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Tobacco isoprenoids – precursors of important aroma constituents

Curt R. Enzell and Inger Wahlberg

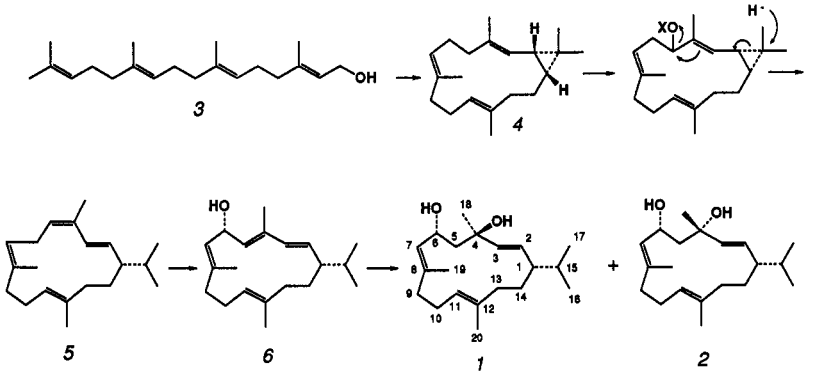
Reserca AB, Box 17007, S-10462 Stockholm , Sweden

Dedicated to Dr Gunther Ohloff on his 65 birthday

*Much of the aroma of tobacco can be viewed as arising by way of biodegradation of tobacco isoprenoids, predominantly of the cembranoid, labdanoid and carotenoid groups. The oxygenation patterns and relative abundance of these diterpenoids imply that most of them are derived from (Z)-abienol and two cembratrienediol epimers (**1** and **2**) by a series of reactions often initiated by singlet oxygen and/or analogous enzymatic systems - assumptions verified by biomimetic synthesis of a large number of them. Further transformations of these C_{20} tobacco constituents furnish a series of degraded diterpenoids having 19 to 8 carbon atoms, many of which contribute to the characteristic aroma of tobacco.*
Here, the interest will be focused on the transformations of the cembranoids. Evidence for the presence of several new cembrane-derived tobacco constituents and of their stereostructures will be presented along with the major biogenetic pathways adopted to explain the formation of most cembranic compounds known in tobacco to date.

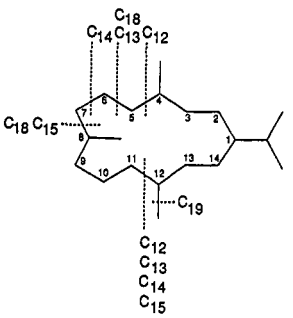
The biosynthesis of the two major major groups of isoprenoids of tobacco, the cembranoids and the labdanoids, occurs in the glandular heads of the trichomes present on the surface of the leaves and in the flowers (ref.1 and 2). The genetic background as well as the edafic conditions determine the abundance of these constituents and, along with the postharvest treatment, govern their degradation to lower molecular weight compounds. Many of these degraded constituents are important flavour substances giving significant contribution to the aroma of commercial tobacco.

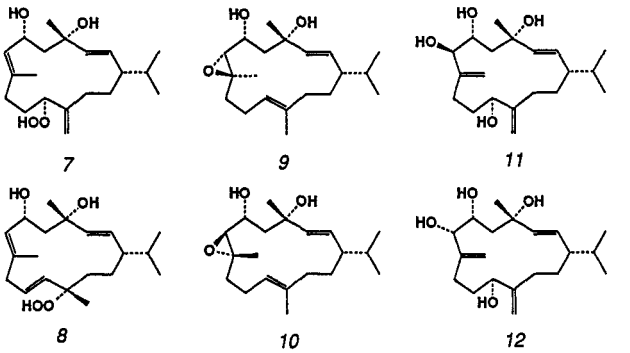
Scheme 1



The major cembranoid components are the two epimeric diols **1** and **2** (ref. 3), which possess growth (ref. 3) and tumor inhibiting (ref. 4) as well as insect repelling properties (ref. 5). According to recent studies (ref. 6) these diols seem to arise from geranylgeraniol (**3**) via *ent*-casbene (**4**), cembrene (**5**) and 2,4,7-cembratetraen-6-ol (**6**), cf. Scheme 1. Our present knowledge about the subsequent metabolism is mainly based on results from biomimetic studies of the two diols **1** and **2**, which are regarded as the major precursors of more than fifty C_{20} cembranoids (ref. 3). Some of these give in turn rise to a large number of degraded cembranoids. The latter can be viewed as being derived via six key metabolites, which have 12, 13, 14, 15, 18 or 19 carbon atoms and are generated by ruptures of the bonds in the cembrane skeleton indicated in scheme 2. Since many of the degraded cembranoids are present in green leaves and fresh flowers, it is concluded that these reactions also occur in the growing plant (ref. 3).

Scheme 2



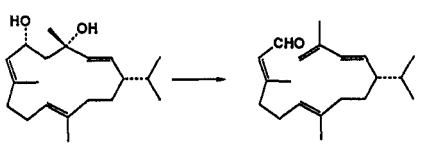


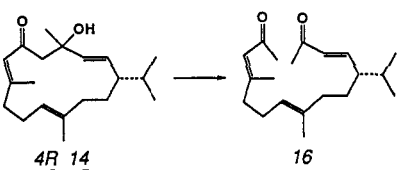
Cleavage of the 11,12 double bond, required for the formation of the C_{12}, C_{13}, C_{14}, and C_{15} key metabolites, probably occurs in an oxidative manner either by an enzyme-assisted reaction or one involving singlet oxygen. Evidence for this comes from the isolation from tobacco flowers of five hydroperoxides having the HOO-group attached to the 11- or 12-position, e.g. **7**, **8** (ref. 3), from photooxygenations studies revealing preferential attack on the 11,12-bond (ref. 3) and from compounds isolated after incubating either diol **1** or **2** with a *Cantharanthus roseus* cell culture (ref. 7).

The 7,8 double bond is less vulnerable to oxidation than is the 11,12 double bond and only two compounds having the 7,8 but not the 11,12 double bond oxidised have so far been isolated from tobacco, i.e. the 7,8-epoxides **9** and **10** (ref. 3). Chemically this regiospecificity can be achieved using t-C_4H_9OOH/$VO(acac)_2$.

The rupture of the 6,7 bond was intially proposed to occur by acid-catalysed rearrangement of the 7,8 epoxides, but lack of success in carrying out this reaction experimentally and the recent isolation of the new tetraols **11** and **12** (ref. 8) suggest the existence of an alternative pathway involving the corresponding 7-hydroperoxides as intermediates.

The fragmentation of the 5,6 bond can be viewed as the result of an acid-catalysed 1,3-diol rearrangement furnishing in the case of the diols **1** and **2** the *seco*-aldehyde **13**, a reaction easily mimicked using dilute H_2SO_4 in dioxane/water (ref. 3).

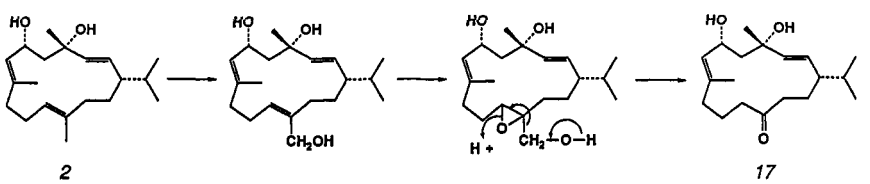




As verified experimentally, the opening of the 4,5 bond can readily be accounted for by a retro-aldol fragmentation of the tobacco ketols **14** and **15**. The latter, which derive from the diols **1** and **2** by oxidation of their secondary hydroxyl group, yield the *seco*-diketone **16** (ref. 3).

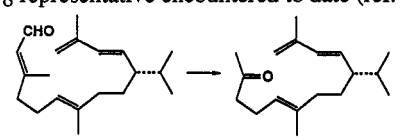
The cleavage of the 12,20 bond leading to the C_{19} key metabolite **17**, recently isolated from tobacco flowers, might occur by the biogenetic pathway shown in Scheme 3 (ref. 3).

Scheme 3

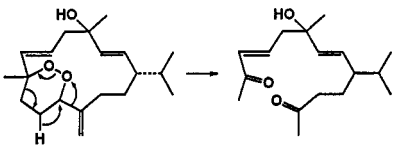


The C_{18}, C_{15}, C_{14}, C_{13} and C_{12} key metabolites are recognised by their irregular isoprenoid skeleton comprising an isopropyl group of *S*-configuration. They undergo further chemical degradation, including loss of carbon atoms, to yield a large number of tobacco constituents of which nearly 70 are known to date. Most of these compounds have only been obtained from tobacco, which makes them unique to this plant (ref. 3).

The C_{18} key metabolite prenylsolanone (**18**), probably formed by a retro-aldol condensation from **13**, is the sole C_{18} representative encountered to date (ref. 3).



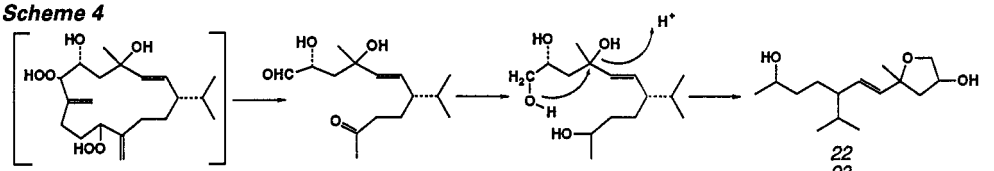
13 *18*



20 *19*

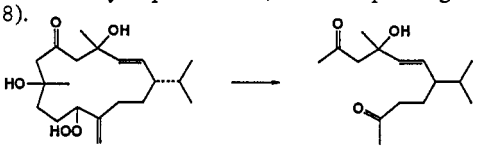
We have recently isolated a new C_{17} tobacco constituent(**19**), which does not fit the general fragmentation pattern shown in Scheme 2 since it seems to arise by cleavages of the 8,9 and 11,12 bonds (ref. 9). One possible route would involve intermediate **20**, readily obtainable from the hydroperoxide **7** on acid treatment (ref. 10).

Scheme 4



21 *22* *23*

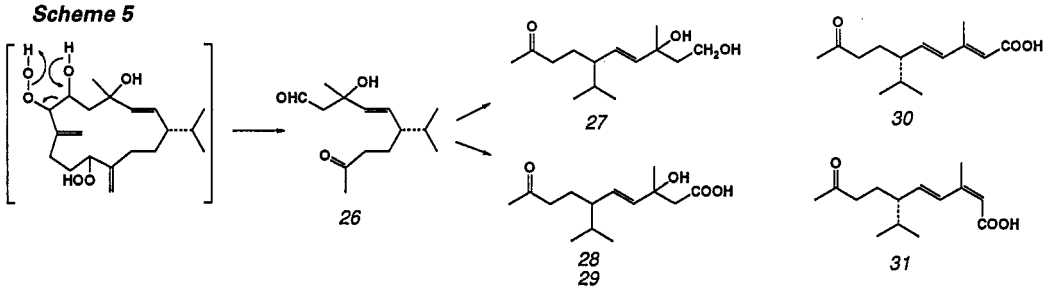
The C_{15} key metabolite (**21**) may arise as shown in Scheme 4. The closely related diols (**22, 23**), derivable by reduction of the oxo groups followed by dehydration, have been isolated from Japanese SUIFU tobacco (ref. 3). Four other C_{15} tobacco compounds having the same skeleton are probably formed from thunbergol by the same set of reactions (ref. 3). The new C_{15} compound (**24**), isolated from Greek tobacco (ref. 9), is apparently derived in a different way, i.e. from the 11-hydroperoxide **25**, the corresponding ketotriol of which has recently been obtained from tobacco (ref. 8).



25 *24*

The predicted C_{14} key metabolite (**26**), like its C_{15} counterpart, is an aldehyde not yet encountered in tobacco. It may be generated as illustrated in Scheme 5, which also shows the five daugther compounds (**27-31**) isolated from tobacco (ref. 3 and 9).

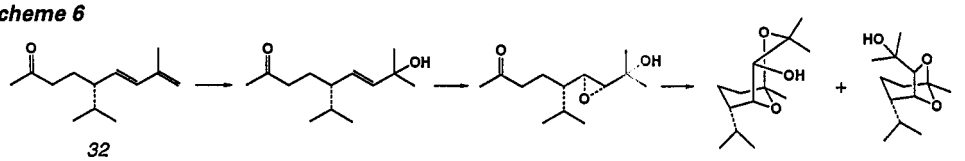
Scheme 5



26 *27* *30* *28* *29* *31*

Cleavage of the 5,6 and 11,12 bonds furnishes the abundant and important C_{13} key metabolite solanone (**32**), itself a major aroma constituent and the parent of a series of compounds contributing to the tobacco aroma (ref. 3). Some of these are shown in Scheme 6.

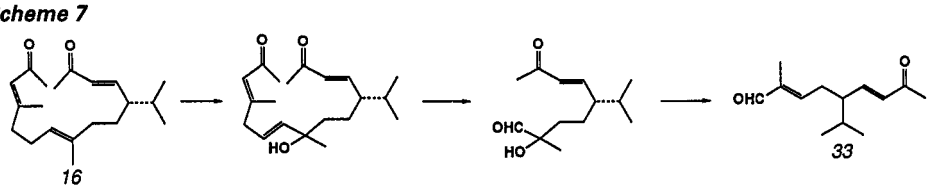
Scheme 6



32

It is suggested from the structure of newly isolated C_{13} ketoaldehyde **33** that it is derived from the parent diols **1** and/or **2** in a different fashion (ref. 9), i.e. by cleavage of the 4,5 and 10,11 bonds as shown in Scheme 7.

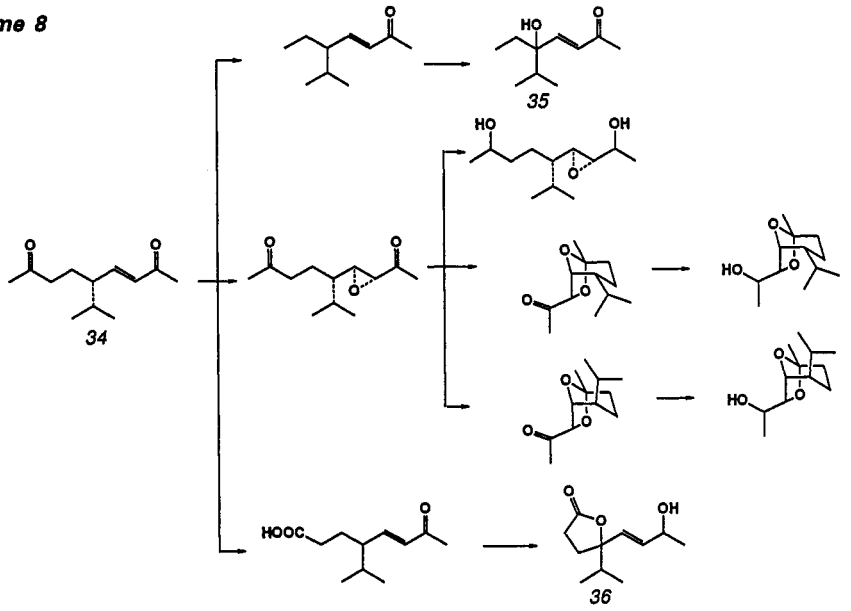
Scheme 7



16 *33*

The C_{12} key metabolite, norsolanadione (**34**), is postulated to arise by cleavage of the 4,5 and 11,12 bonds of parent cembranoids (ref. 3). Not only an important aroma constituent *per se*, norsolanadione is obviously an important precusor of many other C_{12} constituents (Scheme 8) and also of several of C_8-C_{11} tobacco compounds, such as the recently encountered degradation products **35** and **36** (ref. 9).

Scheme 8



REFERENCES

1. A.W. Johnson, R.F. Severson, J. Hudson, G.R. Carner and R.F. Arrendale, Tob. Sci. 29, 67 (1985).
2. C. Keene and G.J. Wagner, Plant Physiol. 79, 1026 (1985).
3. I. Wahlberg and C.R. Enzell, Nat. Prod. Rep. 1987, 237 and ref. cited herein.
4. Y. Saito, Y. Tsujimo, H. Kaneko, D. Yoshida and S. Mizusaki, Carcinogenesis 6, 1189 (1985).
5. A.W. Johnson and R.F. Severson, J. Agric. Entomol. 1,23 (1984).
6. L. Crombie, D. McNamara, D.F. Firth, S. Smith and P.C. Bevan, Phytochem.27, 1685 (1988).
7. J. Kutney, private communication.
8. R. Arndt, J.E. Berg and I. Wahlberg, Acta Chem. Scand., in press.
9. I. Wahlberg, A.-M. Eklund and C.R. Enzell, Acta Chem. Scand., in press.
10. R. Arndt, I. Wahlberg, C.R. Enzell and J.-E. Berg, Acta Chem. Scand. B 42, 294 (1988)