid with the 25*S* configuration. The formation of tomatidine involves functionalization of the isopropyl *pro-R* methyl group in the cholesterol side chain. This *pro-R* methyl group derives either from C-2 of MVA, if saturation at C-25 of the Δ^{24} intermediate (III) occurs from the 24-*si*,25-*si* face (Scheme 2, a) or from C-3′ of MVA, if saturation occurs from the 24-*re*, 25-*re* face (Scheme 2, b).

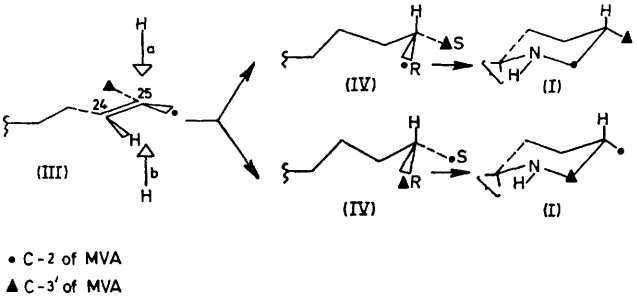
† See K. R. Hanson, *J. Amer. Chem. Soc.*, 1966, **88**, 2731 for an explanation of the *si* and *re* terminology.



SCHEME 1

To determine which of the two cases actually occurs in the biosynthesis of tomatidine, we administered 2-^{14}C-MVA (0·1 mCi) once a week, for four weeks, to young plants of *Lycopersicon pinpinellifolium;* a week after the last treatment the plants were extracted and the basic fraction hydrolysed with methanolic HCl. Chromatography of the hydrolysate afforded tomatidine labelled in positions 1,7,15,22 and 26 (or 27) ($1·7 \times 10^6$ d.p.m.); this compound was purified by t.l.c., diluted with carrier material and acetylated. Hydrogenation in AcOH on Pt afforded (V), which was reduced with $LiAlH_4$ to (VI); *N*-methylation with CH_2O–HCO_2H afforded (VII) which was transformed into the corresponding *NN'*-dimethyl-*N*-ethyl ammonium salt (VIII) by treatment with MeI; Hofmann degradation yielded small amounts of the olefin (IX) and (X); this last compound was transformed into the corresponding *N*-oxide (XI) by treatment with *m*-$ClC_6H_4CO_3H$; pyrolysis of the oxide yielded the olefin (IX) which was combined with the olefin obtained from the Hofmann degradation and treated with OsO_4, to give the diol (XII) ($1·99 \times 10^5$ d.p.m./mM); oxidation of the diol (XII) with $NaIO_4$ afforded the ketone (XIII) and formaldehyde (recovered as the dimedone derivative), corresponding to C-26 of tomatidine.





SCHEME 2

The ketone (XIII) showed a molar radioactivity close to 4/5 of the total radioactivity ($1·64 \times 10^5$ d.p.m./mM = 82·5%), whereas the formaldehyde had a radioactivity close to 1/5 of the total ($3·2 \times 10^4$ d.p.m./mM = 16·1%).

Our results indicate that the C-26 of tomatidine, bearing the nitrogen function, derives from C-2 of MVA; therefore the saturation at C-25 of the Δ^{24}-intermediate occurs from the 24-*si*,25*si* face (Scheme 2, a).

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