Studies related to Ambergris-type odorants

B. Winter
Research Laboratories, Firmenich SA, 1211 Geneva 8, Switzerland

Abstract - Examination of a series of active and inactive analogues of the ambergris-type odorant (-)-Ambrox® (Note a) has highlighted the steric accessibility of the functional group as one of the relevant structural factors for odoriferous activity. In these relatively rigid compounds, this parameter is modulated by the orientation and the close environment of the oxygen atom. Focusing on the polar part of these compounds, the organoleptic properties of several novel analogues of Ambrox® are discussed with respect to their specific structural features.

The valuable properties of ambergris result from the products of oxidative degradation of the main component in the natural product, the triterpene alcohol (-)-ambrein (1) (ref. 1). The tricyclic ether 2 and its hydrogenation product 3, both possessing a typical ambergris odour, were among the volatile compounds isolated in the early chemical elucidation work (ref. 2).

The related tricyclic ethers 5 and 6 were prepared during an investigation of the oxidation products from the labdane diterpenoid (-)-sclareol (4) (ref. 3). Compound 5, known as Ambrox® (Note a), has become a key ambergris-type fragrance used in perfumery and was only later, in 1977, identified among the odoriferous constituents of tincture of ambergris (ref. 4).

The growing demand for ambergris-type odorants, coupled to the dwindling of natural sources, have stimulated the search for substitutes, and a large number of analogues of 5 and 3 have been prepared and characterised (ref. 1). Careful examination of these analogues soon raised the question as to which structural features we required for a compound to have an ambergris-type odour activity. An early answer was the formulation by Ohloff of a structure-odour correlation known as the "triaxial rule of odour sensation" (ref. 5,1); more recently, an "ambergris triangle", based on electronic structural features, was proposed (ref. 6). However, many inactive compounds also fulfill the general structural conditions postulated as being necessary for ambergris-type activity.

Note a: Ambrox® is a registered trade name of Firmenich SA.
We have explored an approach using the concepts of oriented profile and steric accessibility of the functional group (ref. 7), focusing on a quantitative estimation of the degree of possible interaction between the polar (hydrogen bond acceptor) part of an odorant molecule and a hypothetical hydrogen bond donor group (e.g. OH) on the receptor site (ref. 8). Thus, the accessible polar surface area, assuming that it is a measure of the steric accessibility, was calculated (ref. 9) for each structure after optimisation by molecular mechanics (MM2) calculation (ref. 10) employing the molecular modeling software MODEL (ref. 11); the lower limit of accessibility necessary for activity was found to be about 6 Å², when using a probe radius of 1.4 Å. The results for a series of methylated analogues of compounds 2, 3 and 5 are presented in Table 1 (ref. 8)

<table>
<thead>
<tr>
<th>Active</th>
<th>Inactive</th>
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<tbody>
<tr>
<td><img src="image" alt="Structure 2" /> 9.3 Å²</td>
<td><img src="image" alt="Structure 7" /> 3.4 Å²</td>
</tr>
<tr>
<td><img src="image" alt="Structure 3" /> 8.3 Å²</td>
<td><img src="image" alt="Structure 8" /> 7.2 Å²</td>
</tr>
<tr>
<td><img src="image" alt="Structure 5" /> 12.8 Å²</td>
<td><img src="image" alt="Structure 10" /> 9.0 - 11.2 Å²</td>
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<tr>
<td><img src="image" alt="Structure 11" /> 8.8 Å²</td>
<td><img src="image" alt="Structure 12" /> 7.8 Å²</td>
</tr>
<tr>
<td><img src="image" alt="Structure 13" /> 5.5 Å²</td>
<td></td>
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</tbody>
</table>

It is worth noting that for compound 10 (ref. 6, 13) an accessibility range is calculated which takes into account the extended conformational freedom of the ethyl group; a similar situation was found in the study of a series of heteroring-opened analogues of 5 and 6 (ref. 12).

The investigation of regioisomeric analogues of Ambrox was inspired by the two known ethers 15 and 16, derived (ref. 14) from the natural product (+)-alantolactone (14), and which exhibited typical ambergris-type odour activity (ref. 1). On the other hand, the fact that compound 17 (ref. 15) had been found to be odourless was not unexpected when its accessibility (5.3 Å²) was compared to those of 15 (7.5 Å²) and (8.7 Å²). This result allowed us to predict that ether 22 (calculated accessibility: 8.0 Å²)
would be active; its synthesis, based on the work of Marshall and co-workers (ref. 16), confirmed our prediction (Scheme 1).

The syntheses of 24 (accessibility: 10.5 Å²) and 27 (accessibility: 15.7 Å²), two diastereoisomers of 22, were also effected (Scheme 2) and both compounds were found, as expected, to have a typical ambergris-type odour.

Two further derivatives, the spiro-ethers 30 and 31, which have extremely different orientations of the oxygen functionality, might be considered as intermediate cases between the Ambro6-type ethers and the linear-type ethers described above; their syntheses are presented in Scheme 3.

Spiroether 30 (accessibility: 9.2 Å²) was found active, with a predominant woody note, whereas 31 (accessibility: 0.7 Å²) was almost odourless. This result further confirms the hypothesis that steric accessibility of the oxygen atom is essential for activity in these particular ambergris-type odorants.
REFERENCES
11. W.C. Still, Dept. of Chemistry, Columbia University, New York, NY 10027, USA.