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Foreword

An overflow of the papers dealing with isolation, analysis and structure have been accommodated in this volume.

After we know about the structure of an important odorous chemical it is customary to develop a pragmatic synthetic method for its preparation. On the basis of structure odour-relationship it has also become attractive and alluring to synthesize an easily accessible product which will simulate fascinating odour of the natural product. Several interesting papers covering this area have been included in this volume.

As before, there were more papers than we could accommodate. Therefore, many papers had to be taken for Poster presentation only. Response from the scientists whom we had invited has been overwhelming. We had no other way out. We would have liked to accommodate many more papers for oral presentation but this was not possible within the permissible time-frame.

The Congress Committee has decided to publish all the papers including those which have been received very late and also those which have been sent for Poster presentation after the session of the Congress is over. This naturally will take some time and I request the participants to bear with us.

As usual, we have adopted the practice of only minor or marginal editing. This appeared to us to be necessary and desirable because the authors come from about 40 countries with diverse background of the English language. Excessive or over-editing would have affected their personality. We avoided that.

With greetings and good wishes,

PROF. S.C. BHATTACHARYYA
Chairman,
Scientific Programme Committee

Contents

Computer Modelling of Structure Activity Relationship in Sandalwood Odour Molecules

Armin Becker, Gerhard Buchbauer, Susanne Winiwarter*
Institute of Pharmaceutical Chemistry, University of Vienna, Austria

Anton Beyer and Peter Wolschann
Institute of Theoretical and Radiation Chemistry, University of Vienna

Dr. Gerhard Buchbauer, was born in 1943 in Vienna, Austria. He studied Pharmacy at the University of Vienna, obtained a degree of Master of Pharmacy (= Mag. pharm.) in 1966, and degree of Doctor of Philosophy at the faculty of natural science of the University of Vienna in 1971.

He became assistant at the Institute of Pharmaceutical Chemistry in 1966 and later carried on with post-doctoral studies at Prof. Dr. C.H. Eugster, Institute of Organic Chemistry of the University of Zürich, Switzerland, in 1977–78. After being appointed as university lecturer, he was appointed as Head of Department in January 1979. At present, there are about 15 colleagues in the team. The main research topics are structure-activity-relationship of odour molecules and synthesis in the field of terpenes, alicyclics and fragrance compounds.

ABSTRACT

The class of sandalwood aroma compounds consists of more than 70 well-known substances, having the typical sandalwood odour. They seem to be a good model for studying the relationship between structure and activity. There are several possibilities to compare two molecules: one approach is to fit special atoms of each molecule with mathematical methods (e.g. least square fitting or matrix minimizing); another is to use computational graphics to superimpose one molecule upon the other. As only the surface of a molecule can react with a possible receptor, their shape is of great importance, too. In addition, the influence of the electron densities must be considered. The basis of such comparison has to be conformational analysis. For most molecules, structural calculations yield several relevant conformations existing in thermodynamical equilibrium. These computations are based on the method of molecular mechanics (Force field method). Electronic density distributions are calculated by a semiempirical method (AM1).

Our results prove that odour molecules with sandalwood fragrance seem to consist of an almost flat structure linking the polar group on one end to the very voluminous part of the rest of the molecule.

At present, the molecular basis of olfaction is unknown. Many investigations of this sensitive and specific phenomenon have been undertaken leading to theories which relate certain physicochemical properties of odour molecules, such as vapour pressure, partition coefficient, reactivity and molecular shape to olfactory behaviour [1]. Studies of *structure-activity-relationship* (SAR) of biologically active substances try to find a connection between the active site of a molecule and the complementary shape of a receptor place. In the field of pharmaceutical and medicinal chemistry, such a procedure in numerous cases already led to very valuable drugs and thus enabled the scientists to heal a lot of maladies and to gain more information about the biochemical reactivity of a pharmacon. But in order to study such as SAR, one requires complicated and expensive pharmacological screening programs.

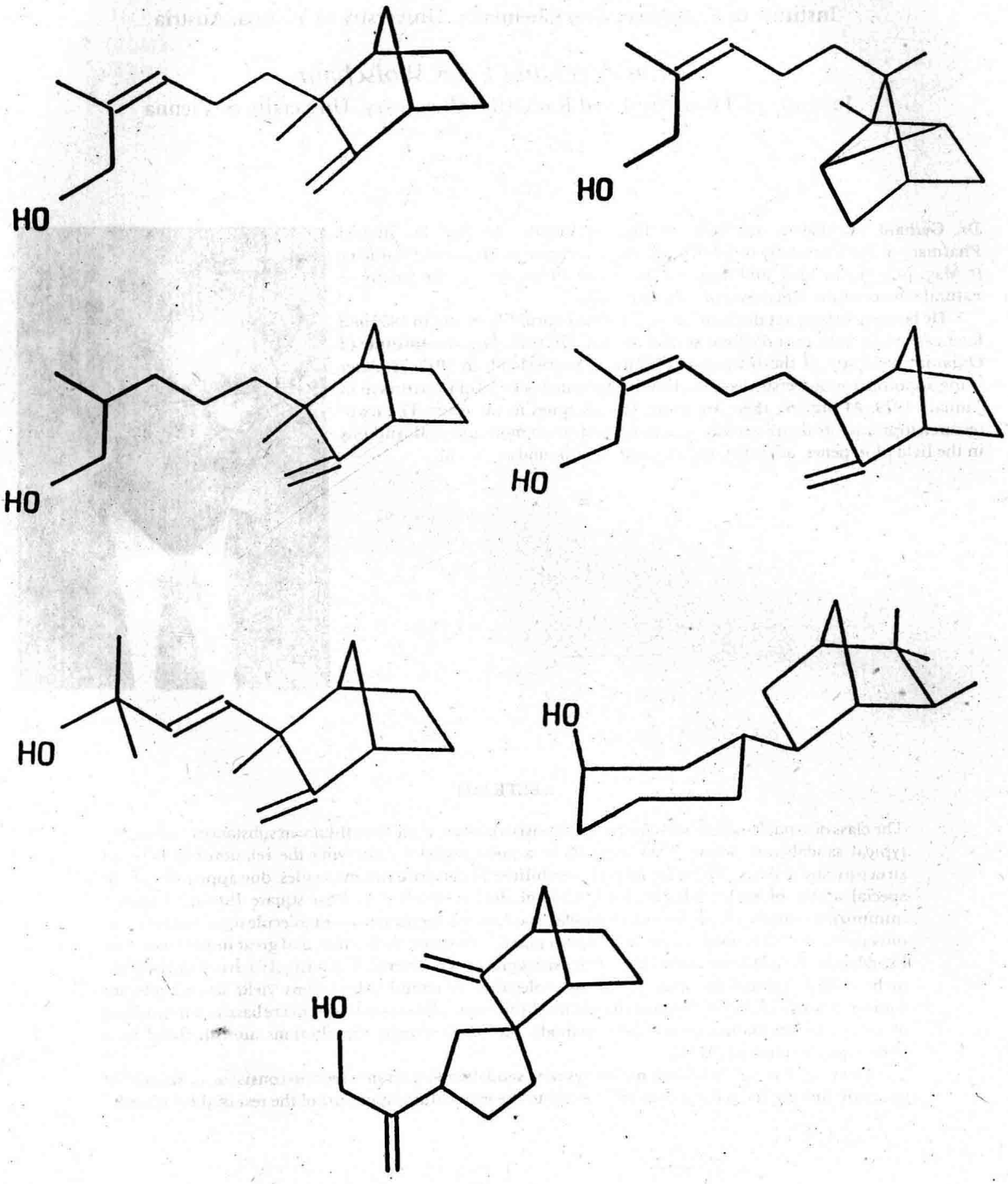

Figure 1.

Now odour molecules are a group of biologically active compounds which do not possess these difficulties and which allow very simple and quick SAR-studies, especially if one compares a distinct odour with a standard one. Even if some knowledge of the receptor proteins of the olfactory epithelium has been obtained [2–5] there is still a great gap in our knowing how a molecule with a certain shape evokes an odour impression whereas a very similar molecule fails to do the same. To gain more insight into the molecular basis of olfaction, we have analysed molecular geometries of a distinct odour quality in order to find common structural elements. Convenient systems for such an

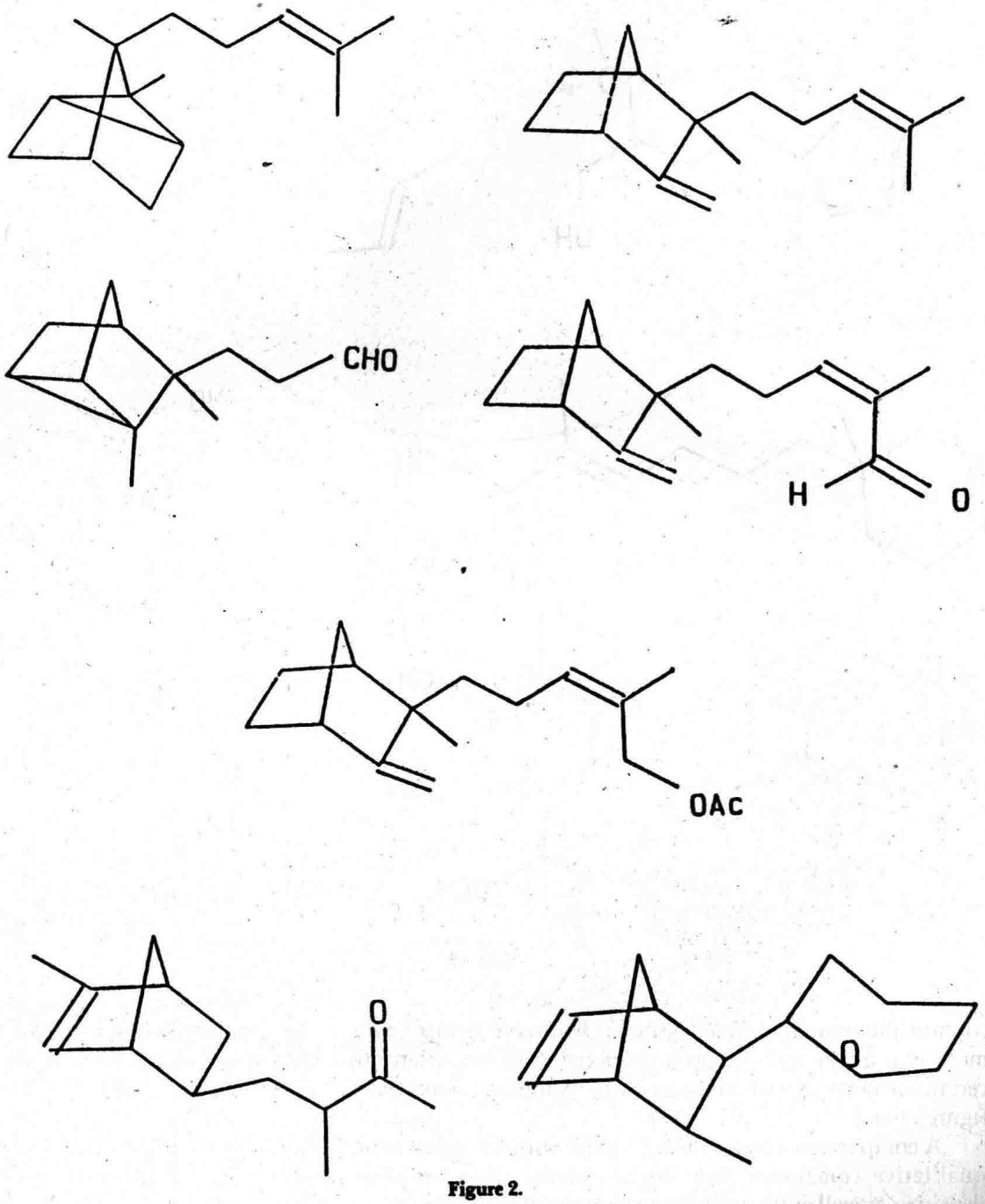

Figure 2.

investigation are compounds possessing a sandalwood odour, because this is such a distinct odour quality and because more than seventy natural and synthetic odour molecules of the same typical woody fragrance partly with various tonalities are known [6]. In the first three figures, some typical compounds with sandalwood odour are shown (figures 1-3).

These odorous molecules are of medium size; they differ somewhat in structure and also

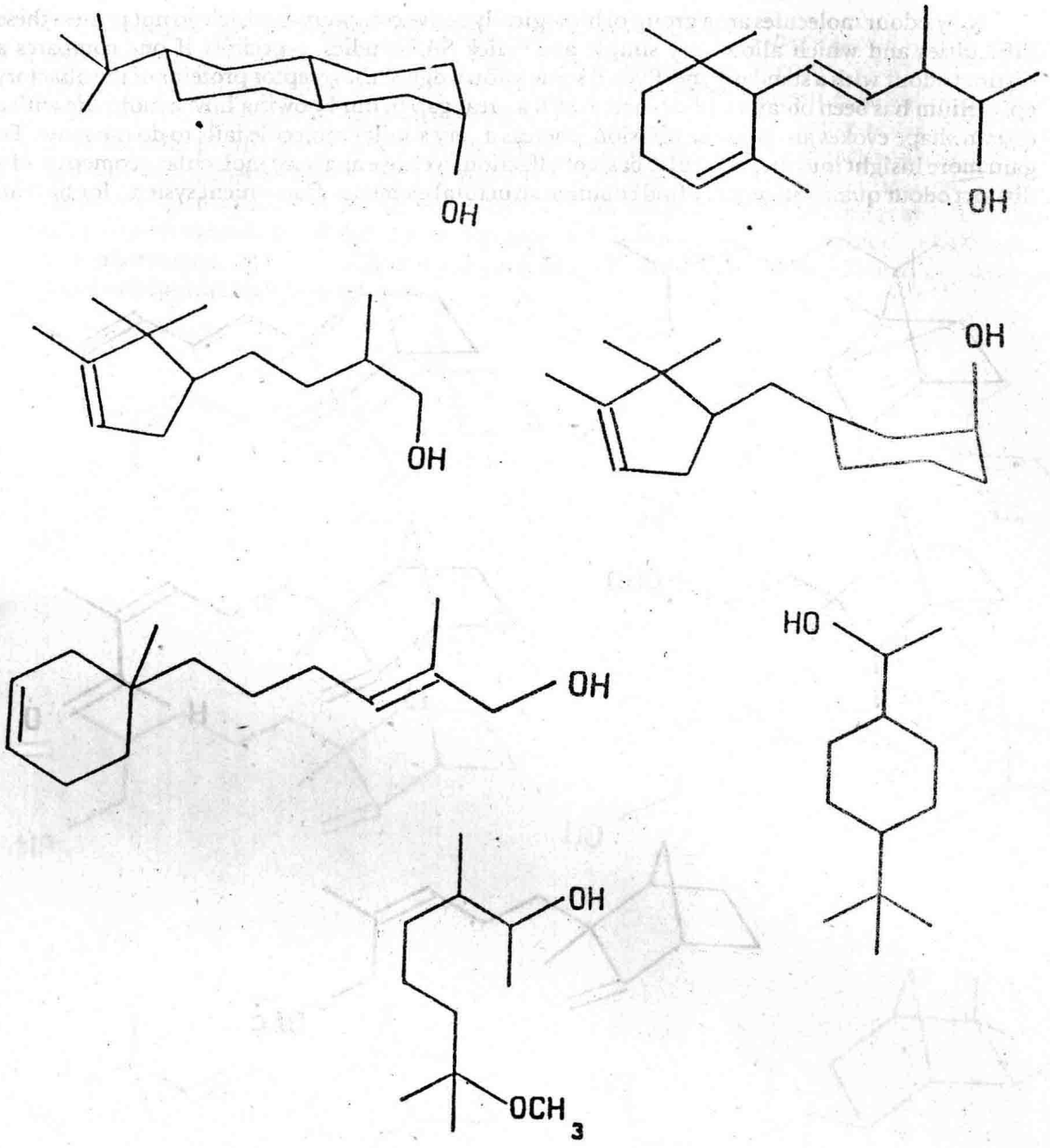

Figure 3.

contain different functional groups, hydroxyl group being dominant. Some properties of the molecular geometry have been proposed to be important for a typical odour, as, for example, a certain distance of a quarternary carbon atom to an oxygen atom of a functional group [7, 8] (see figures 4 and 5).

A comparison of odorous molecules with odourless compounds of similar structure leads to a qualitative conclusion that intramolecular distances of distinct centres of different electron densities, as well as the molecular shape are of importance for the odour activity. In the present work we want to compare β-santalol (**2a**), the main odoriferous constituent of a very valuable sandalwood oil, with the geometries of some other synthetic compounds showing this fragrance.

The first step of our studies was a confromational analysis, using the method of molecular mechanics. This method seems to be convenient for the calculation of molecular geometries in the gas phase and thus enables us to calculate the conformations of the molecules by variation of all

A THEORETICAL MODEL

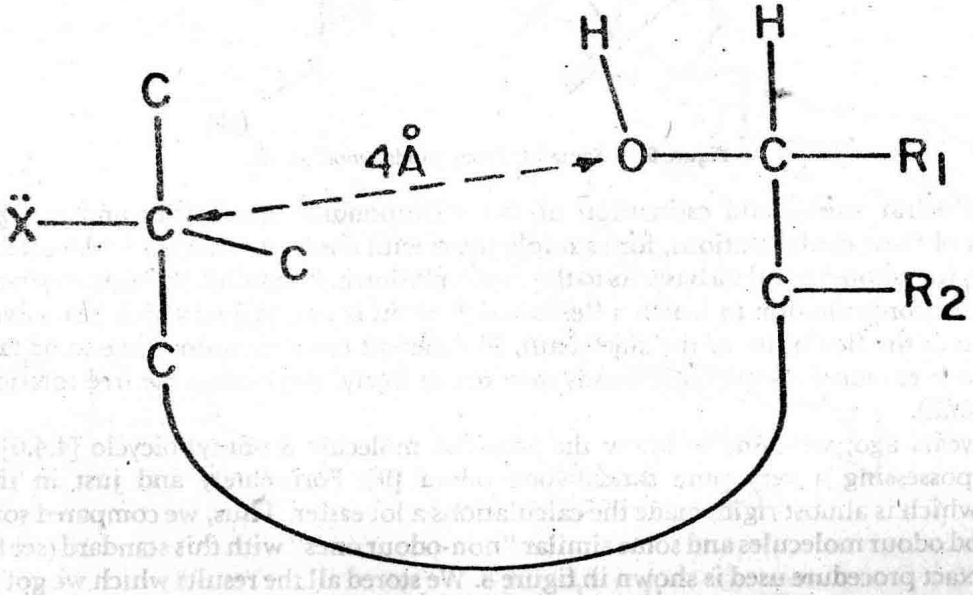

Figure 4. R.E. Naipawer *et al.* [7]

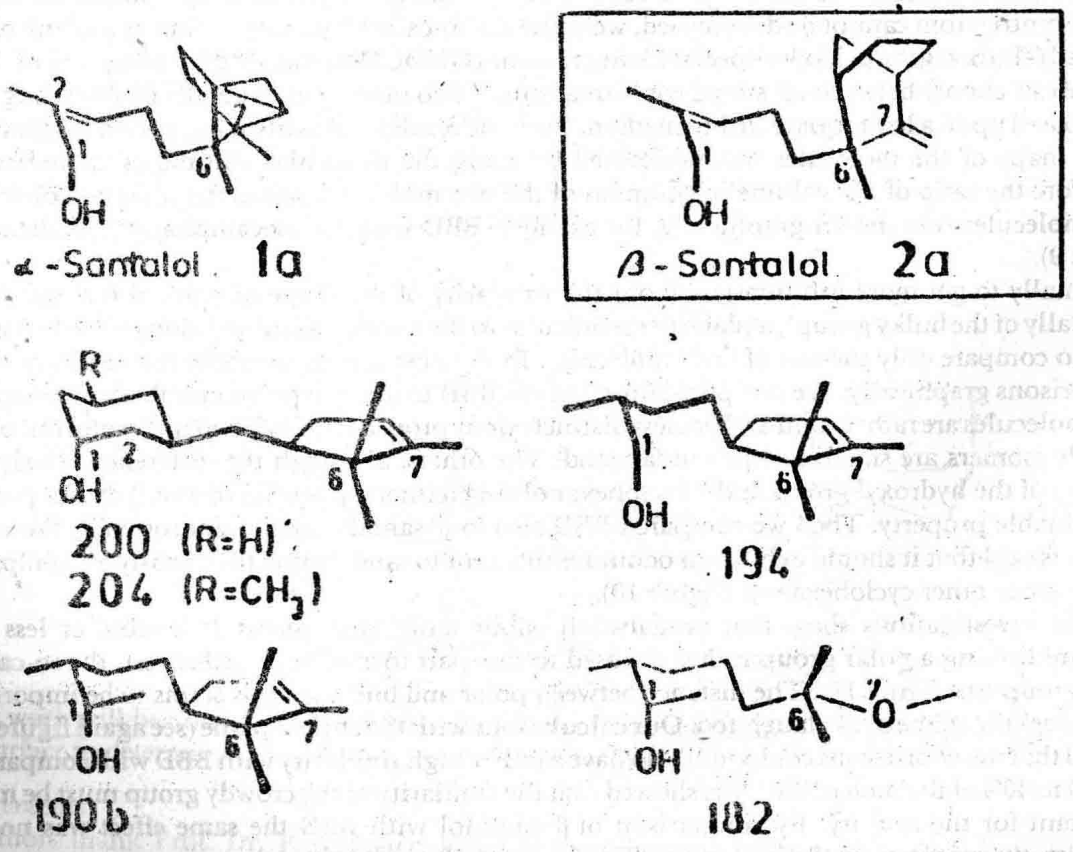

Figure 5. E.J. Brunke and E. Klein. [8]

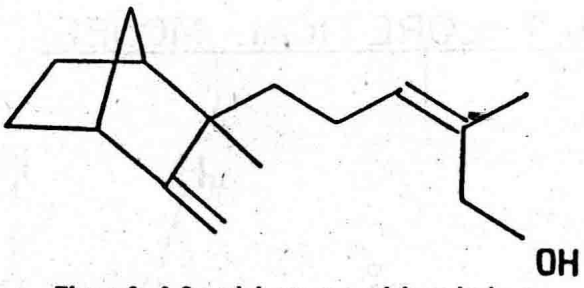

Figure 6. β-Santalol, strong sandalwood odour.

relevant dihedral angles and estimation of the corresponding geometries and energies. The geometries of these conformations, for example those with energies within 3 kcal/mole from the lowest one, were stored in a data base. As to the conformations: β-santalol (see figure 6) consists of a rigid bicyclic conformation to which a flexible side chain is bound and which bears two double bonds. Due to the flexibility of the side chain, 81 different conformations have to be taken into account (four carbon-carbon single bonds may rotate freely, neglecting the free rotation of the carbinol bond).

Two years ago, we came to know the artificial molecule 8-t-butyl-bicyclo [4.4.0] decanol ("BBD") possessing a very pure sandalwood odour [9]. Fortunately and just in time, this molecule which is almost rigid, made the calculations a lot easier. Thus, we compared some other sandalwood odour molecules and some similar "non-odour ones" with this standard (see figure 7).

The exact procedure used is shown in figure 8. We stored all the results which we got from the MOLMEC program package using Allingers MM2 [10] parameter set in a data base, because molecular mechanics give no information on electron densities. As the calculation of, for example, dipole moments is only a rough approximation, semiempirical methods on the minimized geometries were performed using Dewar's AM1 program [11, 12].

In the next step we selected some comparable centres of the molecules—preferentially atoms of least distance-and including common structural elements, such as the hydroxyl group, the adjacent (carbinol) carbon atom and further centres of equal electron density or of similar substitution. If a special centre-atom cannot be determined, we defined a so-called "dummy"-atom as a centre of the crowded (=bulky) group. Now a special fitting routine (GUDCON) was used for comparison. This routine can choose between all stored conformations of two molecules to get the forms fitting best and is based upon a least square fitting method. With the results of this fitting routine a comparison of the shape of the molecules was performed by using the molecular volume as an indicator. Therefore the ratio of the volume in common of the two molecules versus the residual volume of both molecules was shown graphically, for example BBD with the isocamphanyl cyclohexanol (figure 9).

Finally to get more information about the similarity of the shape of parts of the molecules (especially of the bulky group), a plane perpendicular to the x-axis was shifted along this abscissa in order to compare only the rest of both molecules. In the next figure, we show the results of these comparisons graphically, We compared the standard BBD to some terpenyl cyclohexanols because these molecules are rather rigid and possess distinct odour properties. Only two molecules out of ten possible isomers are smelling like sandalwood. The others, although the difference is only the position of the hydroxyl group in the cyclohexanol ring (either equatorial or axial) do not possess this valuable property. Then we compared BBD also to β-santalol and to androstenol. From the latter it is said that it should exhibit an odour reminiscent to sandalwood [9]. Finally we compared BBD to some other cyclohexanols (figure 10).

Our investigations show that sandalwood odour molecules consist of a more or less flat structure linking a polar group rather exposed to this part to a more crowded rest, the so-called bulky group (see figure 11). The distance between polar and bulky groups seems to be important and so does the shape of the latter, too. Our calculations with the shifted plane (see again figure 10) showed that the odoriferous compounds do have a rather high similarity with BBD with comparing only 30 to 40% of the molecules. This showed that the similarity of the crowdy group must be more important for the activity. By comparison of β-santalol with BBD the same effect was noted. However, the orientation of the plane used so far was rather arbitrary.

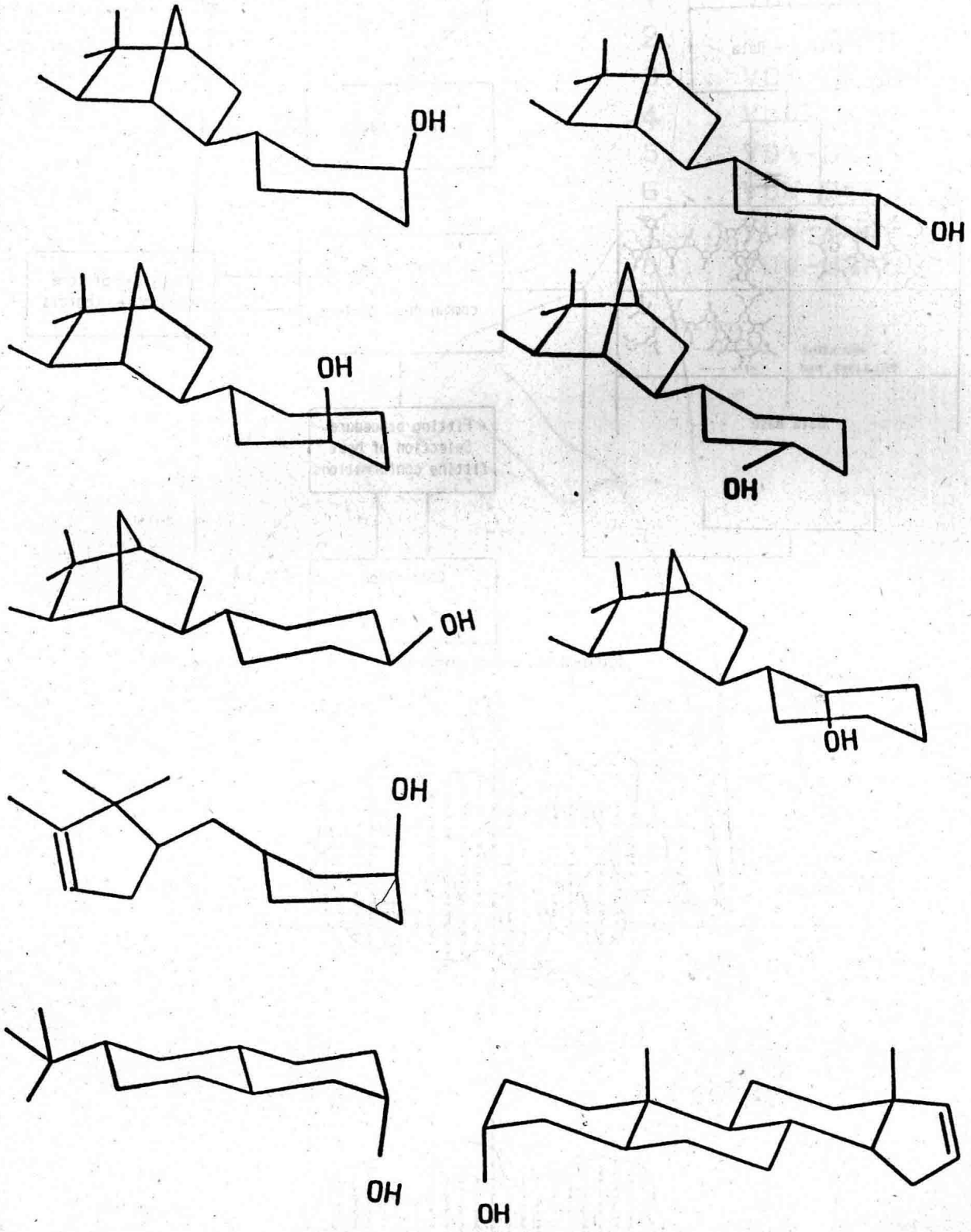

Figure 7. Compared substances.

Further work will be done to calculations with various plane angles and comparisons of the molecular surface to determine the essential part of the bulky group.

Acknowledgements

The authors thank Prof. Dr. P. Schuster, Head of the Institute of Theoretical Chemistry,

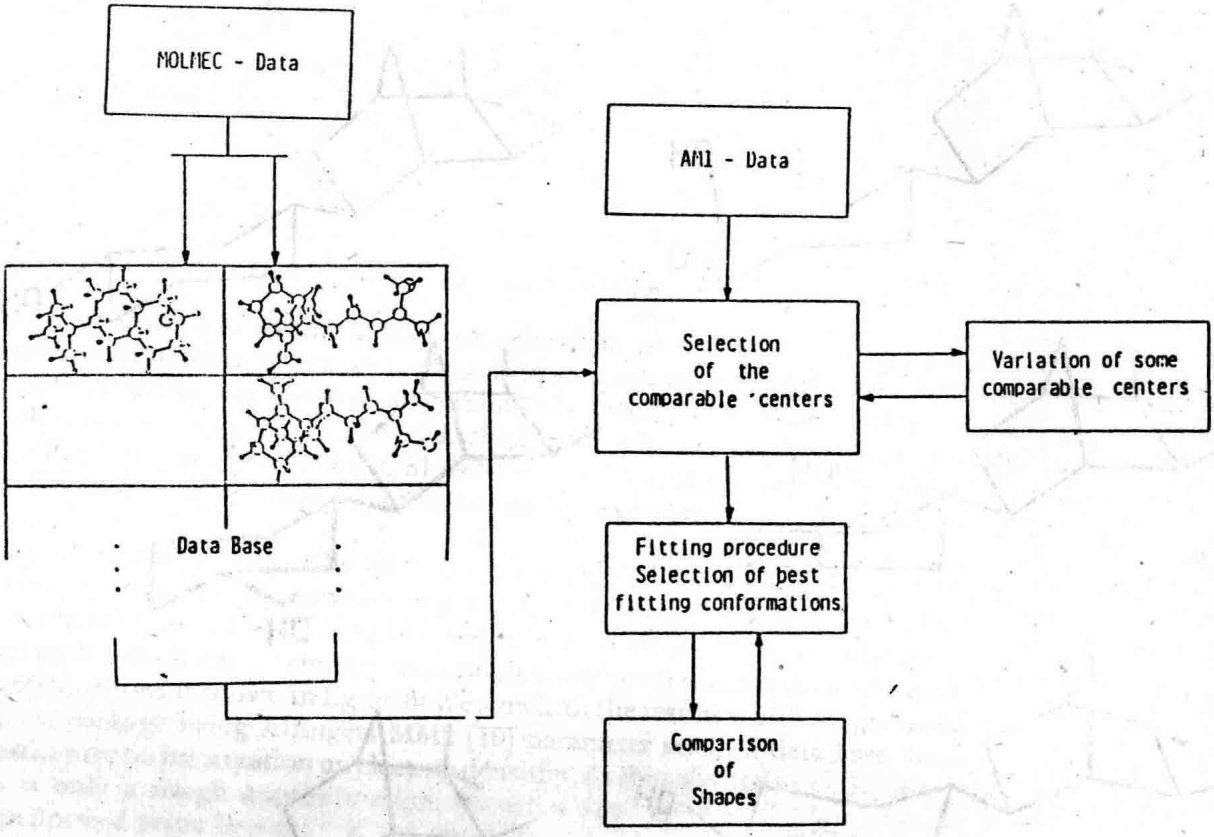

Figure 8. Scheme of investigation.

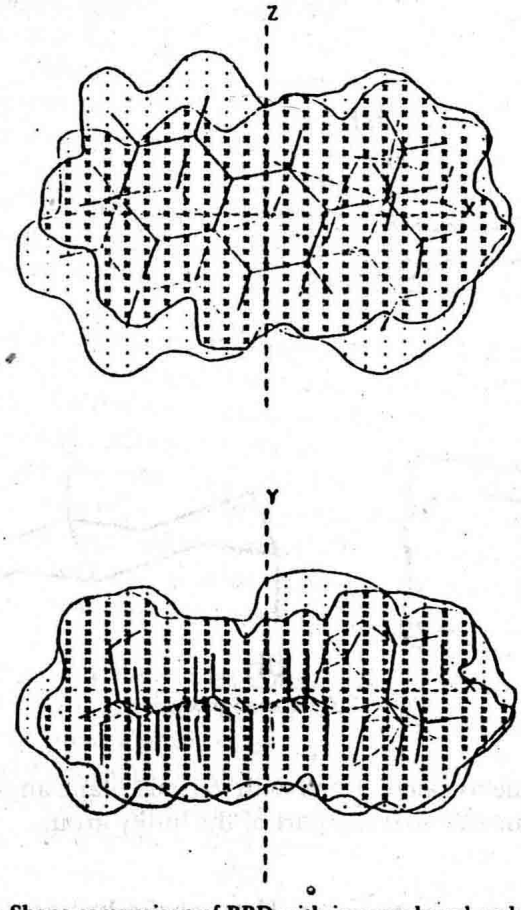

Figure 9. Shape comparison of BBD with isocamphanyl cyclohexanol.

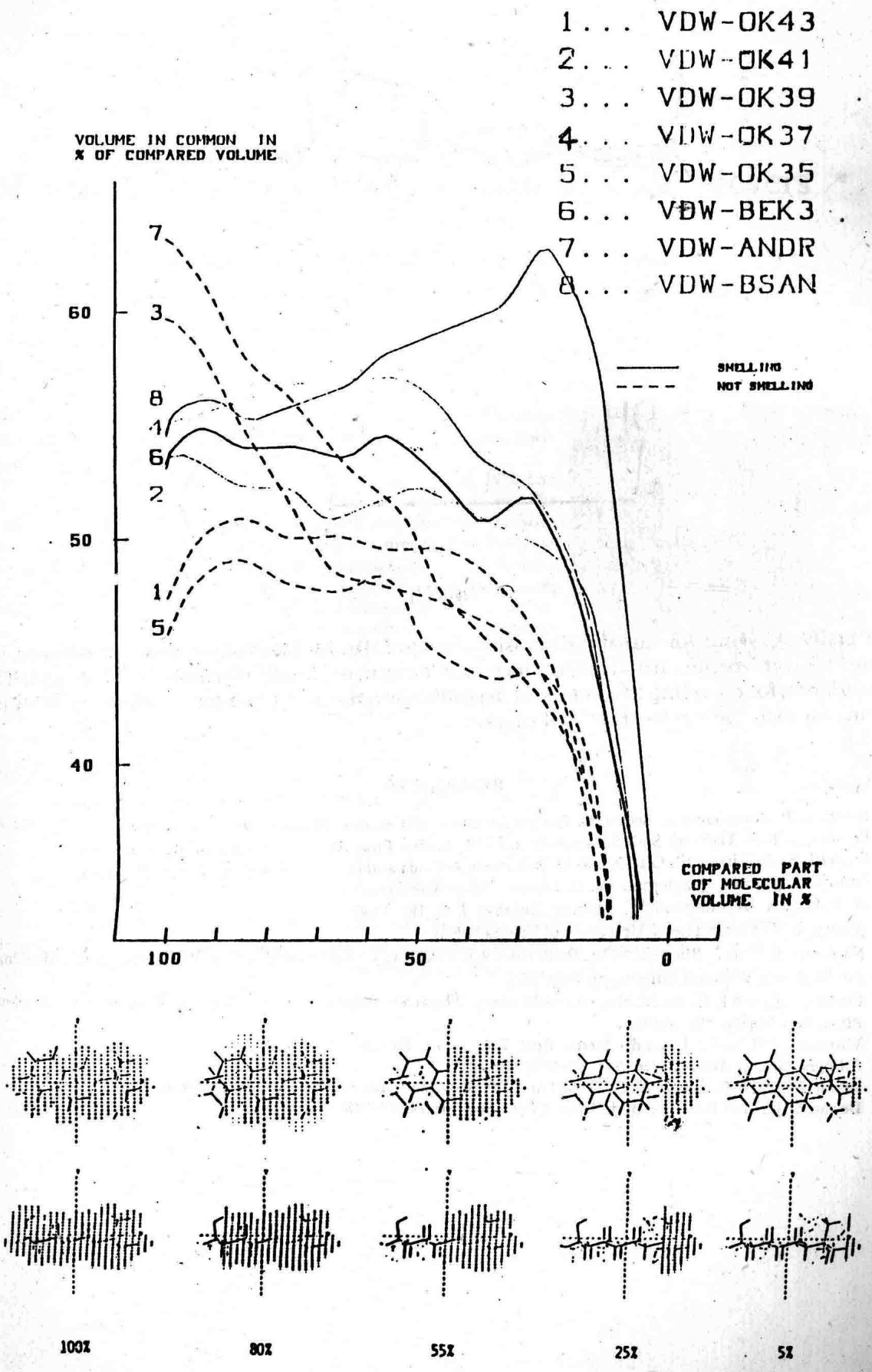
1 . . . VDW-OK43
2 . . . VDW-OK41
3 . . . VDW-OK39
4 . . . VDW-OK37
5 . . . VDW-OK35
6 . . . VDW-BEK3
7 . . . VDW-ANDR
8 . . . VDW-BSAN
VOLUME IN COMMON IN % OF COMPARED VOLUME
60
50
40
SHELLING
NOT SHELLING
COMPARED PART OF MOLECULAR VOLUME IN %
100
50
0
100%
80%
55%
25%
5%

Figure 10.

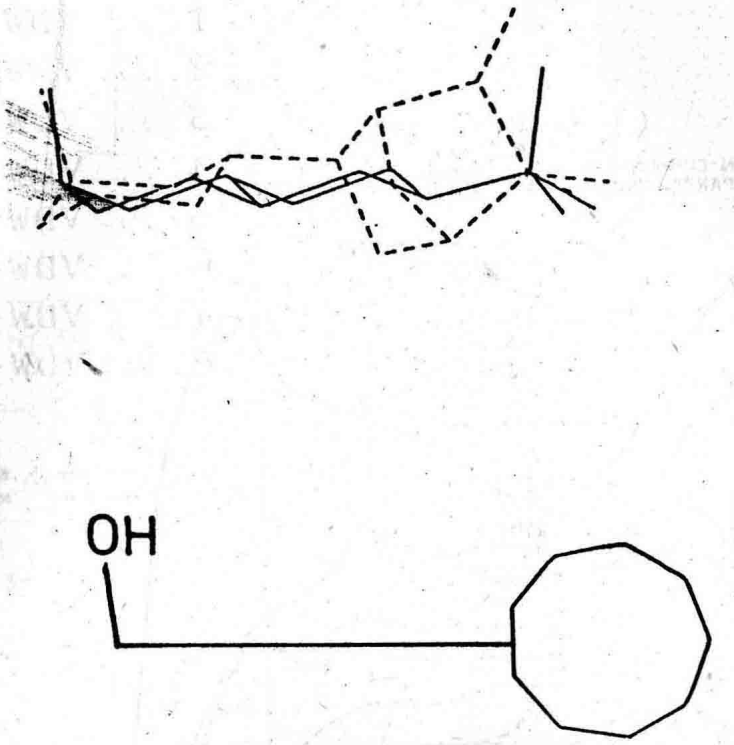

Figure 11.

University of Vienna for valuable discussions, to Prof. Dr. H. Lischka, of the same institute, for using "Silicon Graphics Iris 3115", to Dr. J.G. Witteveen, of Naarden International, Bussum, The Netherlands, for providing us a sample of the BBD-substance and to Dragoco-Vienna and Madaus-Vienna for their interest and financial support.

REFERENCES

1. Beyer, A., P. Wolschann, A. Becker, G. Buchbauer and S. Winiwarter. *Flavour & Fragr. J.* 3 (1988).
2. Pevsner, J., R.R. Trifiletti, S.M. Strittmatter and S.H. Snyder. *Proc. Natl. Acad. Sci. USA* 82: 3050 (1985).
3. Bignetti, E., R. Tirindelli, G.L. Rossi, M. Bolognesi, A. Coda and G. Gatti. *J. Mol. Biol.* 186: 211 (1985).
4. Pace, V., E. Hanski, Y. Salomon and D. Lancet. *Nature* 316: 255 (1985).
5. Heck, G., J.A. De Simone and K. Persaud. *Biophys. J.* 49: 182 (1986).
6. Jelinek, E., Diploma Thesis, University of Vienna (1985).
7. Naipawer, R.E., K.L. Purzycki, G.W. Shaffer and R.E. Erickson. In: *Essential Oils*, B.D. Mookherjee and C. Mussinan, (eds.) Allured, Wheaton, Illinois, pp 105 (1981).
8. Brunke, E.J., and E. Klein. In: *Fragrance Chemistry. The Science of the Sense of Smell*, E.T. Theimer, (ed.), Academic Press, New York p. 397 (1982).
9. Witteveen, J.G. and A.J. van der Werdt. *Recl. Trav. Chim. Pays-Bas*, 106: 29 (1987).
10. Allinger, N.L. *J. Amer. Chem. Soc.*, 99: 8127 (1927).
11. Dewar, M.J.S., E.G. Zoebisch, E.F. Healy and J.P. Stewart. *J. Amer. Chem. Soc.*, 107: 3902 (1985).
12. Dewar, M.J.S. and K.M. Dieter. *J. Amer. Chem. Soc.* 108: 8075 (1986).