Monatshefte für Chemie 125, 1091–1099 (1994)

Monatshefte für Chemie
Chemical Monthly

On the Odour Shift From Bitter Almond Odour to Cinnamic-Floral Notes*

G. Buchbauer[1], **H. Kalchhauser**[2], **P. Wolschann**[3], **M. Yahiaoui**[4], and **D. Zakarya**[5]

[1] Institut für Pharmazeutische Chemie, Universität Wien, A-1090 Vienna, Austria
[2] Institut für Organische Chemie, Universität Wien, A-1090 Vienna, Austria
[3] Institut für Theoretische Chemie und Strahlenchemie, Universität Wien, A-1090 Vienna, Austria
[4] Laboratoire de Chimie des Plantes et de Synthese Organique et Bioorganique, University Mohammed V, Fac. Sciences, Rabat, Morocco
[5] Faculty of Sciences, University "Moulay Ismail", Meknes, Morocco

Summary. The structural differences between bitter almond odour substances and molecules with cinnamic or floral odour notes were investigated by comparison of a number of compounds with various synthetic modifications. An attempt was made to find a systematic principle for the change of the odour notes.

Keywords. Bitter almond odour; Cinnamic odour; Floral odour; Structure odour relationship.

Zum Geruchswechsel von Bittermandelgeruch zu zimt-blumigen Noten

Zusammenfassung. Strukturelle Unterschiede zwischen Substanzen mit Bittermandelgeruch und Molekülen mit zimtartigen oder blumigen Noten wurden durch Vergleich einer Anzahl von durch Synthese verschieden modifizierten Verbindungen studiert. Es wurde versucht, ein systematisches Prinzip für den Geruchswechsel zu finden.

Introduction

Compounds with an odour of the bitter almond type have aroused manifold interest among fragrance chemists especially when discussing odour theories [1,2]. *Amoore*'s sterical theory [3] tries to elucidate the common properties of this class of compounds with regard to the olfactive process as well as *Wright*'s vibrational hypothesis [4,5], and the valence charge distribution for some of the basic compounds of this odour type have been discussed by *Lindner et al.* [6].

The classical bitter almond odour is due to the hydrolysis products of amygdaline (= mandelonitrile-β-gentiobioside), namely benzaldehyde, hydrocyanic acid, mandelic acid and glucose. The essential oil obtained after hydrolysis and distillation is a mixture of benzaldehyde and hydrocyanic acid, both of which are responsible for this characteristic smell.

---

* Dedicated to Prof. Dr. K. Schlögl on the occasion of his 70th anniversary

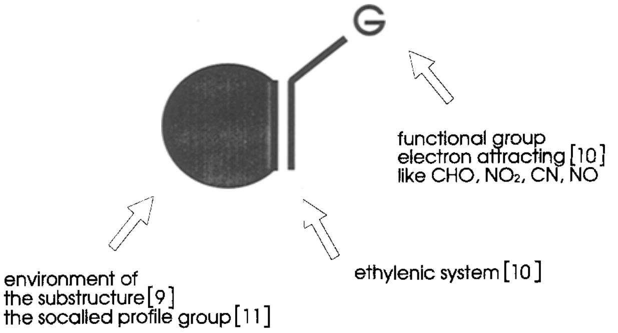


Fig. 1. Structural parameters of the bitter almond odour [9]

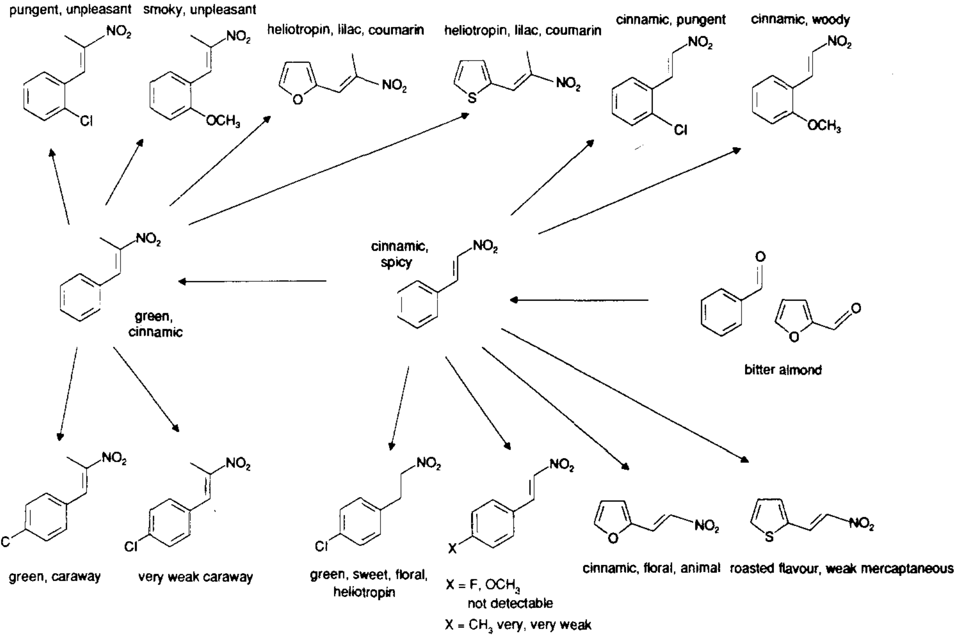
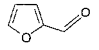
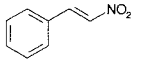
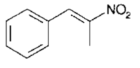
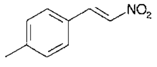
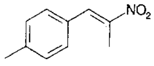
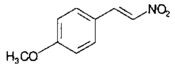
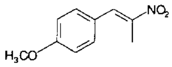
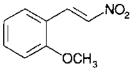
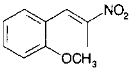
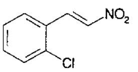
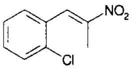
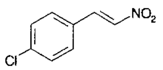
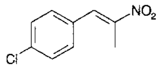
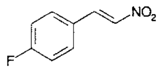
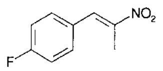
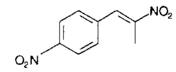
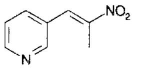
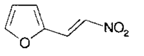
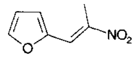
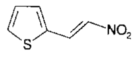
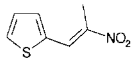
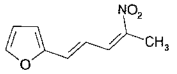
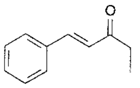
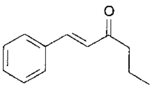
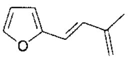
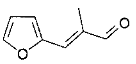
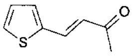
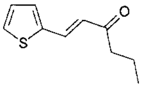
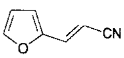
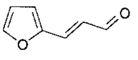
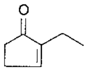
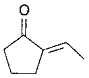
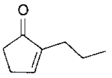
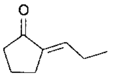


Fig. 2. Shift from bitter almond odour to other notes

In extension to the above mentioned theories, the search for parameters which are responsible for modifications of the classical bitter almond odour still continues. *Wright* tried to explain the change from bitter almond to a cumin type of odour on basis of far infrared vibrations [7]. *Eriksson et al.* [8] studied the odour shift from bitter almond to other notes by inserting an osmophoric substitutent, e.g. 4-methyl nitrobenzene, in the *para*-position of the aromatic nucleus and tried to explain such an odour transition by structural, interactional, sterical and thermal-motion parameters of the molecule. *Zakarya et al.* [9] finally succeeded in putting more light on the substructure which is responsible for the bitter almond odour, and recently proved the importance of the structural environment of this substructure [9–11] (see Fig. 1).

With these parameters in mind, we present in this paper some rules for the shift from bitter almond odour to spicy, floral, cinnamic, and balsamic notes. We also describe the comparison of similarities between molecules belonging to the bitter almond type and those belonging to other groups (Fig. 2).

Table 1. Compounds **1**–**34** listed together with their odour descriptions

1		bitter almond
2		cinnamic aldehyde, a bit clove-like, spicy
3		green note (dill), cinnamic, mild
4		very, very weak cinnamic
5		green (dill), caraway, benzylidene-like
6		not detectable
7		not detectable
8		mild cinnamic, later on woody (cedar)
9		smoky, burnt, spicy, lovage-like, unpleasant
10		cinnamic, aggressive, pungent
11		more aggressive then **10**, pungent, really unpleasant, plastic
12		green, sweet, heliotropin, anisaldehyde, floral
13		very weak caraway-like, carvon
14		not detectable
15		very weak cinnamic, green (dill)
16		not detectable
17		reminiscent of tobacco, weak
18		mild cinnamic, floral, animal
19		anisaldehyde, heliotropin, lilac, tonka, coumarin, very pleasant
20		roasted, someway reminiscent of coffee, weak mercaptaneous
21		sweet, weak cinnamic, heliotropin, lilac, coumarin
22		weak, light green, fatty, similar to **23**, benzylidene acetone
23		fatty, buttery, green, coconut-like, benzylidene acetone
24		fatty, buttery, somewhat rancid, marzipan note, animal (zibeth)
25		methylsalicylate-like, sweet, medicinical, fatty, tonka, resin, coumarin
26		cinnamic, metallic, pungent, strong, unpleasant
27		green, methyl acetophenone, fatty, warm, powdery, very pleasant
28		similar to **24**, rancid, animal
29		benzaldehyde, caramel, tonka, marzipan, sticking
30		benzaldehyde, sweet, anise, cinnamic-like, pleasant
31		unpleasant, metallic, spicy, animal, leathery
32		like **31**, but weaker, woody, acid-note
33		fatty, jasmone-like, reminiscent of myrrh, spicy, sweet, balsamic, later on unpleasant
34		myrrh, carvon, spicy, medicinal

The synthesis of the compounds **1**–**34** (see Table 1) which are discussed within this investigation are based on following considerations:

1) An isosterism between the aromatic nucleus and another aromatic system should show the influence of the electron moiety at one side of the allylic or propenylic side chain double bond on the odour impression.

2) The substitution pattern of this double bond should demonstrate the importance of the (*Z*)-/(*E*)-isomerism and the steric implications caused by a geminal methyl group.

3) Not only the isomerism, but also the conformeric situation is responsible for an odour impression. *E.g.* it is common knowledge that furfural (**1**) exerts a bitter

almond odour, but we still do not know which of the two conformers (O-*trans* or O-*cis*) is responsible for this unique fragrance. Therefore we tried also to fix the conformation and to synthesize some molecules without any flexibility of the functional group.

4) Most of the molecules presented in this paper are β-nitrostyrene derivatives; their syntheses have already been described elsewhere as well as most of their biological activities, but the knowledge of their olfactive properties still is lacking to a great extent. Therefore it seemed worthwhile to include these molecules in the present investigation.

5) Finally, the elongation of the isobutenyl group, which is isosteric to an aromatic system with respect to bitter almond odours, should be investigated.

Results and Discussion

The synthesis of compounds **1**–**34** is described in the literature [12–22] and could be performed without any difficulties. The purified substances (prep. TLC, when selfprepared or bought) were subjected to a thorough spectroscopic analysis and afterwards to an odour evaluation by experts.

Conformation of the Compounds

The results of molecular calculations show that most of the compounds investigated here are more or less planar with only small deviations from the planarity (less than 7 degrees) [23].

For compounds with an ortho or meta substituted benzene ring and for compounds with an heterocyclic ring two different conformations are possible:

For the mentioned compound **19** an energy difference of 0.19 kcal/mole between both minimized planar structures was calculated by the semiempirical program Am1 [24] and a value of 3.3 kcal/mol was obtained using an *ab initio* method (3-21G basis set) [25]. Conformation **A** should therefore be more populated in a thermodynamic equilibrium. As it is commonly accepted that semiempirical methods underestimate conformation differences, the *ab initio* result is more reliable. However, such gas phase information cannot predict the situation in solution exactly. In this case NMR experiments, in particular NOE-experiments, could be used, to give a better answer which of both conformations exists dominantly in solution at room temperature.

NOE difference measurements on **19** establish a *through space*-connectivity from both the olefinic side chain proton (H_D) and the methyl group to the proton H_C. Therefore, both conformations with respect to the single bond between the heterocyclic ring and the olefinic double bond are present in solution.

However, the NOE resulting from irridiation of the methyl group protons seemed to be considerably weaker than the intensity gain of H_D due to irradiation of the olefinic proton. From this evidence it can be concluded that the population of the s-*trans* (**A**) species in solution is obviously higher than that of its s-*cis* (**B**) counterpart. The results of the molecular calculation are supported by these experiments, but the question which of both conformations interacts with a possible receptor site cannot be answered completely.

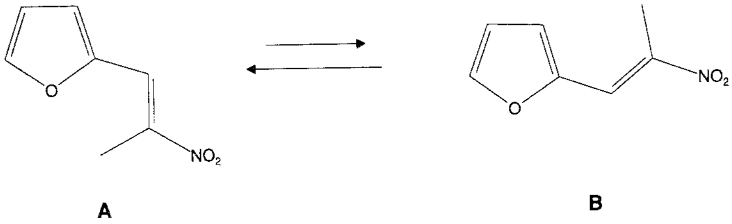


Fig. 3. Equilibrium between both planar conformations of **19**

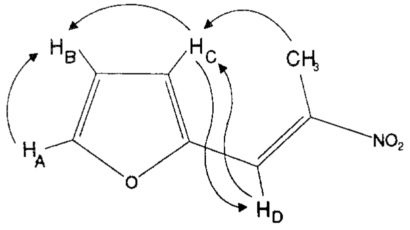


Fig. 4. NOE-experiments on **19**. Arrows indicate the observed effects.

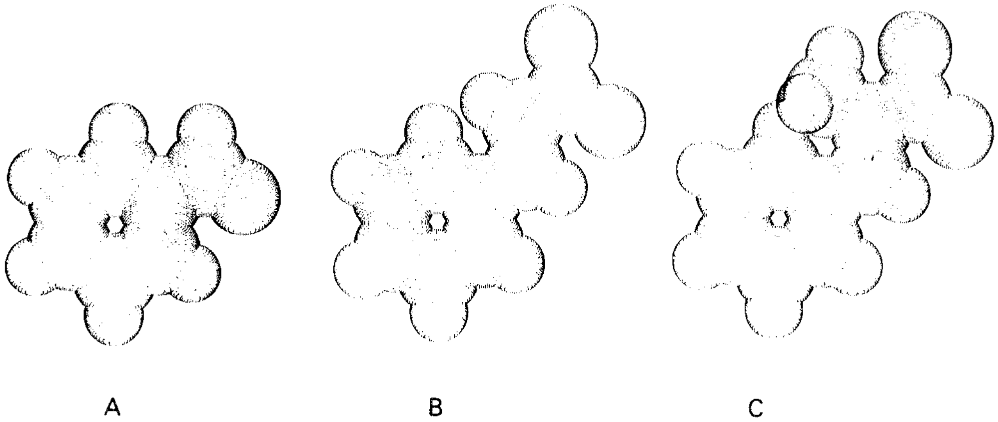


Fig. 5. Molecular shape of a bitter almond molecule (benzaldehyde) (**A**), of a cinnamic odour molecule (**2**) (**B**) and of a compound with a green scent note (**3**) (**C**)

The differences of the odour impression of the various compounds are caused by the electronic properties, but also by the molecular shape of the molecules as demonstrated in Fig. 5.

The extension from *Zakaryas* model for bitter almond odour compounds (**A**) with an additional ethylenic subunit leads to molecules with cinnamic notes (**B**); the addition of the (nonplanar) methyl group evaluates a more greeen scent (**C**), as described extensively in the following part.

Structure-Odour-Relationships

Examining 21 nitro-olefines among the 34 compounds under investigation (see Table 1), some striking similarities in their structure-odour-relationship can be noticed. With the exception of **6**, **7**, **14**, and **16**, which could not be detected olfactively at all, all other nitro-olefines exert a distinct aroma. This lacking of an odour impression can be explained by a disturbance of the polarity of the molecules which possess another more or the less hydrophilic group opposite of the nitro-olefine moiety [26]. It is obvious that the para positioned substituets $-OCH_3$, $-F$ and $-NO_2$ cause this disappearance or at least drastic weakening of the odour, as we can observe with compounds **13** and **15**, which are hardly perceptible. Only **4**, bearing a hydrophobic toluene moiety at the other side of the olefinic group seems to be an exception of this rule.

The great odour shift to other olfactive tonalities caused by the addition of a geminal methyl group to the nitro-olefin is remarkable. **3**, **5**, and **15** possess a green note, reminiscent to dill, the flavour of the herb *Anethum graveolens*, which is very estimated in European kitchen, whereas the "blank" nitro-olefines **2** (and with some indulgence also **4**) show a clear cinnamic odour (see also Table 1). A strong cinnamic fragrance can also be noticed with **8**, **10**, and **18**, whereas their methyl homologues show unpleasant, spicy-woody (**9**) or disagreeable, very aggressive (**11**, probably due to the halogene substituent) odours, and only **19** exerts a very pleasant fragrance, reminiscent to heliotropin, tonka, coumarin and lilac, like its sulfur analogue **21**. The corresponding desmethyl derivative **20** possesses a typical roast flavour, as is part of the coffee aroma. Obviously, the nitro-olefine moiety serves as a contact group to a receptor site whose accessibility is not suited any more for the sterically more demanding methyl-nitro olefines. This steric hindrance of a bulky group substituted near the osmophoric group is encountered very often in fragrance chemistry (see *e.g.* Ref. [11, 27]).

Looking on the aromatic substituent of the nitro-olefine, we observe a shift from cinnamic (**2**, **8**, **10**, and **18**) to either undetectable smells (**6**, **14**, and **16**) or roast flavour (**20**), green-floral, lilac and sweet (**12**) and weak, green and fatty (**22**). Here the substituent in *para*-position of the aromatic nucleus renders the molecule undetectable as has already been mentioned above [26]. On the other hand, the same substituent in the *ortho*-position creates only a small modification as we can notice with the couple **6**/**8** (*p*-methoxy or *o*-methoxy). The exception from this phenomenon are the couples **10**/**12** and **11**/**13**, where we can smell very different notes. The substitutent in *ortho*-position renders the odour very disagreeable, even repulsive, whereas the fragrance of **12** and **13** – even if different due to the methyl group at the double bond — is quite pleasant. This again is in agreement with the findings of *Boelens et al.* [2], who state that already a tiny modification of the functional group causes a drastic odour shift within this type of odour molecules, whereas the influence of relatively small substituents in the aromatic nucleus is rather neglectable on the odour character of the molecule.

With the exception of **17** and **20**, the replacement of the aromatic nucleus by a heteroaromatic system is without any great influence on the odour (**18**, **19** and **21**) (see also Ref. [2]), whereas the elongation of the olefinic side chain in **22** (a vinylogue of **19**) shifts the aroma to a fatty green odour. *Karner et al.* [28] already described the great influence of double bonds on the odour character (probably due to the restricted rotation possibilities) within the class of terpenoid fragrance compounds. This seems to be in agreement with our findings within the group of nitro-olefines. *Boelens et al.* [2] found that additional conjugated double bonds in alicyclic or aliphatic molecules reduce the bitter almond character and induce a sharp note in the small. The odour impression of **17** reminds of tobacco and **20** exerts the aforementioned roast-flavour and smells a bit mercaptaneous if concentrated. Finally, the great odour differences between the methylnitro-olefines and their desmethyl derivatives should be accentuated again (**2** → **3**, **4** → **5**, **8** → **9**, **10** → **11**, **12** → **13**, **14** → **15**, **20** → **21**, **25** → **26**, and even **18** → **19**).

Regarding another set of molecules characterized by a carbonyl function instead of the nitro group (**23**–**30**), we observe as a common olfactive tonality a fatty, somewhat rancid note. The dominating cinnamic — vegetable-like — spicy odours of most of the nitro-olefines discussed above has changed due to the completely different substitution pattern of the side chain double bond. Only compound **26** is an exception of this common rule because of its unpleasant, pungent and still somewhat cinnamic-metallic odour. Again the isosterism between the phenyl-, thienyl- and furyl-system is perceivable and again a modification near the functional group causes a greater change of the odour impression than the replacement of the aromatic nucleus by a similar heteroaromatic system: **24** and **28**, possessing butanone function instead of the acetyl or proply group, as it is the case in **23**, **25** and **27**, show a warm, animalic tonality. Remarkable is the great difference between the pungent, rather repulsive cinnamic odour of **26** and the pleasant bitter almond odour of the similar furyl derivative **30**. In the latter molecule the carbonyl group is vinylogous to **1**, and a steric hindrance by a methyl group (as we encounter it in **26**) does not exist. It is known that furyl is isosteric to phenyl regarding bitter almond odours [2]; therefore, **30** seems to be a derivative of benzaldehyde as well as a derivative of cinnamic aldehyde, which is easy to grasp considering the fact that both odour notes can be detected upon sniffing this interesting substance. The bitter almond odour of nitril **29** finally confirms all aforementioned rules and considerations on structure-activity-relationships within this class of odour compounds [2, 6, 10, 11, 29].

Finally, the odours of the cyclopentenone derivatives **31**–**34** should be discussed with respect to the difference between a fixed conformation of the substituent as in **31** and **33** and *E*/*Z*-isomerism as in **32** and **34**. No great odour difference could be observed between these couples; only minor bynotes characterize these odour compounds and differentiate them from one another. Also the elongation of the side chain does not cause a remarkable odour shift: all 4 compounds of this series show a spicy tonality. The enone-moiety is probably more odour determining than the substitution pattern of the double bond within this group of molecules or a sort of a double-bond-equilibrium, which is created directly upon contact with the receptor site, prevents a clear differentiation between these two isomeric forms.

Coming to a conclusion of our investigations on structure-odour-relationships within the class of bitter almond like compounds we can say that the extension of the functional group directly bound to the aromatic system by insertion of an ethylene unit between nucleus and osmophoric group generally shifts the odour from bitter almond to cinnamic-floral-spicy notes, whereby the cinnamic character could be met more frequently than the other tonalities. It seems to be a fact that the inserted ethylene unit weakens the strong electron attracting functional group (dipole moment: 2.5–4 Debye [10, 30]) in a certain way and also by creating another moiety causes other bynotes and tonalities. This vinylogue principle is only contradicted by nitril **29** and aldehyde **30**. Looking at Fig. 2, a balsamic note is not observed

Table 2. Compounds with synthetic procedures given in literature, but synthesized according to [14] in the present investigation.

	m.p.	yield	reference
4	101–102 °C	95%	[31]
10	48 °C	83%	[32]
12	113–114 °C	45%	[33]
14	101–103 °C	90%	[34]
15	64–66 °C	71%	[34]
20	79–80 °C	62%	[35]
21	68–69 °C	50%	[35]

anywhere among these 34 olefines, with the exception of compound **33**, where it could be detected as a minor tonality. Generally, there is no difference in the basic fragrance characteristics between aromatic and heteroaromatic systems, whereas the subsitution pattern of the nucleus as well as of the double bond itself proved to be very important.

Experimental

Some of the compounds used in our investigation were commercially available (Fa. Merck and Fa. Fluka). The others were synthesized according to literature: **2** and **8** [12], **3**, **6**, and **8** [13], **5**, **11**, and **13** [14], **7** [13, 14, 15], **9** [15], **16** [14, 15], **17** and **19** [16], **23**, **24**, and **28** [17], **25** [18], **26** and **30** [19], **27** [20], **29** [21], **31**, **32**, **33**, and **34** [22]. Compounds **4**, **10**, **12**, **14**, **15**, **20**, and **21** were prepared following the procedure given in [14], their syntheses are described by different methods as listed in Table 2.

Compound **22** was synthesized in anlogy to [14], m.p. 70 °–71 °C (recrystallized from petrol ether, yield 30%). UV-spectrum: $\lambda_{max} = 378.4$ nm ($\varepsilon = 1.84.10^4$), $\lambda = 270$ nm ($\varepsilon = 6.1.10^3$); ^{1}H NMR: 2.35 ppm(s), 6.5 ppm, 6.8 ppm, 7.75 ppm (multipletts), 7.5 ppm(s); IR-bands: 1625, 1510, 1482, 1310 cm^{-1}; mass spectrum: 179 (molecular peak), 163, 147, 131, 122, 118, 94.

NMR spectra were recorded on Bruker AC 250 F (^{1}H, ^{13}C) and Bruker AM 400 WB (NOE difference experiments) spectrometers in $CDCl_3$ solution at room temperature.

Acknowledgements

The authors are grateful to ÖAD (Austrian Academic Exchange Service) for providing a generous grant to one of us (*M.Y.*), which enabled him to study in Vienna, to *V. Hausmann* and *W. Höppner*, chief perfumers of Dragoco Comp., Vienna, for their thorough odour evaluation, and to DRAGOCO Comp. for their interest in our work. We also thank Dr. H.-P. Kählig for recording the 400 MHz NMR spectra.

References

[1] Beets M. G. J. (1971) In: Beidler L. M. (ed) Handbook of sensory physiology, vol. IV. Chemical senses 1. Olfaction. Springer, Berlin Heidelberg New York, p 257 ff
[2] Boelens H., Heydel J. (1973) Chemiker Ztg. **97**: 8
[3] Amoore J. E. (1971) In: Ohloff G., Thomas A. F. (eds) Gustation and olfaction. Academic Press, London New York, p. 147
[4] Wright R. H. (1954) J. Appl. Chem. **4**: 611
[5] Wright R. H. (1969) Exc. Med. Int. Cong. Ser. **206**: 3

[6] Lindner P., Märtensson O. (1972) Int. J. Quant. Chem. **6**: 363
[7] Wright R. H., Robson A. (1969) Nature **222**: 290
[8] Ericksson A., Lindner R., Märtensson O. (1981) In: Srinivasian R. (ed.) Biomolecular structure, conformation, function and evolution, vol. 2. Pergamon Press
[9] Zakarya D., Yahiaoui M., Fkih-Tetouani S. (1992) J. Soc. Maroc. Chim. **1**: 14
[10] Boelens H. (1974) Cosmet. & Perf. **89**: 70
[11] Beets M. G. J. (1978) In: "Structure-activity-relationships in human chemoreception", p. 162ff, Appl. Sci. Publ., London
[12] Worrall D. E. (1941) Org. Synthesis, Vol I, 413
[13] Gairaud C. B., Lappain G. R. (1953) J. Org. Chem. **18**: 1
[14] Koremura M., Oku H., Shono T., Nakanishi T. (1961) Takamine Kenkyusho Nempo **13**: 212; C.A. (1962) **57**: 16451a
[15] Karmarkar S. N., Kelkar S. L., Wadia M. S. (1985) Synth. Commun. **15**: 510
[16] Agafonov N. E., Sedishev I. P., Dudin A. V., Kutin A. A., Stashina G. A., Zhulin V. M. (1991) Izv. Akad. Nauk. SSSR, Ser. Khim., 426; C.A. (1991) **115**: 28781x
[17] Smith P. J., Dimmock J. R., Taylor G. (1972) Can. J. Chem. **50**: 871
[18] Lenek G. J., Cejka L. (1941) Org. Synthesis, Vol I, 283
[19] Ivanoff D. (1924) Bull. Soc. Chim. France **35**: 1658
[20] Keskin H., Miller R. E., Nord F. F. (1951) J. Org. Chem. **16**: 199
[21] Patterson J. M. (1973) Org. Synthesis, Vol V, 585
[22] Tietze L. F., Eicher Th. (1989) Reactions and Syntheses in the organic Chemistry Laboratory 176
[23] Buchbauer G., Kalchhauser H., Wolschann P., Yahiaoui M., Zakarya D.; in preparation
[24] Allinger N. L. (1972) J. Am. Chem. Soc. **99**: 8127
[25] Gaussian 90, Revision J; Frisch M. J., Heat-Gordon M., Trucks G. W., Foresman J. B., Schlegel H. B., Raghavachari K., Robb M., Binkley J. S., Gonzales C., Defrees D. J., Fox D. J., Whiteside R. A., Seeger R., Melius C. F., Baker J., Martin R. L., Kahn L. R., Stewart J. J. P., Topiol S., Pople J. A.; Gaussian Inc., Pittsburgh PA, 1990
[26] Steiner W. (1969) J. Soc. Cosmet. Chem. **20**: 729
[27] Brower K. R., Schafer R. (1975) J. Chem. Educ. **52**: 538
[28] Karner K., Seib K. (1977) Seifen-Fette-Öle-Wachse **103**: 117
[29] Moncrieff R. W. (1967) In: "The chemical senses", p. 483. Leonhard Hill, London
[30] Boelens H. (1976) In: Benz G. (ed) Structure-acitivity-relationships in chemoreception. Retrieval, London, p. 197, Inform.
[31] Lerner O. M. (1958) Zhur. Priklad. Khim. **31**: 663; C.A. (1959) V52, 18271g
[32] Worrall D. E. (1938) J. Am. Chem. Soc. **60**: 2845
[33] Campbell N., Anderson W., Gilmore J. (1940) J. Chem. Soc. 446
[34] Byrdy S., Eckstein Z., Plenkiewica J. (1961) Bull. Acad. Polon. Sci, Ser. Sci. Chim. **9**: 627
[35] Koremura M., Oku H., Shono T., Nakanishi T. (1961) Takamine Kenkyusho Nempo **13**: 216; C.A. (1962) **57**: 16451d

Received November 11, 1993. Accepted December 18, 1993