

Material study

Heterocyclic Nitrogen- and Sulfur-Containing Aroma Chemicals*

A look at the two groups that comprise this section of heterocyclic chemicals, with a focus on the aromatic molecules

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Of the ca. 20 million chemical compounds presently characterized, almost half are heterocyclic molecules. Heterocyclic molecules are significant due to their abundance in nature, as well as their chemical and biological importance. In the flavor and fragrance industry, heterocyclic compounds are of interest because of their varied occurrence in food flavors and their valuable organoleptic characteristics. Even though heterocyclic aroma chemicals are found only in minute amounts in foods, their powerful odors and low odor thresholds, as expressed by high ϕ values (see below), make them key in boosting flavors and fragrances.

The main heterocyclic aroma chemicals are oxygen-, sulfur- and nitrogen-containing rings. The oxygen-containing heterocyclic aroma chemicals belong to the oxirane, furan, pyran and oxepine groups. The sulfur-containing aroma chemicals belong to the thiophene family and, together with nitrogen, to the thiazole and dithiazine systems. Nitrogen-containing aroma chemicals belong to pyrrole, indole, pyridine, quinoline, pyrazine and quinoxaline systems, and, together with sulfur, as mentioned above, the thiazole and dithiazine families. The oxygen-containing heterocyclic aroma chemicals already have been examined (*P&F* magazine, May 2006, page 34). Here, the nitrogen- and sulfur-containing aroma chemicals are studied.

Due to the highly potent odor character of a majority of the heterocyclic compounds used in flavors and fragrances, the term ϕ Value will be used for some of the materials described. A relatively new concept, ϕ Value gives a better understanding

of the odor intensity of a single molecule, taking into consideration its molecular mass (MM), analogous to ϵ value in UV/VIS data of particular molecules.

ϕ Value of a molecule is defined as the following:¹

$$\phi = \frac{MM \times 10^3}{\text{Threshold (ppm)}}$$

The nitrogen- and sulfur-containing heterocyclic aroma chemicals can be divided into the following main groups:

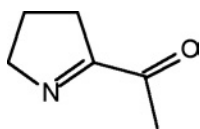
1. nonaromatic molecules
2. aromatic molecules

Want More?

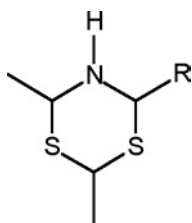
Want to find out more about heterocyclic aroma chemicals? In the *P&F* May 2006 issue (page 34), Michael Zviely examined the oxygen-containing group of heterocyclic aroma chemicals. To order a copy of this article, visit the *P&F* magazine Article Archives at www.PerfumerFlavorist.com/articles, and click on the May issue.



*This is a part of a chapter that appeared in *Chemistry and Technology of Flavors and Fragrances*, M. Zviely, Edit., D.J. Rowe, Blackwell Publishing Ltd.

2-Acetyl-3,4-dihydro-5H-pyrrole (41)**F-1****1-Pyrroline (42)****F-2****Nonaromatic Molecules**

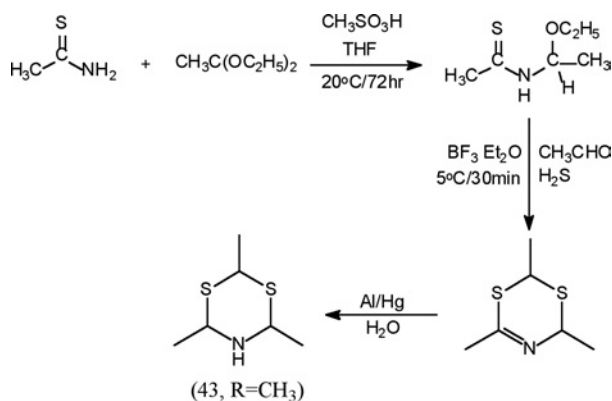
2-Acetyl-3,4-dihydro-5H-pyrrole (41) (F-1), which has a characteristic odor of white bread crust but isn't stable enough to use, and 2-isobutyl-4,6-dimethyl-dihydro-1,3,5-dithiazine, representing several other derivatives, are examples of this group. The isobutyl derivative occurs in yeast extract, having a fruity, tropical fruit note, green roasted, cocoa odor and flavor. These molecules are applied in fruity and roasted formulations. 1-Pyrroline (3,4-dihydro-[2H]-pyrroline, 42) (F-2) occurs in sea fruit, clam and squid. It has a fishy flavor and is applied in seafood formulations.

2,4,6-Trimethyldihydro-1,3,5-dithiazine (R = Me, iPr, iBu, 2-Bu; 43)**F-3**

The synthesis of 2,4,6-trimethyldihydro-1,3,5-dithiazine (43) (F-3) can be seen in F-4. Thioacetamide is reacted with acetaldehyde diethylacetal in the presence of methane-sulfonic acid to yield *N*-(1-ethoxyethyl)thioamide as an intermediate. The thioamide cyclizes with acetaldehyde and hydrogen sulfide in the presence of borontrifluoride etherate as a catalyst to produce 2,4,6-trimethyl-4H-1,3,5-dithiazine. Reducing the double bond is obtained by using aluminum amalgam to finally furnish 2,4,6-trimethyldihydro-1,3,5-dithiazine (43, R = CH₃).

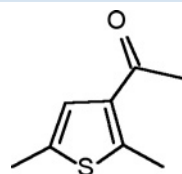
Aromatic Molecules

Aromatic molecules containing nitrogen and/or sulfur belong to the following groups:

Synthesis scheme of 2,4,6-trimethyldihydro-1,3,5-dithiazine (43)**F-4**

1. thiophene derivatives
2. pyrrole and indole derivatives
3. pyridine and quinoline derivatives
4. pyrazine and quinoxaline derivatives
5. thiazole derivatives

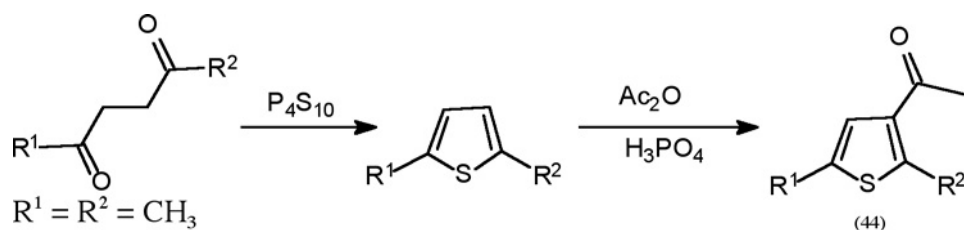
Thiophene derivatives: 3-Acetyl-2,5-dimethylthiophene (44) (F-5) occurs in boiled and cooked beef. It has a burnt roasted flavor, and is used for roasted and smoked flavorings, e.g., boiled and fried meat. 3-Acetyl-2,5-dimethylthiophene (44) can be synthesized by the cyclization of 1,4-dicarbonyl compound analogs in the presence of phosphorous pentasulfide or H₂S, followed by acetylation of the 2,5-dimethyl-thiophene intermediate (F-6).²

Acetyl-2,5-dimethylthiophene (44)**F-5**

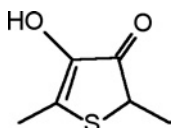
4-Hydroxy-2,5-dimethyl-2,3-dihydrothiophen-3-one (45) (F-7) is not yet reported as being found in flavors, but is probably present in prepared meat. It has a sulfurous aroma and, upon dilution, a fried and prepared meatlike flavor. It is used in meat and vegetable formulations.

Pyrrole and indole derivatives:

2-Acetylpyrrole (45) (F-8) occurs in vegetables, bread, meat and roasted products. It has a sweet musty, nutty and tealike odor and flavor. 2-Acetylpyrrole is applied mainly


 4-Hydroxy-2,5-dimethyl-
2,3-dihydrothiophen-3-one
(45) pyrrole (41)

F-7



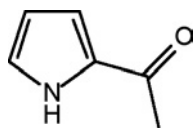
in baked, fried and roasted flavorings. Indole (2,3-benzopyrrole) can be found in bread, cheese, egg, beef, wine, beer, brandy, cocoa, coffee, tea, etc. It has an

erogenic-floral, animal, slightly musky and slightly fecal odor on dilution. Indole is applied in erogenic-floral fragrance compounds.

Pyrrole 2-carboxaldehyde (46) (F-9) can be found in asparagus, onion (roasted), wheat bread, beef, beer, white wine, cocoa, coffee, tea and barley. This material is used in roasted flavorings, such as nuts and meat. A well-established cycloaddition of pyrroles is the [2+2] cycloaddition with dichlorocarbene, which is in competition with the Reimer-Tiemann formulation (F-10).³ Under strongly basic conditions, i.e., the generation of dichlorocarbene from chloroform and potassium hydroxide, electrophilic substitution of pyrrole by dichlorocarbene dominates, leading eventually to pyrrole-2-carboxaldehyde (46). In a weakly basic

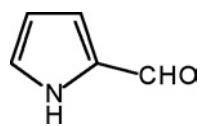
2-Acetylpyrrole (45)

F-8



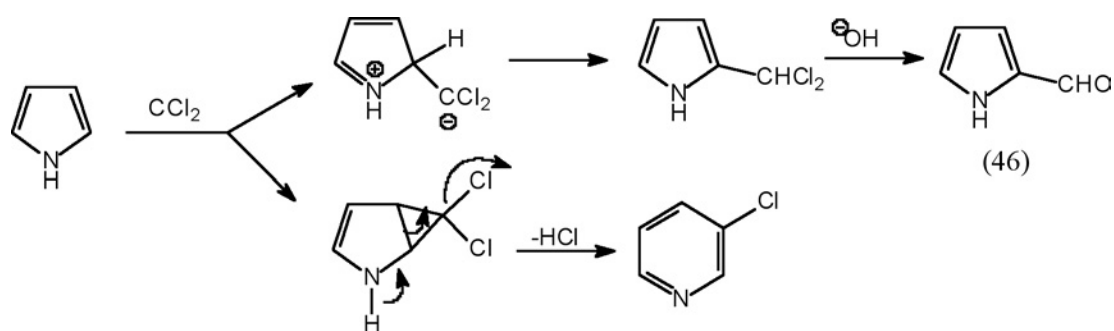
Pyrrole 2-carboxaldehyde (46)

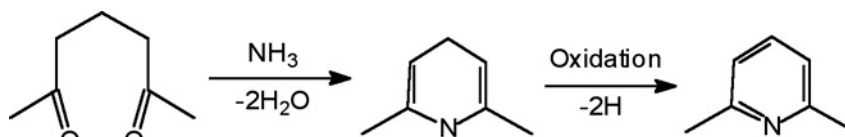
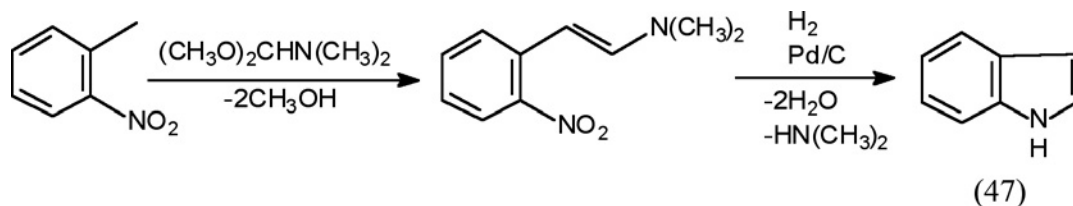
F-9



[2+2] Cycloaddition with dichlorocarbene

F-10



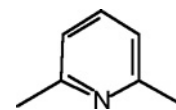


medium (generation of dichlorocarbene by heating sodium trichloroacetate), the [2+1] cycloaddition prevails. The primary product eliminates hydrogen chloride to produce 3-chloropyridine.

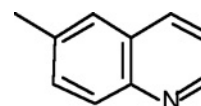
Indole (1H-Benzo[b]pyrrole, 47) (F-11) occurs in bread, cheese, egg, beef, wine, beer, brandy, cocoa, coffee, tea and cauliflower. Indole has erogenic-floral, animalic, cheeselike odor and flavor, which becomes slightly fecal on dilution. Indole is applied in some cheese modifications and in erogenic-floral fragrances. Its homologue skatole (3-methylindole, 48) (F-12) can be detected in jasmine, dairy products (cheese), coffee, tea and dried bonito fish. It has a putrid, sickening, mothball, decayed fecal odor; on extreme dilution it

2,6-Dimethylpyridine (49)
pyrrole (41)

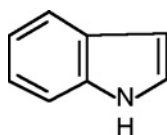
F-14

6-Methylquinoline (50)
pyrrole (41)

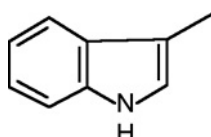
F-16

Indole (47), ϕ 1.17x10⁹

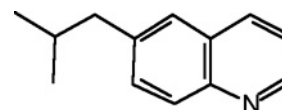
F-11

Skatole (3-methylindole, 48),
 ϕ 1.31x10⁸

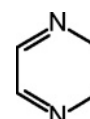
F-12

6-Isobutylquinoline
(51)pyrrole (41)

F-17

Pyrazine (1,4-Diazine)
pyrrole (41)

F-18



has a jasminelike odor. It is a degradation product of tryptophan, and, as the name implies, it is found in fecal material. Skatole is applied in very low concentration in floral fragrances.

1-Dimethylamino-2-(*o*-nitrophenyl) ethenes obtained from *o*-nitrotoluene and *N,N*-dimethylformamide dimethyl acetal yield indoles on reductive cyclization of the corresponding *o*-aminophenyl derivative (F-13).⁴

Pyridine and quinoline derivatives: 2,6-Dimethylpyridine (2,6-lutidine, 49) (F-14) occurs in bread, cheese, beef, lamb, sherry, coffee and tea. It has a nutty, coffee, cocoa, musty, bread and meaty flavor. It is used in roasted and fried flavors, such as nuts, cocoa, coffee, maple, bread, tobacco and vegetable. On treatment with ammonia, 1,5-Dicarbonyl compounds undergo cyclocondensation to produce 1,4-dihydropyridines, which, on dehydrogenation, yield pyridines (F-15).⁵

Quinolines, or benzopyridines, are a small group of aroma ingredients used mainly in flavors.

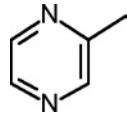
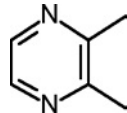
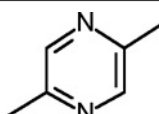
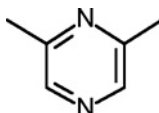
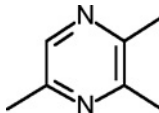
6-Methylquinoline (50) (F-16) is found in tea, and it has a narcotic, earthy green odor. 6-Methylquinoline is used in tea formulations. 6-Isobutylquinoline (51) (F-17) has a narcotic, slightly roasted-burnt, somewhat green rootlike odor and flavor, and is used in roasted formulations.

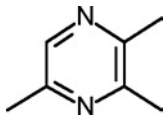
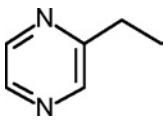
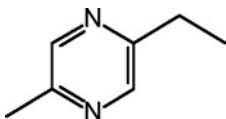
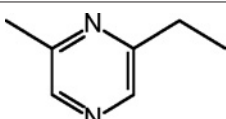
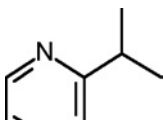
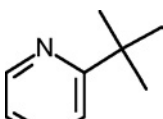
Pyrazine and quinoxaline derivatives:

This group of aroma ingredients contains a 1,4-diazine group (F-18) in its structure. Pyrazines are well-known aroma substances with unique flavor properties and, usually, low odor thresholds, that occur in nature and are formed in thermal reactions, such as the Maillard reaction.⁶⁻⁸ For example, 2-methoxy 3-(1-methylpropyl)-pyrazine smells like green peas, and 2-methoxy-3-(2-methylbutyl)-pyrazine is the key odor compound of bell pepper. Alkyl-substituted pyrazines are found in roasted beef and coffee. Because of these findings, pyrazines

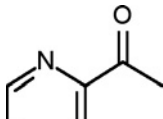
Alkylpyrazine compounds

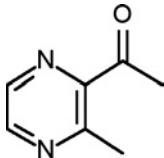
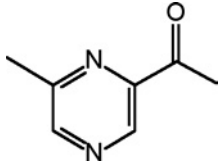
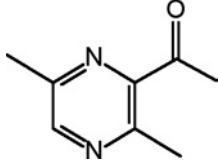
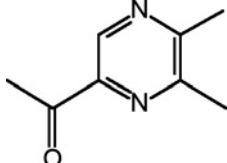
F-19

Compound	Odor and flavor	Occurrence	Structure (ϕ value)
2-Methylpyrazine	Musty, nutty, roasted, cocoa, light, peanut.	Baked, fried and roasted products.	 (51) $\phi 9.41 \times 10^2$
2,3-Dimethyl-pyrazine	Roasted meat; in higher dilution it is vanilla- and chocolatelike.	Vegetables, dairy, meat, roasted products, cocoa, coffee, potato chips, shrimp, papaya, asparagus, cabbage and fried potato.	 (52) $\phi 3.09 \times 10^3$
2,5-Dimethyl-pyrazine	Earthy, nutlike, raw potato, musty.	Vegetable, dairy, meat and roasted products.	 (53) $\phi 6.0 \times 10^4$
2,6-Dimethyl-pyrazine	Roasted, cocoalike.	Vegetable, dairy, meat and roasted products.	 (54) $\phi 7.20 \times 10^4$
2,3,5-Trimethyl-pyrazine	Burnt roasted, earthy, tobaccolike.	Nuts, meat, roasted products (coffee, cocoa), rum, whiskey and popcorn.	 (55) $\phi 3.05 \times 10^5$

Compound	Odor and flavor	Occurrence	Structure (ϕ value)
2,3,5,6-Tetramethylpyrazine	Caramellic-milky, fermented soy beans, slightly woody.	Guava, boiled egg, roasted beef, cocoa, coffee, green tea, whiskey, shrimp.	 (56)
2-Ethylpyrazine	Musty, nutty, burnt.	Bread, beef, brandy, rum, whiskey, coffee, cocoa, etc.	 (57) $\phi 1.8 \times 10^4$
2-Ethyl-5-methylpyrazine	Roasted, coffeelike.	Vegetables, bread, meat, whiskey, coffee, cocoa.	 (58) $\phi 7.33 \times 10^5$
2-Ethyl-6-methylpyrazine	Roasted, cocoa and coffee connotations.	Fish, meat, roasted products, alcoholic beverages.	 (59) $\phi 1.22 \times 10^6$
2-Isopropylpyrazine	Dusty, roasted nuts.	Fried chicken, cocoa, filbert, peanut.	 (60)
2-tert-Butylpyrazine	Green, earthy, carrot.	Not yet reported as being found in nature, but probably exists in roasted products.	 (61)

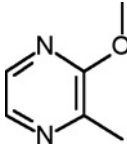
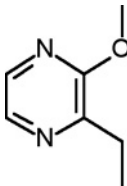
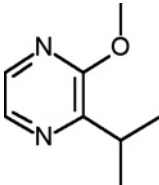
Acetylpyrazine compounds

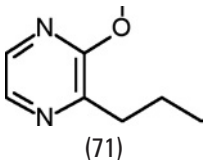
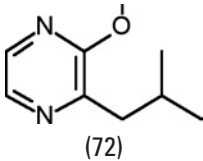
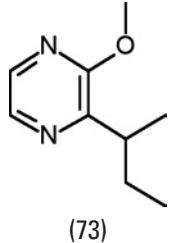
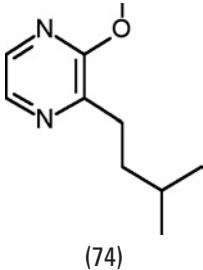
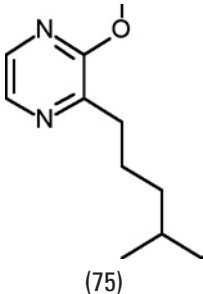
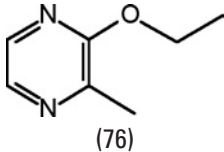
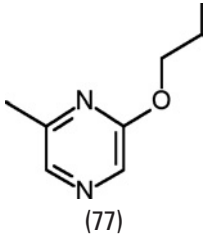
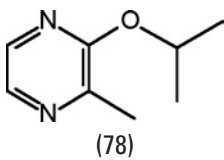
Compound	Odor and flavor	Occurrence	Structure (ϕ value)
2-Acetylpyrazine	Popcorn, bread crustlike, nutty.	Bread, popcorn, cocoa, coffee, barley, peanut, filbert.	 (63) $\phi 1.97 \times 10^6$

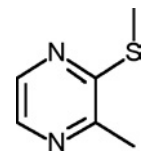
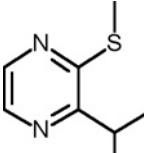
Compound	Odor and flavor	Occurrence	Structure (φ value)
2-Acetyl-3-methylpyrazine	Roasted potatoes, nutty, vegetable and cereal.	Meat, cocoa, coffee, fried potato.	 (64)
2-Acetyl-6-methylpyrazine	Aromatic and roasted, coffee and cocoalike.	Coffee, roasted sesame seeds.	 (65)
2-Acetyl-3,6-dimethylpyrazine	Roasted, caramellic, hazelnut, popcorn.	Coffee.	 (66)
5-Acetyl-2,3-dimethylpyrazine	Roasted, slightly aromatic, green.	Coffee.	 (67)

Alkoxy pyrazine compounds

F-21

Compound	Odor and flavor	Occurrence	Structure (φ value)
2-Methoxy-3-methylpyrazine	Roasted, peanut, somewhat green.	Sherry, coffee, krill.	 (68) $\varphi 2.48 \times 10^7$
2-Methoxy-3-ethylpyrazine	Green, earthy, nutty.	Sherry.	 (69)
2-Methoxy-3-isopropylpyrazine	Bell pepper, earthy, green.	Asparagus, carrot, cucumber, lettuce, garlic, pea, potato, capsicum, etc.	 (70)

Compound	Odor and flavor	Occurrence	Structure (φ value)
2-Methoxy-3-n-propylpyrazine	Vegetable, earthy, green.	Sherry.	 (71)
2-Methoxy-3-isobutylpyrazine	Green bell pepper, green pea.	Green bell pepper, petitgrain oil.	 (72)
2-Methoxy-3-sec-butylpyrazine	Pea, green, earthy, potato, galbanum.	Coffee and green peas.	 (73)
2-Methoxy-3-isopentylpyrazine	Green, leafy, lavender at low levels.	Not yet reported as being found in nature.	 (74)
2-Methoxy-3-isohexylpyrazine	Powerful, sweet greenish, with asparagus note.	Not yet reported as being found in nature.	 (75)
2-Ethoxy-3-methylpyrazine	Roasted, baked, fried, somewhat nutlike.	Not yet reported as being found in nature (probably in coffee, krill).	 (76)
2-n-Propoxy-6-methylpyrazine	Green, woody, mint at low levels.	Not yet reported as being found in nature (probably in roasted products, e.g., coffee).	 (77)
2-Isopropoxy-3-methylpyrazine	Dusty, green; somewhat paprikalike.	Not yet reported as being found in nature.	 (78)

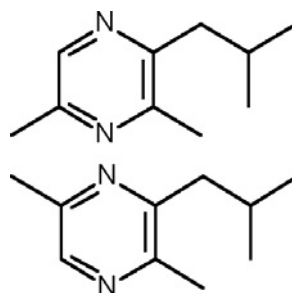
Compound	Odor and flavor	Occurrence	Structure (φ value)
2-Methylthio-3-methylpyrazine	Nutty, sweet, meaty, slightly green.	Not yet reported as being found in nature.	 (79)
2-Methylthio-3-isopropylpyrazine	Nutty, burnt, vegetable.	Not yet reported as being found in nature.	 (80)

are of high relevance for the flavor industry—especially those with acetyl-, alkyl-, alkoxy- and sulfur-containing groups. Pyrazines are the most important and may be divided into four main subgroups: alkylpyrazines (F-19), acetylpyrazines (F-20), alkoxy pyrazines (F-21) and thio-alkoxypyrazines (F-22).⁹

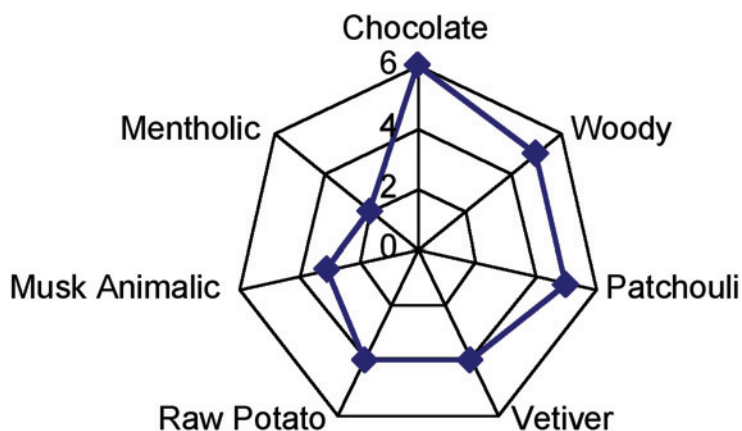
A very special alkylpyrazine is the isomeric mixture of 3,5-dimethyl-2-isobutyl-pyrazine and 3,6-dimethyl-2-isobutylpyrazine (62) (F-23). These isomers were isolated from several natural sources, e.g., the skin and flesh of potato cultivars after baking.¹⁰ The odor threshold of 3,5-dimethyl-2-isobutylpyrazine and 3,6-dimethyl-2-isobutyl-pyrazine indicates a relatively low φ value.

The odor and flavor of 3,5-dimethyl-2-isobutyl-pyrazine and 3,6-dimethyl-2-isobutyl-pyrazine mix has the warmth of cocoa and hazelnut, and is slightly musky animalic, with patchouli and vetiver tones

Mixture of 3,5-dimethyl-2-isobutyl-pyrazine and 3,6-dimethyl-2-isobutylpyrazine (62), φ 8.21×10^4

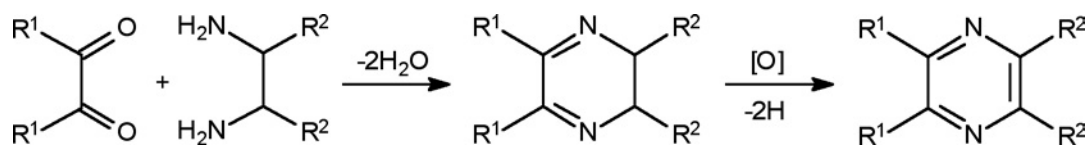


Radar organoleptic description of 3,5-dimethyl-2-isobutylpyrazine and 3,6-dimethyl-2-isobutylpyrazine mixture



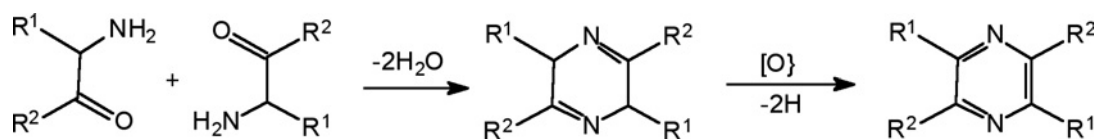
Pyrazines synthesis by cyclocondensation between 1,2-dicarbonyl compounds and 1,2-diaminoethanes

F-25



Classical pyrazine synthesis with self-condensation of two molecules of an α -aminocarbonyl compound

F-26



and a menthol note. The main uses of 3,5-dimethyl-2-isobutylpyrazine and 3,6-dimethyl-2-isobutylpyrazine mix for food are in chocolate, cocoa, baked goods, breakfast cereals, milk products, and roasted applications, and in processed vegetables, soups, baked potatoes, sweet sauces and mint flavors.¹¹ This unique pyrazine mix can be used for a distinctive value in fragrances because it imparts a strong and natural, original, and long-lasting effect. Useful for both women's and men's creations, it boosts woody notes, chypre, Oriental and fougère. It is also very useful in floral accords for providing depth and warmth. The organoleptic profile of 3,5-dimethyl-2-isobutylpyrazine and 3,6-dimethyl-2-isobutylpyrazine mixture is shown by the radar description in F-24.¹

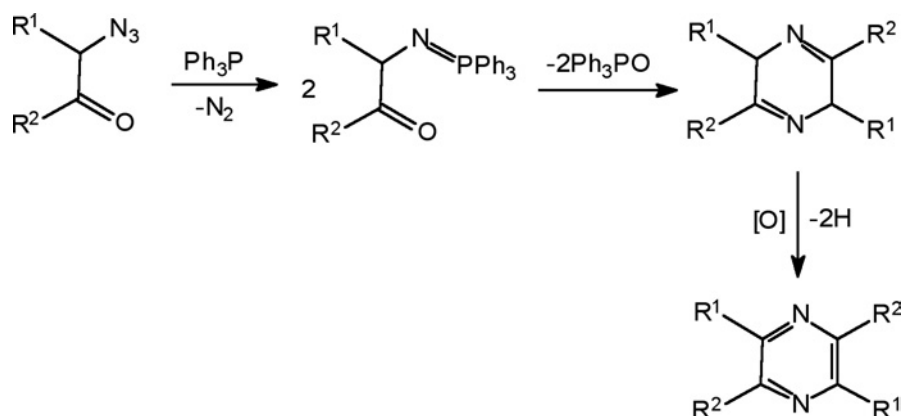
A convenient method for pyrazines synthesis is cyclocondensation between 1,2-dicarbonyl compounds and 1,2-diaminoethanes, with double imine formation to afford 2,3-dihydropyrazines, which are conveniently oxidized to pyrazines by manganese dioxide in KOH/ethanol (F-25).¹² This method yields the best results with symmetrical starting compounds.

The classical pyrazine synthesis involves the self-condensation of two molecules of an α -aminocarbonyl compound furnishing 3,6-dihydropyrazine, followed by oxidation—usually under mild conditions—to pyrazine (F-26).¹³ This route is restricted by the commercial nonavailability of the amino-carbonyl precursor.

An alternative synthesis of the dihydropyrazine utilizes a cyclizing aza-Wittig reaction of two molecules of α -phosphaziny ketones, which are accessible from α -azido ketones and triphenylphosphane (F-27).¹³

Alternative synthesis of the dihydropyrazine utilizing a cyclizing aza-Wittig reaction of two molecules of α -phosphaziny ketones

F-27



Quinoxalines are benzopyrazines (F-28), and several derivatives also are used in the F&F industry. 2-Methylquinoxaline (2-methylbenzopyrazine, 81) (F-29) occurs in pork, cocoa, coffee and passion fruit juice. It has a dusty, roasted flavor and is used in roasted and meat flavorings. 6-Methylquinoxaline (82) (F-30) occurs in pork liver, has a roasted and toasted flavor, and is used in roasted flavorings, such as coffee and meat preparations.

5,6,7,8-Tetrahydroquinoxaline (cyclohexapyrazine, 83) (F-31) occurs in bread, heated beef and pork, cocoa, coffee and roasted peanut. It is applied in fried and roasted flavorings. 5,6,7,8-Tetrahydroquinoxaline can be prepared using either 1,2-diaminocyclohexane or 1,2-cyclohexanedione as starting materials. 1,2-Diamino-cyclohexane is condensed with glyoxal to produce the dihydro intermediate, which undergoes dehydrogenation to produce the quinoxaline. The second alternative is a double condensation of 1,2-diaminoethane with 1,2-cyclohexanedione to produce something similar to the former intermediate, followed by the dehydrogenation-aromatization step (F-32).

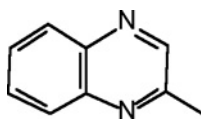
Thiazole derivatives: Thiazoles are sulfur- and nitrogen-containing five-membered aromatic rings. The most important types are alkylthiazoles, acetylthiazoles and hydroxyethylthiazoles.

Alkylthiazoles: 2,4,5-Trimethylthiazole (84) (F-33) occurs in meat, potato, coffee, cooked beef, heated lamb and cooked chicken. It has a chocolaty, nutty, coffeelike aroma and a roasted-with-meaty note flavor. It can be used in roasted flavors, beverages, sauces and ice cream. 2-Ethyl-4-methylthiazole (85) (F-34) occurs in coffee. It has a coffee, cocoa, meaty, rubbery odor and flavor, and is applied in baked goods, candy, coffee, cocoa, nut, savory and meat flavorings. 2-Isopropyl-4-methylthiazole (86) (F-35) occurs in tomato. It has a green, vegetative character with a nutlike, alliaceous, earthy, sulfur, coffee and tropical fruity nuance odor and flavor. It can be used in fruit and meat flavorings, such as peach, tomato, meat and coffee.

Another example of an alkylthiazole is 4-vinyl-5-methylthiazole (87) (F-36).¹⁴ This molecule occurs in coffee, filbert and yellow passion fruit. It has a nutty, musty, earthy, cocoa powderlike flavor and is applied to nut, cocoa and chocolate, coffee, meat, and potato flavorings. 2-Isobutylthiazole (88) (F-37) occurs in tomato leaves. It has a powerful green, tomato, vinelike with a raw musty nuance flavor, and is used in tomato soup vegetable flavorings.

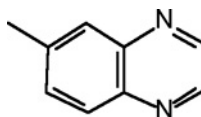
2-Methylquinoxaline (81)

F-29



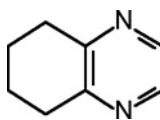
6-Methylquinoxaline (82)

F-30



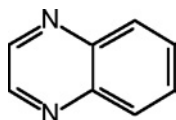
5,6,7,8-Tetrahydroquinoxaline (83)

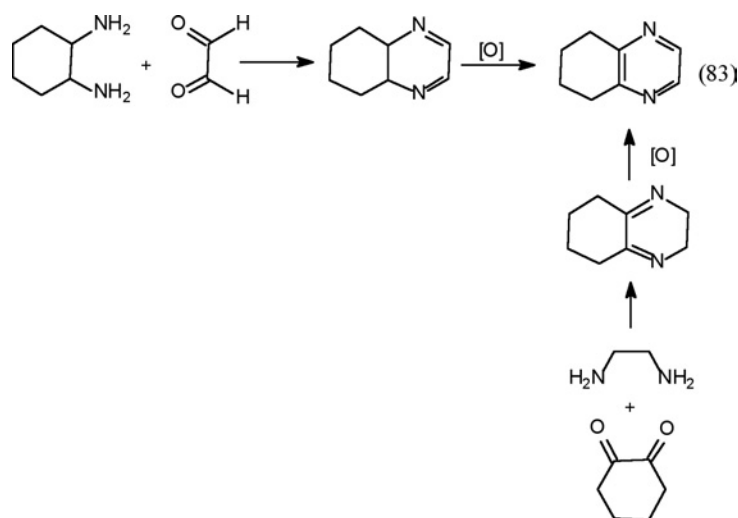
F-31



Quinoxaline
(benzopyrazine)

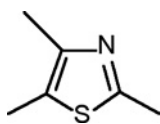
F-28





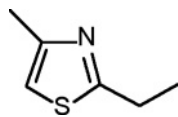
2,4,5-Trimethylthiazole (84)

F-33



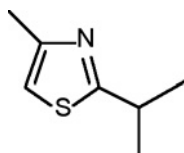
2-Isopropyl-4-methylthiazole (86)

F-34



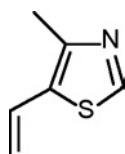
2-Acetyl-3,4-dihydro-5H-pyrrole (41)

F-35



4-Vinyl-5-methylthiazole (87)

F-36

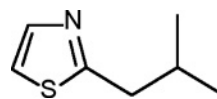


Acetylthiazoles: 2-Acetylthiazole (methyl 2-thiazole ketone) (F-38) occurs in asparagus, potato, beef, pork, beer, whiskey, coffee, beans and white bread. It has a nutty, cereal, hazelnut, cocoa and popcornlike flavor. 2-Acetylthiazole is used in roasted flavorings, such as nut and meat flavors, and in corn chip, popcorn and bread. 2,4-Dimethyl-5-acetylthiazole (F-39) has not yet been reported as being found in nature, but it probably can be found in meat. It has a meaty, roasted, nutty, sulfur, boiled beef, savory with woody and coffee nuances flavor, and is used in roasted flavors, coffee, cocoa, meat flavorings, nut, hazelnut, corn, chocolate and savory nuances. Acetylthiazoles cannot be made by direct substitution of a thiazole. For example, 2-acetylthiazole can be prepared via a diazonium ion, using the route shown in F-40.

Hydroxyethylthiazole: This type of thiazole is derived from thiamine (vitamin B-1, 91) (F-41). Thiamine occurs in yeast, rice husk and other cereals.

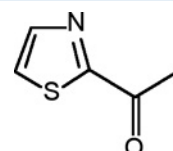
2-Isobutylthiazole (88), φ 4.7×10^7

F-37



2-Acetylthiazole (89)

F-38



The first and most important derivative is 4-methyl-5-thiazoleethanol (sulfurol, 92), and the second is the ester, namely 4-methyl-5-thiazoleethylacetate (sulfurol acetate 93) (F-42).

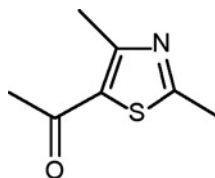
4-Methyl-5-thiazoleethanol (92) occurs in cocoa, cooked beef, roasted peanut, beer, cognac and liver. It has a beefy, somewhat nutty, meaty, broth, roasted, metallic flavor, and is used in meat flavorings, meat and savory, bread, nut, yeast, milk, and dairy. 4-Methyl-5-thiazoleethanol (92) seems to have a relatively low ϕ value of 1.43×10^4 . However, from purification experiments conducted on this thiazole, it appears as though it is practically odorless.

4-Methyl-5-thiazoleethylacetate (93) has not yet been reported as being found in nature, but it probably can be found in ham, beef and liver. It has a meaty, broth, bread, beefy, bloody and chicken note flavor, and is applied in meat, nut and dairy, cocoa, and bread flavorings. 4-Methyl-5-thiazoleethylacetate also is used in fragrances to impart woody, sandal-like odor.

Thiazoles generally are prepared by the cyclocondensation of α -halocarbonyl compounds with thioamides, known as Hantzsch synthesis, as shown in F-43. The Hantzsch synthesis involves three intermediate steps. In the first, the halogen atom

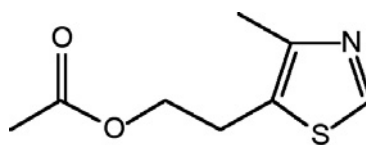
2,4-Dimethyl-5-acetylthiazole (90)

F-39



4-Methyl-5-thiazoleethylacetate (93)

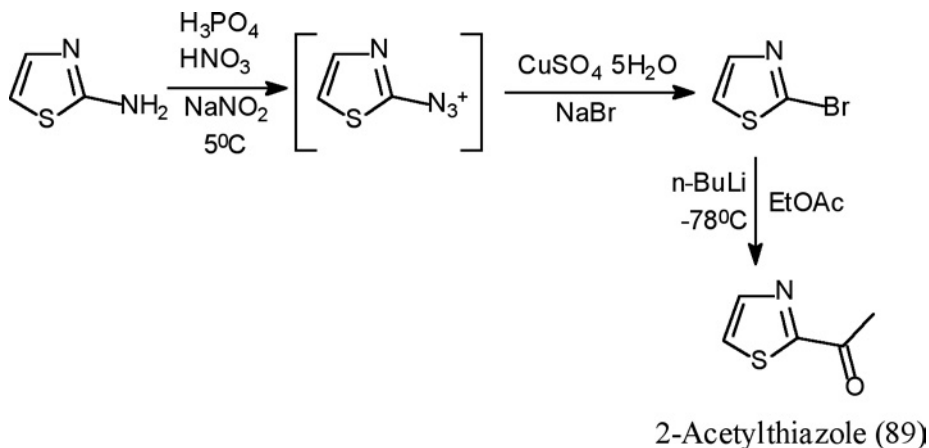
F-42



33

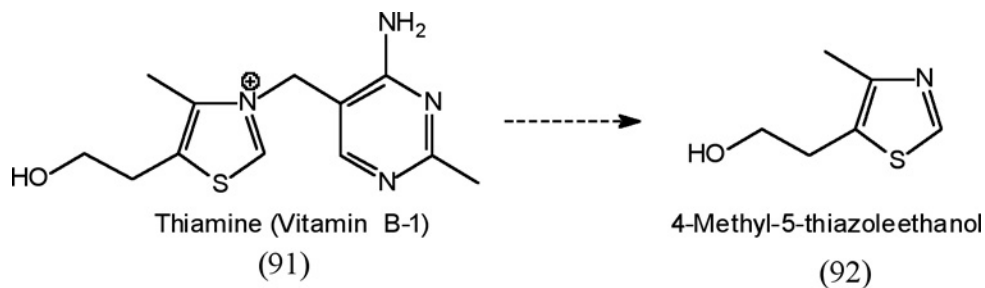
2-Acetylthiazole prepared via a diazonium ion

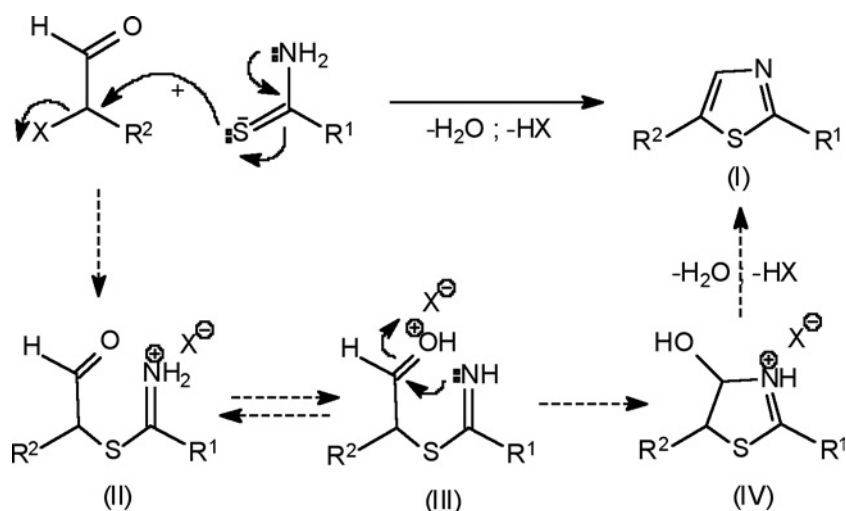
F-40



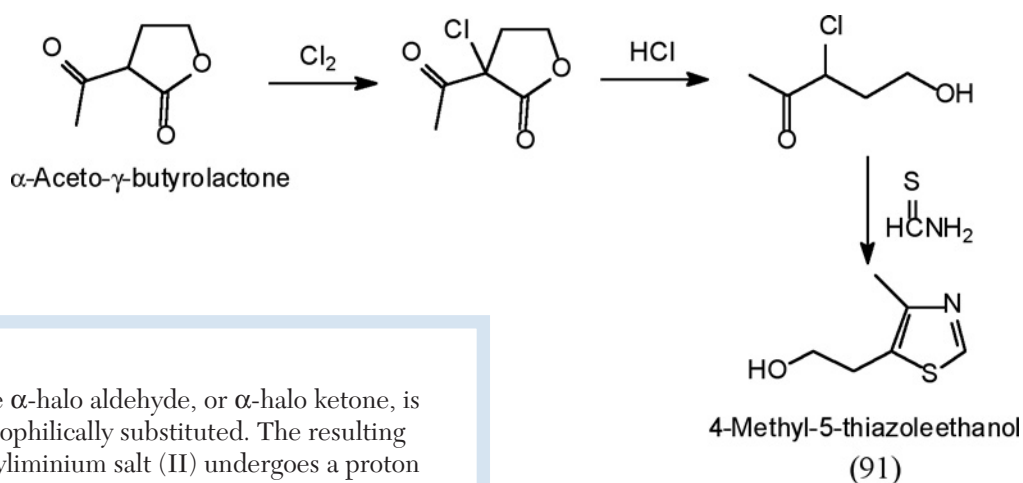
Hydroxyethylthiazole derived from thiamine (vitamin B-1, 91)

F-41





4-Methylthiazoleethanol (92) prepared from α -aceto- γ -butyrolactone by chlorination, followed by hydrolysis and decarboxylation



of the α -halo aldehyde, or α -halo ketone, is nucleophilically substituted. The resulting S-alkyliminium salt (II) undergoes a proton transfer (II $\rightarrow$ III); cyclization produces a salt of a 4-hydroxy-2-thiazoline (IV) that is converted into a 2,5-disubstituted thiazole (I) in protic solvents by an acid-catalyzed elimination of water.¹⁵

4-Methylthiazoleethanol (92) can be prepared from α -aceto- γ -butyrolactone by chlorination, followed by hydrolysis and decarboxylation. The obtained oxo-chloropentanol is cyclized with thioformamide in the Hantzsch synthesis, as shown in F-44.¹⁶

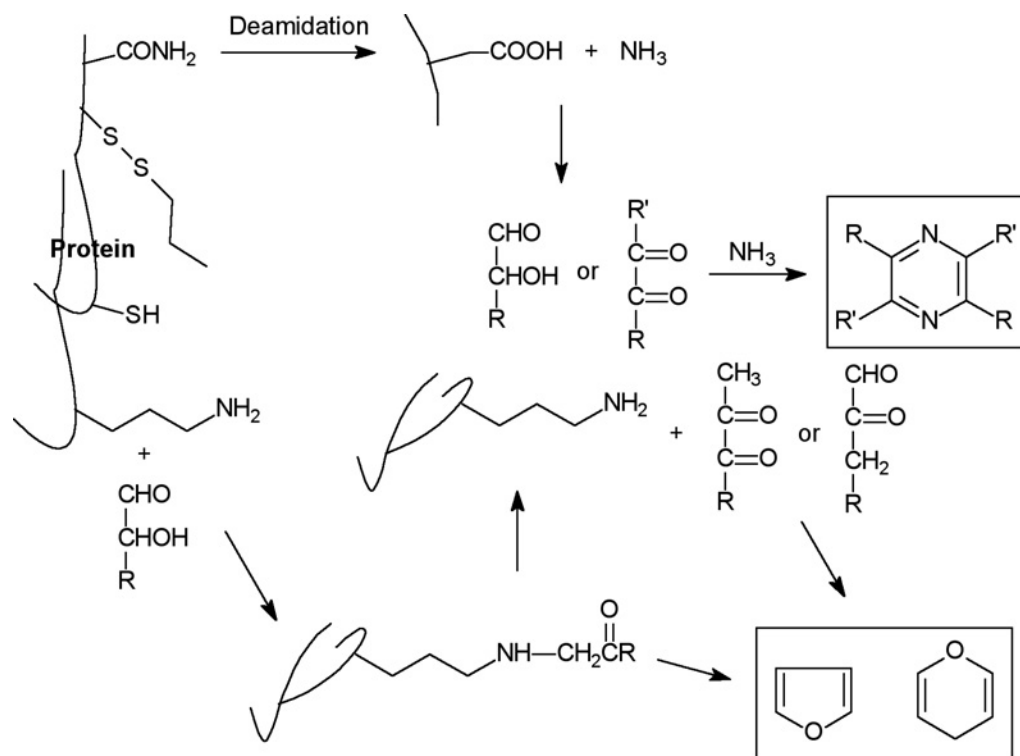
The Formation of Heterocyclic Compounds in Food

Heterocyclic molecules are obtained primarily by thermal treatment of food, in the Maillard reaction. The Maillard

reaction occurs between the amino groups of amino acids, peptides or proteins with the glycosidic hydroxyl group of sugars, ultimately resulting in the formation of brown pigments. A very general scheme of the Maillard reaction is shown in F-45, and it is discussed thoroughly elsewhere.

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