Musk Alcohols

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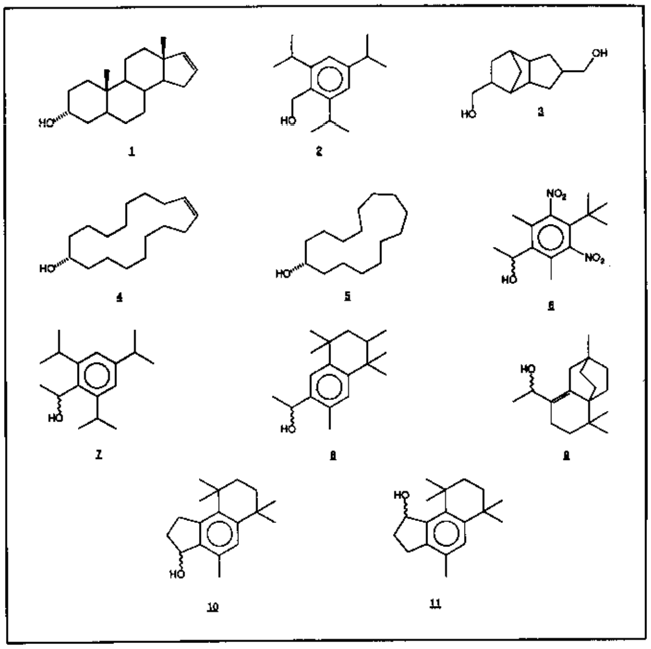
Structure-odor relationships among musk odorants, including both the shape and size of the hydrophobic portion of the molecule together with the position and identity of the functional groups(s), have been very widely studied.[1,2] A variety of functional groups are tolerated with retention of musk odor. Examples are ketone, ester, aldehyde, ether, nitro, cyano, and anhydride. Notably absent from the class of musk odorants are compounds bearing one or more hydroxyl group.

There are, however, a very few alcohols that have been reported to have a musk odor. For example 5α-androst-16-en-3α-ol [1] is still occasionally described as possessing a musky odor, although this has been shown not to be the case.[2] 2,4,6-Triisopropylbenzyl alcohol [2] has also been described as possessing a musky odor,[3] as has "muscomere" [3] although this apparently acts primarily as a fixative for other materials rather than being musky per se.[4]

The purpose of the research described herein is to investigate the odors of some alcohols which might otherwise be expected to be musky were it not for their possession of that particular functional group.

Methods

In order to limit variation due to the nature and placement of the polar functional group, the set of test compounds was generally limited to secondary alcohols derived by reduction of ketones known or reputed to have a musk odor. Within this constraint the test compounds [4-11] were chosen to have widely differing structures in order to probe the structure-odor relationship within this group. Thus the set includes two macrocycles [4, 5], two monocyclic benzenoids [6, 7], one bicyclic compound [8], and three tricyclic compounds [9-11].



With the exception of the tricyclic compounds, the corresponding ketones are commercially available, and the alcohols [4-8] were prepared by reduction of civettone, cyclopentadecanone, musk ketone, 2,4,6-triisopropylacetophenone, and tonalid respectively. It should be noted that 2,4,6-triisopropylacetophenone is not a musk odorant and was chosen by virtue of its relationship to the reputed musk alcohol [2]. The production of the corresponding alcohol [7] was achieved by using lithium aluminum hydride, and the other reductions were performed with sodium borohydride in ethanol to give the alcohols [4-6, 8]. In the cases where a chiral center is introduced by the reduction, the odor evaluation was done on the purified racemic mixture without attempt to resolve the enantiomers.

The ketones corresponding to the alcohols [9, 10] were prepared according to the literature procedures[5,6] and reduced with diisobutylaluminum hydride and sodium borohydride respectively. In the former case the mixture of ketones produced by the

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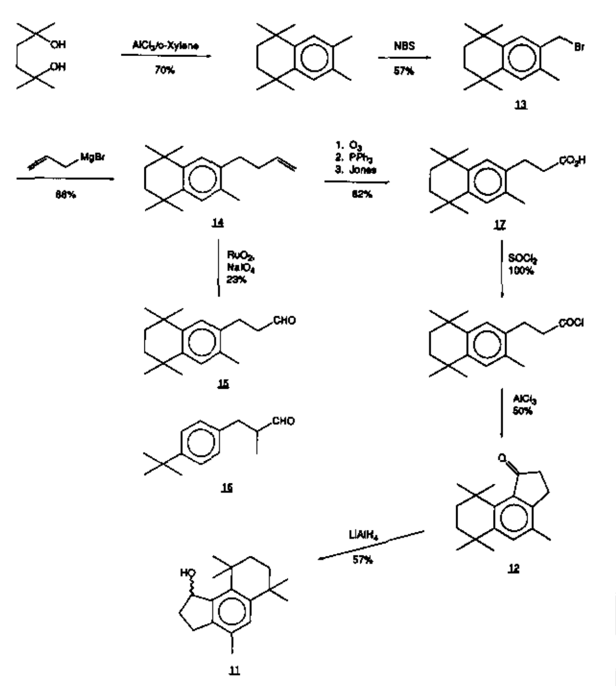

Scheme 1

Table I. Results of the evaluation of test compounds [4-11] at SRI International

Test compound	Odor characteristic
4	Sterolic
5	Woody
6	Woody
7	Woody
8	Woody
9 (each isomer)	Woody
10	Sterolic
11	Woody

acetylation of thujopsene was reduced, and the isomers of the alcohol were separated by flash chromatography after the reduction.

The ketone [12, Scheme 1] has been reported to have a musk odor although it is not clear whether the central ring was intended to be benzenoid or saturated.[7] In any case the synthesis was not reported and one therefore had to be devised. The successful route is shown in Scheme 1. Several intermediates and by-products along the way have odors worthy of note. Firstly the bromide [13] has a strong and pleasant musk odor. This is not unreasonable given its very close structural relationship with tonalid (compare the hyacinth odorants β-bromostyrene and phenylacetaldehyde).

However the nature of the polar functional group is indeed unusual for a musk odorant and it is interesting from the point of view of structure-odor relationship that a bromide is able to function in this capacity. Of course from a practical point of view it is of little value as a musk odorant due to the toxicity of organic halides. It is nevertheless possible that such compounds may be of use in preparing irreversibly bound odorant-receptor complexes for X-ray or other study, due to the irreversible electrophilic nature of benzylic bromides. An alternate hypothesis for the odor of this bromide [13] could be its in vivo conversion to the corresponding aldehyde prior to its activation of the putative musk receptor; that is the bromide would be a pre-odorant.

Oxidation of the olefin [14] with ruthenium dioxide/sodium periodate unexpectedly gave the aldehyde [15] which has a beautiful odor resembling that of lilial [16]. The structural similarity between the two aldehydes is clear and the higher molecular weight compound could well be useful as an odorant of the lilial type with lower volatility. It should be noted that the conversion to the aldehyde was not optimized and it is likely that more efficient means could be found for this transformation.

A good method of converting the olefin [14] to the required carboxylic acid [17] was found in sequential treatment with ozone, triphenylphosphine, and Jones reagent. Unexpectedly the crude reaction product had a strong musk odor. This was traced to 6-formyl-1,1,4,4,7-pentamethyltetralin which was formed as a by-product, and is known to have a strong musk odor.[1]

The ketone [12] has a very faint woody odor and is not at all musky. This is not surprising, as the 1,2,3 arrangement of the polar functionality and the quaternary centers around the central ring is known not to be conducive for the generation of musk odor.[1] By contrast musk odorants with the 1,2,4 or more commonly the 1,3,4 and 1,3,5 arrangements are well known.[1] The published claim that a particular compound with the 1,2,3 arrangement should theoretically have a good musk odor is therefore somewhat unusual.[7]

Results

The test compounds [4-11] were evaluated for their main odor characteristic by the author and other personnel of the Bio-Organic Chemistry Laboratory at SRI International. The results are shown in Table I.

None of the alcohols possess a musky odor, even to the slightest degree, and all but two are woody. The two exceptions, civettol [4] and 4,6,6,9,9-pentamethyl 6,7,8,9-tetrahydro α-naphthindan-3-ol [10] have an odor resembling that of 5α-androst-16-en-3-α-ol [1]. Although the odor of this sterol has been described as "sexual,"[8] "sterolic" is perhaps a more neutral term pending definitive evidence that it is indeed a human pheromone.[9] However, it should be noted that far from all sterols possess this odor quality.[10]

Although the structural resemblance of civettone to 5α-androst-16-en-3-one has long been recognized,[11] it has nevertheless been demonstrated that they possess quite different odors from each other (musky and urinous respectively).[2] It is therefore somewhat surprising that the alcohols [4 and 1 respectively], resulting from the reduction of these compounds, have odors that are quite similar to each other. Indeed, a three-way comparison of [1, 4] and 5α-androstan-3α-ol showed that [1] and [4] were the most similar to each other in odor.

Civettol, of course, is a substance which has been known about for a long time and is indeed a natural component of civet.[12] However, the value to perfumery of its odor in its own right appears to have been largely overlooked.

Not surprisingly the other alcohol [10] with a sterolic odor also has significant structural resemblance to the androstenol [1]. Specifically the spatial relationship of the three rings and the disposition of the hydroxyl group are similar. The lack of sterolic odor in tonalol [8] is additional confirmation that an axial or pseudo-axial configuration of the hydroxyl group [as in **10**] is required for the generation of this odor.[10]

Conclusions

In the absence of specific evidence to the contrary, a tentative conclusion of this study is the general hypothesis that alcohols do not possess a musk odor. Also confirmed is the notion that a 1,2,3 arrangement of polar functionality and quaternary centers around a central ring is not conducive for the generation of musk odor.

Finally, the most useful result is that it is easy to prepare non-steroidal olfactory analogs of 5α-androst-16-en-3α-ol. This is both of scientific value for the study of structure-odor relationships, and also of potential commercial value for less expensive replacements of the odorous steroids which have seen successful use in the 1980s.

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