Fragrance Proceedings of the Second International Haarmann & Reimer Symposium on Fragrance and Flavor Substances. (New Products, Processes and Aspects of Product Safety) September 24 – 25, 1979, New York City Flavor Substances Su

Edited by Rodney Croteau
Washington State University
Institute of Biological Chemistry
and Biochemistry/Biophysics Program
Pullman, Washington 99164

Fragrance and Flavor Substances

Proceedings of the Second International
Haarmann & Reimer Symposium
on Fragrance and Flavor Substances
(New Products, Processes and Aspects of Product Safety)

September 24-25, 1979 New York City

Edited by
Rodney Croteau
Washington State University
Institute of Biological Chemistry
and Biochemistry/Biophysics Program
Pullman, Washington 99164

D & PS. Verlag, 3017 Pattensen 1, W.-Germany 1980

13	The Biosynthesis of Terpene Compounds, R. Croteau	1.
37	Simple Syntheses of Sesquiterpenes, P. K. Weyerstahl	2.
53	A Review of the Reaction Between Aldehydes and Phenols or Phenol Ethers and Its Application to the Synthesis of Fragrance and Flavor Substances, K. A. Bauer, A. Krempel, R. G. Mölleken, H. Fiege and K. Wedemeyer	3.
63	Further Development of a Classical Process for the Synthesis of Aromatic Hydroxy-aldehydes, H. Fiege, K. Wedemeyer, K.A. Bauer, A. Krempel and R.G. Mölleken	4.
75	. A New Method for the Production of Heliotropin, R. G. Mölleken and K. A. Bauer	5.
83	. An Economical Synthesis of Pepper Alkaloids, H. J. Oediger and A. Schulze	6.
93	A Two-step Procedure for the Synthesis of Anethole, R. G. Mölleken and K. A. Bauer	7.
99	The Addition of Aldehydes to Activated Double Bonds and its Application in the Synthesis of Jasmine Fragrances, H. Kuhlmann and H. Stetter	8.
111	Progress in the Synthesis of the Sandalwood Fragrance trans-3-Isocamphylcyclohexanol, G. K. Lange and K. A. Bauer	9.
123	. Influence of the Position of the Methyl Group upon the Odor of Fatty Aldehydes having an α- or β-Methyl Substituent, D. J. Hagena and K. A. Bauer	10.
129	Old and New Macrocyclic Musks: A General Review from the Industrial Standpoint, K. A. Bauer and A. K. Körber	11.
137	. New Ways for the Synthesis of 15-Pentadecanolide, A.K. Körber and K.A. Bauer	12.
145	Readily Accessible Intermediates of Macrocyclic Musks, D. J. Hagena and K. A. Bauer	13.
155	Influence of Molecular Structure Upon the Musk Odor Characteristics of Macro-eyelic Ketones. A. K. Körber and K. A. Bauer	14.

15.	Cutaneous Toxicity and Sensitization Properties of Chemically Defined Fragrance Substances: Review and Chemical Studies of the Mechanism of Sensitization,	
	C. Benezra	167
16.	FDA'S Research and Regulatory Programs for Cosmetics and Fragrances, J. A. Wenninger	177
17.	FDA'S Flavor and Spice Safety Review Program, M. V. Smith	185
18.	Changing Food Safety Principles Applied to Flavor Ingredients, R. D. Middlekauff	191

Fragrance and Flavor Substances

Fragrance and Flavor Substances

Proceedings of the Second International
Haarmann & Reimer Symposium
on Fragrance and Flavor Substances
(New Products, Processes and Aspects of Product Safety)

September 24-25, 1979 New York City

Edited by
Rodney Croteau
Washington State University
Institute of Biological Chemistry
and Biochemistry/Biophysics Program
Pullman, Washington 99164

D & PS. Verlag, 3017 Pattensen 1, W.-Germany 1980

FOREWORD

The First International Symposium on Fragrance and Flavor Substances was held in Bad Pyrmont in 1974 to commemorate Haarmann & Reimer's first one hundred years of service. The dual themes of the First Symposium were "Chemistry and Biochemistry of Fragrance and Flavor Substances" and "Chemical Structure and Biological Effects", themes of very broad scope encompassing many different facets of the fragrance and flavor field. This meeting brought together experts from research areas as diverse as electrophysiology, analytic and synthetic chemistry, and biochemistry, but all having a common interest in fragrance and flavor materials. The First Symposium provided a level of interaction among the attending scientists that was unprecedented in this field. The success of the first meeting encouraged Haarmann & Reimer to convene this conference, the Second International Symposium on Fragrance and Flavor Substances, an event which marks the retirement of Dr. Kurt Bauer as Vice President for Research and Development of Haarmann & Reimer.

The theme of this Second Symposium is "New Products, Processes, and Aspects of Product Safety", a theme of defined focus on topics of crucial importance. New Products and new syntheses are, of course, aspects of long standing interest, for they are the mainstay of the fragrance and flavor industry. The topic of product safety reflects an increasing universal concern for man and his changing environment. Indeed, new products and new applications are now inseparable from health and safety considerations. In this Symposium, the latest advances in the preparative chemistry and the odor characteristics of a wide range of compounds are reviewed. Safety considerations in the broad sense are discussed, and recent work on the mechanisms of cutaneous toxicity is described. Included also is a review of terpene biosynthesis which compliments synthetic studies in this area and underscores the larger point that fundamental biochemical processes are the basis of both odor and taste perception as well as toxicity considerations.

An important role of this Symposium, as was true of the First, is to bring together scientists having a common interest in fragrance and flavor materials in a setting in which the present can be assessed and a perspective of the future formulated. As Chairman, one of my functions is to describe, in brief overview, the unifying concepts of this Symposium, and to provide such a look to the future. At first this might seem like a difficult task for me in that my perceptions are those of a biochemist looking at the biochemical foundations underlying the production, acceptance and safety considerations of a fragrance or flavor product. Thus, on one level, I see the synthesis of a fragrance, such as jasmine, as mimicking a natural biosynthetic process; I regard the perception of an odor, such as a musk, as the interaction of a small molecule with a protein receptor that results in a sensory signal; and I view the toxicity of a potentially useful aromatic chemical as the metabolic inability to deal with a reactive compound. On a more fundamental level, however, I see the economic synthesis of a fragrance or flavor substance, indeed process chemistry in general, in terms of catalysis - the exploitation of the inherent reactivity of molecules. Catalysis is also the essence of biosynthesis - synthesis by enzymes, the protein catalysts. Our understanding of chemical catalysis is far more advanced than is our understanding of biochemical catalysis, and this point is well illustrated by the contents of this Symposium. Yet, significant advances are being made in the enzymology of fragrance and flavor

biosynthesis. Continued progress, when coupled with the tremendous strides in molecular biology, can in the foreseeable future provide the basis for industrial scale production of fragrances, flavors and other fine chemicals by enzymatic means. We can also look forward to a greater understanding of the chemistry, biochemistry and physiology of odor and taste perception and to a deeper appreciation of the molecular basis for toxicity, both of which will allow a rational, more integrated approach to the design of effective and safe fragrance and flavor materials. It is symposia of this type that provide a forum for the exchange of ideas among scientists, from which the seeds of such innovations will grow.

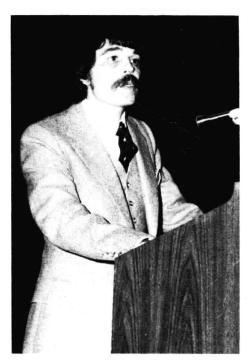
Many people, in addition to the speakers and their coauthors, contributed in a significant way to the success of this Symposium. In particular, I wish to thank Peter Weyerstahl for his assistance at the podium, and Ian Gatfield and Lothar F. Kümper and his staff for their outstanding job in maintaining the smooth pace of the sessions. For his encouragement and guidance, I thank Jim Adams, and, for contributions far too numerous to list, I extend my sincerest gratitude to Kurt Bauer. Finally, on behalf of all of the participants, I especially thank Haarmann & Reimer for making this Symposium possible.

Rodney Croteau

CONTRIBUTORS

- KURT A. BAUER, Research Department, Haarmann & Reimer GmbH, 3450 Holzminden, West Germany.
- CLAUDE BENEZRA, Laboratoire de Dermato-Chimie, Université Louis Pasteur, Strasbourg, France.
- RODNEY CROTEAU, Institute of Biological Chemistry and Biochemistry/Biophysics Program, Washington State University, Pullman, WA 99164, U.S.A.
- HELMUT FIEGE, Research Department II, Bayer AG, 5090 Leverkusen, West Germany.
- DETLEF J. HAGENA, Research Department, Haarmann & Reimer GmbH, 3450 Holzminden, West Germany.
- ALFRED K. KÖRBER, Research Department, Haarmann & Reimer GmbH, 3450 Holzminden, West Germany.
- ALFRED KREMPEL, Research Department, Haarmann & Reimer GmbH, 3450 Holzminden, West Germany.
- HEINRICH KUHLMANN, Department of Organic Chemistry, Technical University Aachen, 5100 Aachen, West Germany.
- GERD K. LANGE, Research Department, Haarmann & Reimer GmbH, 3450 Holzminden, West Germany.
- ROGER D. MIDDLEKAUFF, Bonner, Thompson, O'Connell and Gaynes, 900 17th St. N.W., Washington, D.C. 20006, U.S.A.
- REINER G. MÖLLEKEN, Research Department, Haarmann & Reimer GmbH, 3450 Holzminden, West Germany.
- HERMANN J. OEDIGER, Central Research and Development, Bayer AG, 5090 Leverkusen, West Germany.
- ANDREAS SCHULZE, Central Research and Development, Bayer AG, 5090 Leverkusen, West Germany.
- MERTON V. SMITH, Division of Food and Color Additives, Food and Drug Administration, Washington, D.C. 20204, U.S.A.
- HERMANN STETTER, Department of Organic Chemistry, Technical University Aachen, 5100 Aachen, West Germany.
- KARLFRIED WEDEMEYER, Research Department II, Bayer AG, 5090 Leverkusen, West Germany.
- JOHN A. WENNINGER, Division of Cosmetics Technology, Food and Drug Administration, Washington, D.C. 20204, U.S.A.
- PETER K. WEYERSTAHL, Department of Organic Chemistry, Technical University Berlin, D-1000 Berlin 12, West Germany.

CONTRIBUTORS



Prof. Rodney Croteau



Dr. Kurt A. Bauer

CONTRIBUTORS



1.	The Biosynthesis of Terpene Compounds, R. Croteau	13
2.	Simple Syntheses of Sesquiterpenes, P. K. Weyerstahl	37
3.	A Review of the Reaction Between Aldehydes and Phenols or Phenol Ethers and Its Application to the Synthesis of Fragrance and Flavor Substances, K. A. Bauer, A. Krempel, R. G. Mölleken, H. Fiege and K. Wedemeyer	53
4.	Further Development of a Classical Process for the Synthesis of Aromatic Hydroxyaldehydes, H. Fiege, K. Wedemeyer, K. A. Bauer, A. Krempel and R. G. Mölleken	63
5.	A New Method for the Production of Heliotropin, R. G. Mölleken and K. A. Bauer	75
6.	An Economical Synthesis of Pepper Alkaloids, H. J. Oediger and A. Schulze	83
7.	A Two-step Procedure for the Synthesis of Anethole, R. G. Mölleken and K. A. Bauer	93
8.	The Addition of Aldehydes to Activated Double Bonds and its Application in the Synthesis of Jasmine Fragrances, H. Kuhlmann and H. Stetter	99
9.	Progress in the Synthesis of the Sandalwood Fragrance trans-3-Isocamphylcyclohexanol, G. K. Lange and K. A. Bauer	111
10.	Influence of the Position of the Methyl Group upon the Odor of Fatty Aldehydes having an α - or β -Methyl Substituent, $D. J. Hagena \ and \ K. A. Bauer$	123
11.	Old and New Macrocyclic Musks: A General Review from the Industrial Standpoint, K. A. Bauer and A. K. Körber	129
12.	New Ways for the Synthesis of 15-Pentadecanolide, A.K. Körber and K.A. Bauer	137
13.	Readily Accessible Intermediates of Macrocyclic Musks, D. J. Hagena and K.A. Bauer	145
14.	Influence of Molecular Structure Upon the Musk Odor Characteristics of Macro-cyclic Ketones. A. K. Körber and K. A. Bauer	155

15.	Cutaneous Toxicity and Sensitization Properties of Chemically Defined Fragrance Substances: Review and Chemical Studies of the Mechanism of Sensitization,	
	C. Benezra	167
16.	FDA'S Research and Regulatory Programs for Cosmetics and Fragrances, J. A. Wenninger	177
17.	FDA'S Flavor and Spice Safety Review Program, M. V. Smith	185
18.	Changing Food Safety Principles Applied to Flavor Ingredients, R. D. Middlekauff	191