

**(12) PATENT ABRIDGMENT (11) Document No. AU-B-22740/88**  
**(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 620342**

(54) Title  
**SUBSTITUTED (2-HYDROXY-2-PHENYLETHYL)PYRAZINES AND THEIR USE IN SMOKING COMPOSITIONS**

International Patent Classification(s)  
(51)<sup>d</sup> **C07D 241/12 A24B 015/28**

(21) Application No. : **22740/88**

(22) Application Date : **23.09.88**

(30) Priority Data

(31) Number (32) Date (33) Country  
**100964 24.09.87 US UNITED STATES OF AMERICA**

(43) Publication Date : **06.04.89**

(44) Publication Date of Accepted Application : **20.02.92**

(71) Applicant(s)  
**PHILIP MORRIS PRODUCTS INC.**

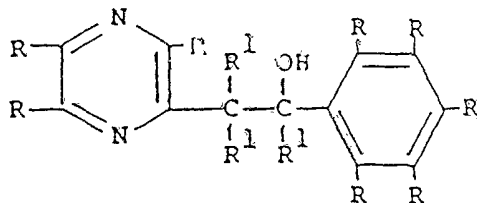
(72) Inventor(s)  
**YORAM HOUMINER; HENRY V. SECOR; JEFFREY I. SEEMAN**

(74) Attorney or Agent  
**CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101**

(56) Prior Art Documents  
**AU 525717 55061/50 C07D 241/12**  
**AU 31820/77 C07D 241/12**  
**AU 38930/89 C07D 241/12**

(57) Claim

1. A pyrazine compound corresponding to the formula:



where R is hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group; and R<sup>1</sup> is hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group; with the proviso that at least two R<sup>1</sup> groups are C<sub>1</sub>-C<sub>8</sub> alkyl radicals.

6. 2-(2-Hydroxy-2-phenylethyl)-3-tertiary-butylpyrazine.

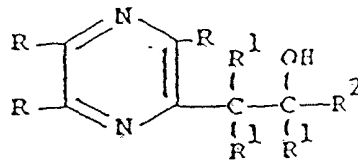
7. A smoking composition comprising an admixture of (1) combustible filler selected from natural tobacco, reconstituted tobacco and tobacco substitutes, and (2) a flavorant-release additive, comprising a pyrazine compound according to any of claims 1 to 6 in an amount between 0.0001 and 5 weight percent, based on the total

(11) AU-B-22740/88  
(10) 620342

-2-

weight of filler.

8. A smoking composition comprising an admixture of (1) combustible filler selected from natural tobacco, reconstituted tobacco and tobacco substitutes, and (2) a flavorant-release additive corresponding to the formula:



where R is hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group; R<sup>1</sup> is hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group; and R<sup>2</sup> is a C<sub>3</sub>-C<sub>12</sub> aromatic <sup>or heteroaromatic</sup> substituent; with the proviso that at least two R<sup>1</sup> groups are C<sub>1</sub>-C<sub>8</sub> alkyl radicals; which is present in an amount between 0.0001 and 5 weight percent based on the total weight of filler.

Australia

620342

Form 10

PATENTS ACT 1952

# COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl.:

Application Number:

Lodged:

Complete Specification—Lodged:

Accepted:

Lapsed:

Published:

Priority:

Related Art:

---

TO BE COMPLETED BY APPLICANT

Name of Applicant: PHILIP MORRIS PRODUCTS INC.

Address of Applicant: 3601 Commerce Road,  
Richmond,  
VIRGINIA 23234. U.S.A.

Actual Inventor: Yoram HOUMINER  
Henry V. SECOR  
Jeffrey I. SEEMAN

Address for Service: CALLINANS [REDACTED] Patent Attorneys, of  
48-50 Bridge Road, Richmond, State of Victoria, Australia.

Complete Specification for the invention entitled: SMOKING COMPOSITIONS CONTAINING A  
HETEROAROMATIC FLAVORANT-RELEASE ADDITIVE

The following statement is a full description of this invention, including the best method of performing it known to me:—

---

\* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

PM-86-3

SMOKING COMPOSITIONS CONTAINING A  
HETEROAROMATIC FLAVOPANT-RELEASE ADDITIVE

BACKGROUND OF THE INVENTION

5 It has been established that alkylpyrazines  
are natural components of tobacco smoke, and are  
contributors to tobacco smoke flavor [A. Baccetti et al  
J. Chromatog, 97, 79 (1974)]. Further, it has been  
disclosed in the patent literature that addition of  
10 alkyl pyrazines to tobacco results in an improvement  
in the flavor of smoking compositions as perceived by  
a test panel.

15 U.S. Pat. No. 3,402,051 describes a process  
for imparting a popcorn-like flavor and aroma to  
tobacco and foodstuffs by the incorporation of a  
2-acetylpyrazine derivative therein.

20 Other patents which disclose the addition of  
various pyrazine compounds to tobacco and foodstuffs  
as a means of providing flavor or flavor enhancement  
include U.S. Pat. Nos. 3,684,804; 3,705,158;  
3,754,934; 3,764,349; 3,767,426; and 3,881,025.

25 U.S. Pat. No. 3,914,227 discloses pyridyl and  
pyrazyl ketones and their use in altering the  
organoleptic properties of tobacco and foodstuffs, and  
U.S. Pat. No. 4,166,869 discloses acylpyrimidines  
useful as flavorants for the same type of applications.

Alkylpyridines have also been found to be  
useful tobacco additives. As an example, U.S. Pat.  
No. 3,625,224 describes the use of methylpyridines,

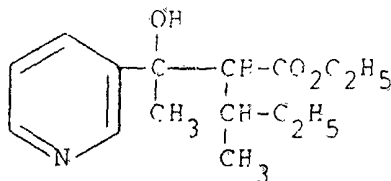
ethylpyridine and various dialkylpyridines as tobacco  
additives. U.S. Pat. No. 3,381,691 discloses  
2-methyl-5-isopropylpyridine as a tobacco additive.

5 It is characteristic of pyridine, pyrazine,  
pyrimidine and other heterocyclic derivatives employed  
as tobacco flavorants in the prior art, as illustrated  
by the above described technical literature, that the  
respective heterocyclic derivatives have the  
10 disadvantage of both high volatility and low odor  
threshold. Both of these properties significantly  
restrict the extent that these heterocyclic  
derivatives can be utilized as flavorants in tobacco  
compositions. A quantity of a pyrazine or pyridine  
15 derivative in a tobacco composition sufficient to have  
a noticeable effect in low deliver cigarettes causes  
a marked pack aroma.

U.S. Pat. No. 4,036,237 endeavors to overcome  
some of the disadvantages of the above-described  
flavorant technology. The said patent provides for  
20 the incorporation in smoking compositions of a  
flavorant compound which imparts cherry-like or fruity  
flavor to the smoke thereof, which flavorant compound  
is not lost during the manufacture and storage of the  
flavored smoking composition, and which is readily  
25 released when the smoking composition is burned.  
Illustrative of a U.S. Pat. No. 4,036,237 flavorant  
compound is ethyl 2,2-dimethyl-3-hydroxy-3-  
phenylpropionate.

U.S. Pat. No. 4,259,969 describes smoking  
flavorant-release additives such as  
2,3-dihydroxy-2,3-dimethyl-1,4-bis(3,5,6-trimethyl-2  
pyrazinyl)butane. Under smoking conditions there are  
5 released substituted-pyrazine pyrolysis products which  
enhance the flavor of the mainstream smoke and improve  
the aroma of the sidestream smoke.

U.S. Pat. No. 4,312,368 and related U.S. Pat.  
No. 4,479,003 describe heterocyclic-hydroxy-substituted  
10 alkanolate flavorant additives such as ethyl  
2-(2-butyl)-3-hydroxy-3-methyl-3-(3-pyridyl)propionate:



Under normal smoking conditions the flavorant additive  
pyrolyzes into components which contribute enhanced  
15 flavor and aroma to the smoke streams.

U.S. Pat. No. 4,171,214 is of general  
interest as disclosing pyrazine intermediates which  
are related structurally to the present invention  
smoking composition additives.

20 There is continuing research effort to  
develop improved smoking compositions which contain a  
new and efficient low volatility flavorant-release  
additive, and which generate mainstream smoke with  
flavorant-enhanced taste and character under smoking  
25 conditions.

Accordingly, it is an object of this invention to provide smoking compositions having incorporated therein a flavorant component which is characterized by lack of mobility and/or volatility at ambient temperature.

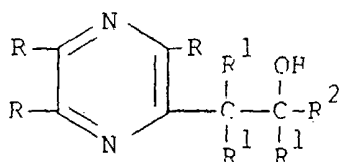
It is another object of this invention to provide smoking compositions having incorporated therein a flavorant-release additive which under normal smoking conditions yields pyrolysis constituents which impart improved flavorant properties to mainstream and sidestream smoke.

It is a further object of this invention to provide novel heteroaromatic compounds of low volatility which are adapted to be incorporated into cigarette fillers, and which under normal smoking conditions release volatile alkylpyrazine and other flavorant constituents into cigarette smoke.

Other objects and advantages of the present invention shall become apparent from the following description and examples.

DESCRIPTION OF THE INVENTION

One or more objects of the present invention are accomplished by the provision of a smoking composition comprising an admixture of (1) combustible filler selected from natural tobacco, reconstituted tobacco and tobacco substitutes, and (2) between about 0.0001-5 weight percent, based on the total weight of filler, of a novel flavorant-release additive corresponding to the formula:



where R is hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group; R<sup>1</sup> is hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group; and R<sup>2</sup> is a C<sub>3</sub>-C<sub>12</sub> aromatic substituent; with the proviso that at least two R<sup>1</sup> groups are C<sub>1</sub>-C<sub>8</sub> alkyl groups.

Illustrative of the R substituent are hydrogen, methyl, ethyl, propyl, butyl, isobutyl and 2-butyl radicals.

Illustrative of the R<sup>1</sup> substituent are R type of alkyl groups, and additionally can be selected from higher alkyl radicals such as pentyl, 2-pentyl, hexyl, 2-hexyl, heptyl, octyl, isoctyl, and the like.

Illustrative of the R<sup>2</sup> substituents are substituted and unsubstituted aromatic structures such as phenyl, methoxyphenyl, tolyl, xylyl, naphthyl, and the like, and heteroaromatic structures

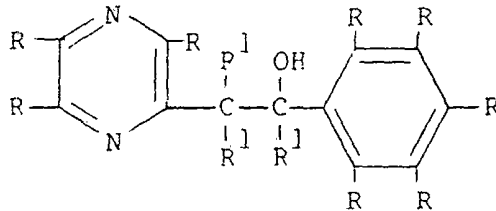


such as substituted and unsubstituted pyridyl, methylpyridyl, pyrazyl, thiazyl, furyl, and thienyl monovalent radicals.

5 The preferred  $R^2$  substituents are substituted and unsubstituted phenyl, pyridyl and pyrazyl monovalent radicals.

In another embodiment this invention provides a novel pyrazine composition corresponding to the formula:

10



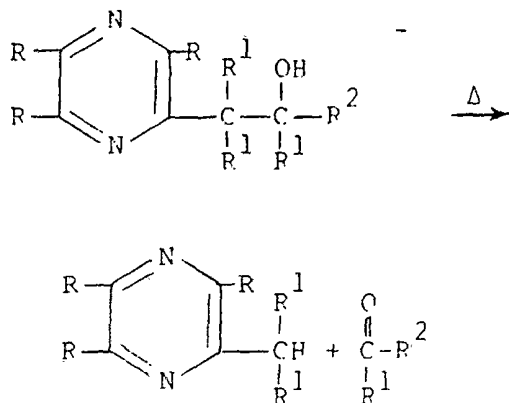
where R is hydrogen or a  $C_1-C_4$  alkyl group; and  $R^1$  is hydrogen or a  $C_1-C_8$  alkyl group; with the proviso that at least two  $R^1$  groups are  $C_1-C_8$  alkyl radicals.

.....  
.....  
.....  
.....15

When a present invention smoking composition is subjected to normal smoking conditions, the low volatility heteroaromatic additive pyrolyzes into volatile components which enhance the flavor and aroma of low delivery cigarette smoke:

.....  
.....  
.....

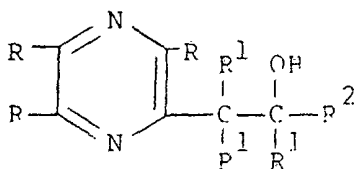
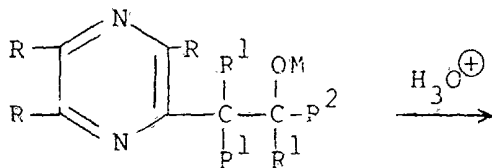
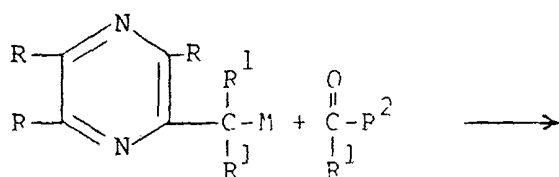
.....  
.....



The present invention heteroaromatic  
flavorant-release additives are stable and odorless  
compounds at ambient temperature. In addition, the  
additives decompose at a relatively low pyrolysis  
5 temperature (e.g., 150°-300°C) to release a high yield  
of desirable flavor-enhancing heteroaromatic and  
carbonyl components in mainstream smoke.

Preparation Of Heteroaromatic Compounds

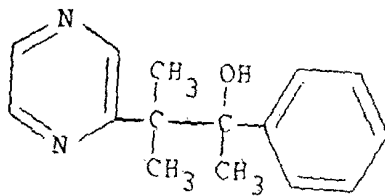
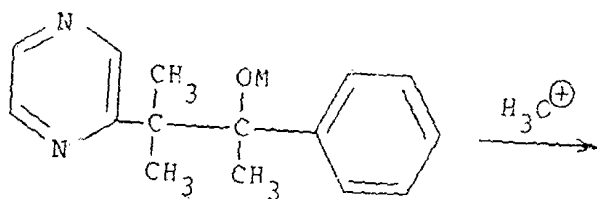
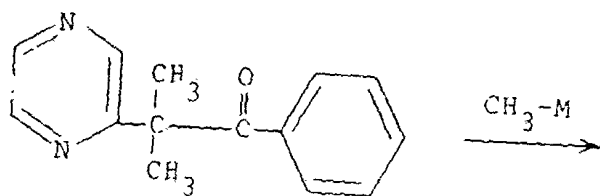
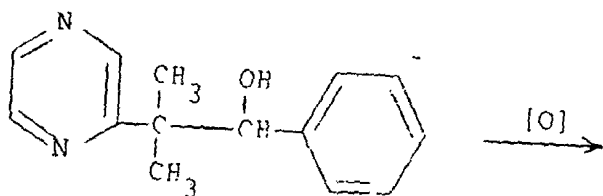
A general procedure for the preparation of present invention heteroaromatic flavorant-release compounds involves the reaction of a selected alkylpyrazine anion with a carbonyl derivative in a solvent medium:



where M is a metal atom such as lithium, and R, R<sup>1</sup> and R<sup>2</sup> are as previously defined.

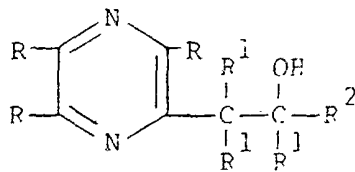
10 An alternative procedure is preferred for the synthesis of a compound such as

(R,S)-2-(1,1-dimethyl-2-hydroxy-2-phenylethyl)pyrazine in which steric hindrance by substituents is a factor:



Preparation Of Smoking Compositions

In a further embodiment this invention provides a method of preparing a smoking composition which is adapted to impart flavor and aroma to mainstream and sidestream smoke under smoking conditions, which method comprises incorporating into natural tobacco, reconstituted tobacco or tobacco substitute between about 0.0001-5 weight percent, based on composition weight, of a flavorant-release additive corresponding to the formula:



where R is hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group; R<sup>1</sup> is hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group; and R<sup>2</sup> is a C<sub>3</sub>-C<sub>12</sub> aromatic substituent; with the proviso that at least two R<sup>1</sup> groups are C<sub>1</sub>-C<sub>8</sub> alkyl radicals.

The invention flavorant-release additive can be incorporated into the tobacco or tobacco substitute in accordance with methods known and used in the art. Preferably the flavorant-release additive is dissolved in a solvent such as alcohol or aqueous alcohol and then sprayed or injected into the tobacco and/or tobacco substitute matrix. Such method ensures an even distribution of the flavorant additive throughout the filler, and thereby facilitates the production of a more uniform smoking composition. Alternatively,

the flavorant may be incorporated as part of a concentrated tobacco extract which is applied to a fibrous tobacco web as in the manufacture of reconstituted tobacco. Another suitable procedure is to incorporate the flavorant in tobacco and/or tobacco substitute filler in a concentration between about 0.5-5 weight percent, based on the weight of filler, and then subsequently to blend the treated filler with filler which does not contain flavorant additive.

The term "tobacco substitute" is meant to include non-tobacco smoking filler materials such as are disclosed in United States patents 3,703,177; 3,796,222; 4,019,521; 4,079,742; and references cited therein; incorporated herein by reference.

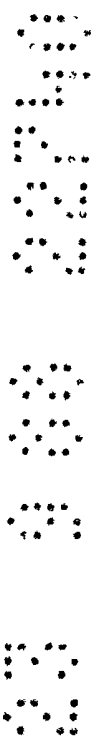
U.S. 3,703,177 describes a process for preparing a non-tobacco smoking product from sugar beet pulp, which process involves the acid hydrolysis of the beet pulp to release beet pectins, and at least an alkaline earth treatment thereafter to cause crosslinking of the pectins and the formation of a binding agent for the exhausted beet matrix.

U.S. 3,796,222 describes a smoking product derived from coffee bean hulls. The hulls are treated with reagents that attack the alkaline earth metal crosslinks causing the release of the coffee pectins. The pectins act as a binding agent and together with the treated hulls may be handled and used similarly to a tobacco product.

U.S. 4,019,521 discloses a process for forming a smoking material which involves heating a cellulosic or carbohydrate material at a temperature of 150°-750°C in an inert atmosphere for a period of time sufficient to effect a weight loss of at least 60 percent but not more than 90 percent.

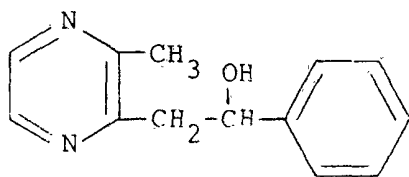
U.S. 4,079,742 discloses a process for the manufacture of a synthetic smoking product from a cellulosic material, which process involves a pyrolysis step and a basic extraction step to yield a resultant matrix which has a tobacco-like brown color and has improved smoking characteristics.

The following Examples are further illustrative of the present invention. The specific ingredients and processing parameters are presented as being typical, and various modifications can be derived in view of the foregoing disclosure within the scope of the invention.



EXAMPLE I

Preparation Of  
(R,S)-2-(2-Hydroxy-2-phenylethyl)-3-methylpyrazine



5           A solution of diisopropylamine (22.2 g,  
0.22 mole) in ether (500 ml) is stirred under nitrogen  
atmosphere and treated with n-BuLi (0.20 mole) in  
hexane (119 ml) at  $-75^{\circ}\text{C}$ . The resulting solution is  
warmed to  $0^{\circ}\text{C}$  and a solution of 2,3-dimethylpyrazine  
10 (21.6 g, 0.20 mole) in ether (30 ml) is added slowly  
and the reaction mixture is stirred at  $0^{\circ}\text{C}$  for  
30 minutes.

15           A solution of benzaldehyde (21.2 g,  
0.20 mole) in ether (30 ml) is added and stirring at  
 $0^{\circ}\text{C}$  is continued for an additional 30 minutes. Water  
is added to the reaction medium, then the organic  
layer is separated, washed with water, and dried over  
 $\text{Na}_2\text{SO}_4$ .

20           Evaporation of the solvent under reduced  
pressure provides an orange colored oil which is  
distilled bulb-to-bulb [ $155^{\circ}\text{-}165^{\circ}\text{C}$  (oven), 0.02 mm Hg]  
to give 22.2 g of a light yellow colored oil which  
crystallizes on standing. Recrystallization of the



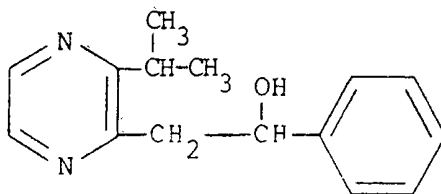
crude product from ether yields 13.84 g (32.3%) of  
product: mp 85°-86°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.47  
(s, 3H), 3.14 (m, 2H), 4.83 (d, 2H,  $J = 2.9$  Hz), 5.30  
(m, 1H), 7.27-7.45 (m, 5H), 8.35 (q, 2H,  $J = 2.7$  Hz).

5 Anal. Calc. for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$ : C, 72.87; H, 6.59; N, 13.08  
Found: C, 73.19; H, 6.88; N, 13.09



EXAMPLE III

Preparation Of  
(R,S)-2-(2-Hydroxy-2-phenylethyl)-3-isopropylpyrazine

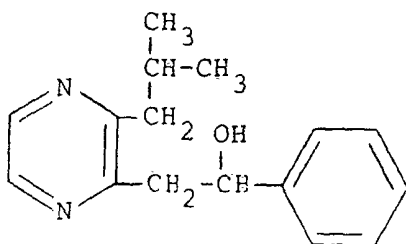


5            A reaction of 2-isopropyl-3-methylpyrazine  
(0.62 g, 4.56 mmoles) with benzaldehyde (0.48 g,  
4.56 mmoles) is conducted in accordance with the  
procedure of Example I. Workup followed by  
bulb-to-bulb distillation [100°-135°C (oven),  
10   0.01 mm Hg] provides 800 mg of a yellow-orange colored  
oil. The material is chromatographed on silica gel  
using 199:1 CHCl<sub>3</sub>/EtOH to give 386 (34.9%) of a  
colorless oil product which crystallizes below room  
temperature: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.20, 1.21, 1.24,  
15   1.26 (two doublets, 6, diastereotopic isopropyl methyl  
signals), 3.15-3.27 (m, 3H), 5.02 (d, 1H, J = 2.6 Hz),  
5.3 (m, 1H), 7.28-7.50 (m, 5H), 8.35 (d, 1H,  
J = 2.4 Hz), 8.47 (d, 1H, J = 2.4 Hz).

Anal. Calc. for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O: C, 74.35; H, 7.49; N, 11.56  
20            Found: C, 74.16; H, 7.35; N, 11.33

EXAMPLE IV

Preparation Of  
(R,S)-2-(2-Hydroxy-2-phenylethyl)-3-isobutylpyrazine

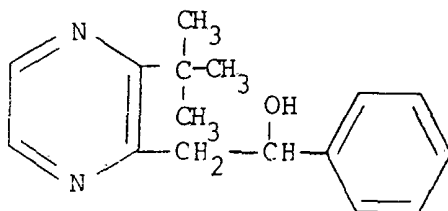


5            A reaction of 2-isobutyl-3-methylpyrazine  
(3.0 g, 20 mmoles) with benzaldehyde (2.12 g,  
20 mmoles) is conducted in accordance with the  
procedure of Example I. Standard workup is followed  
by bulb-to-bulb distillation [153°C (oven),  
10    0.005 mm Hg]. The resulting oil crystallizes on  
trituration with hexane to yield 2.5 g (48.8%) of the  
desired product; mp 52°-53°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  
15    δ 0.92 (d, 3H, J = 6.7 Hz), 2.0-2.2 (m, 1H), 2.62-2.64  
(m, 2H), 3.17 (m, 2H), 5.24-5.28 (m, 1H), 7.25-7.45  
(m, 5H), 8.34 (d, 1H, J = 2.5 Hz), 8.43 (d, 1H,  
J = 2.5 Hz).

Anal. Calc. for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O: C, 74.96; H, 7.86; N, 10.93  
Found: C, 75.20; H, 7.73; N, 10.87

EXAMPLE V

Preparation Of  
(R,S)-2-(2-Hydroxy-2-phenylethyl)-3-tert.-butylpyrazine



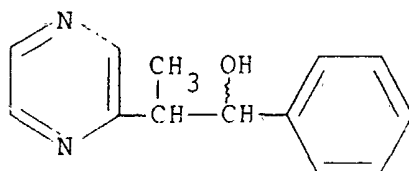
5 A reaction of 2-tert.-butyl-3-methylpyrazine  
(0.89 g, 5.95 mmoles) with benzaldehyde (0.63 g,  
5.95 mmoles) is conducted in accordance with the  
procedure of Example I. Standard workup is followed  
by bulb-to-bulb distillation [up to 100°C (oven),  
10 0.025 mm Hg]. Centrifugal chromatography of the  
residual fraction using silica gel and 85:15  
hexanes/acetone is followed by bulb-to-bulb  
distillation [150°C (oven), 0.01 mm Hg] and  
recrystallization from hexane to yield 0.643 g (42%)  
15 of the desired product: mp 89°-90°C; <sup>1</sup>H NMR  
(CDCl<sub>3</sub>) δ 1.44 (s, 9H), 3.25 (dd, 1H, J = 16.0,  
9.5 Hz), 3.50 (dd, 1H, J = 16.0, 2.2 Hz), 5.23  
(br d, 1H, J = 9.0 Hz), 5.78 (s, 1H), 7.30-7.52  
(m, 5H), 8.38 (d, 1H, J = 2.2 Hz), 8.47 (d, 1H,  
20 J = 2.2 Hz).

Anal. Calc. for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O: C, 74.96; H, 7.86; N, 10.93  
Found: C, 74.83; H, 7.98; N, 10.88

EXAMPLE VI

Preparation Of  
(1RS, 2SR)-2-(1-Methyl-2-hydroxy-2-phenylethyl)pyrazine (A) and  
(1RS, 2RS)-2-(1-Methyl-2-hydroxy-2-phenylethyl)pyrazine (B)

5



A reaction of ethylpyrazine (10.8 g, 0.1 mole) with benzaldehyde (10.6 g, 0.1 mole) is conducted in accordance with the procedure of Example I. Workup afforded a diastereoisomeric mixture of (A) ( $R_f$  0.25 on silica 4:1 hexane/acetone) and (B) ( $R_f$  0.18). The mixture is separated by centrifugal chromatography using 100:15 hexanes/acetone to yield pure diastereoisomers.

10

15

(A): mp 79°-80°C;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.30 (d, 3H,  $J = 7.0$  Hz), 3.23 (dq, 1H,  $J = 7.0, 3.5$  Hz), 4.19 (d, 1H,  $J = 2.0$  Hz), 5.16 (br t, 1H), 7.38 (br s, 5H), 8.42 (m, 3H).

20

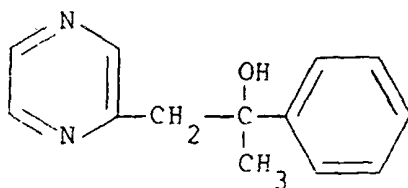
Anal. Calc. for  $C_{13}H_{14}N_2O$ : C, 72.87; H, 6.59; N, 13.08  
Found: C, 72.82; H, 6.66; N, 13.05

(B): mp 58°-59°C,  $^1\text{H}$  NMP ( $\text{CDCl}_3$ )  $\delta$  1.28  
(d, 3H,  $\underline{J} = 7.0$  Hz), 3.35 (pentet, 1H,  $\underline{J} = 7.0$  Hz),  
3.70 (d, 1H,  $\underline{J} = 5.8$  Hz), 5.05 (dd, 1H,  $\underline{J} = 7.0, 5.8$   
Hz), 7.40 (br s, 5H), 8.50-8.68 (m, 3H).

Anal. Calc. for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$ : C, 72.87; H, 6.59; N, 13.08  
Found: C, 72.95; H, 6.50; N, 13.13

EXAMPLE VII

Preparation Of  
(R,S)-2-(2-Hydroxy-2-phenylpropyl)pyrazine



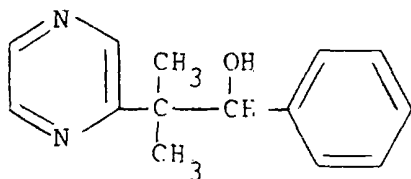
5            A reaction of 2-methylpyrazine (4.7 g,  
0.05 mole) with acetophenone (6.6 g, 0.055 mole) is  
conducted in accordance with the procedure of  
Example I. Workup followed by bulb-to-bulb  
distillation and centrifugal chromatography using  
10 85:15 hexanes/acetone on silica gel yields 454 mg  
(4.2%) of the desired product: mp 53°-54°C  
(from hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.61 (s, 3H),  
3.35 (s, 2H), 5.35 (br s, 1H), 7.18-7.63 (m, 5H),  
8.38-8.55 (m, 3H).

15 Anal. Calc. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O: C, 72.87; H, 6.59; N, 13.08  
Found: C, 73.03; H, 6.58; N, 13.04



EXAMPLE VIII

Preparation Of  
(R,S)-2-(1,1-Dimethyl-2-hydroxy-2-phenylethyl)pyrazine



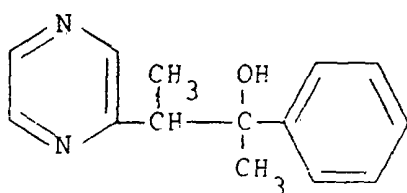
5 A reaction of isopropylpyrazine (439 mg,  
3.6 mmoles) with benzaldehyde (456 mg, 4.33 mmoles) is  
conducted by means of the Example I procedure with the  
stirring time extended to 1.5 hours. Workup is  
followed by bulb-to-bulb distillation [105°-160°C  
10 (oven), 0.01 mm Hg] to give a semi-solid. The  
resultant material is purified directly by centrifugal  
chromatography on silica gel using 100:14:3.6  
hexanes/acetone/EtOH to yield 177 mg (21%) of  
product: mp 90°-91°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.39  
15 (s, 3H), 1.40 (s, 3H), 4.50 (d, 1H, J = 4.5 Hz), 4.95  
(d, 1H, J = 4.5 Hz), 7.10-7.12 (m, 2H), 7.24-7.28  
(m, 3H), 8.51-8.58 (m, 3H).

Anal. Calc. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O: C, 73.65; H, 7.06; N, 12.27  
20 Found: C, 73.27; H, 6.96; N, 12.13

A reaction of tetramethylpyrazine with  
3-acetylpyridine yields (R,S)-2-[2-hydroxy-2-  
(3-pyridyl)propyl]-3,5,6-trimethylpyrazine.

EXAMPLE IX

Preparation Of A Mixture Of  
(1RS,2RS)-2-(1-methyl-2-hydroxy-2-phenylpropyl)pyrazine and  
5 (1RS,2SR)-2-(1-methyl-2-hydroxy-2-phenylpropyl)pyrazine



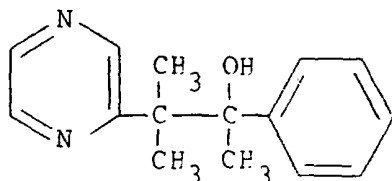
A reaction of ethylpyrazine (5.40 g,  
0.05 mole) with acetophenone (6.0 g, 0.05 mole) is  
10 conducted in accordance with the previously described  
procedure. Workup afforded an oil which was  
crystallized from cyclohexane to yield 3.7 g of the  
desired product: m.p. 88°-108°C. <sup>1</sup>H NMR confirms  
the above structure and indicates about 1:1 mixture of  
15 the two diastereoisomers.

Anal. Calc. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O: C,73.65; H,7.06; N,12.27  
Found: C,73.60; H,7.20; N,12.19

A reaction of tetraethylpyrazine with  
acetophenone yields a 1-position diastereoisomeric  
20 mixture of 2-(1-methyl-2-hydroxy-2-phenylpropyl)-3,5,6-  
triethylpyrazines.

EXAMPLE X

Preparation Of  
(R,S)-2-(1,1-dimethyl-2-hydroxy-2-phenylpropyl)pyrazine



5            A stirred and cooled (0°C) solution of  
2-(1,1-dimethyl-2-hydroxy-2-phenylethyl)pyrazine  
(1 g, 4.38 mmoles) in acetone (150 ml) is treated with  
an aqueous solution of CrO<sub>3</sub>-H<sub>2</sub>SO<sub>4</sub> (1.39 ml,  
3.72 mmoles). The solution is stirred for 10 minutes,  
10 diluted with water (500 ml), allowed to stand for  
1 hour and then basified (Na<sub>2</sub>CO<sub>3</sub>). The solution  
is extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the CH<sub>2</sub>Cl<sub>2</sub>  
extract is dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to  
provide 1.2 g of a turbid oil. Purification by  
15 centrifugal chromatography on silica gel and eluting  
with 100:15:3 hexanes/acetone/EtOH yields 710 mg (71%)  
of 1-(1-phenyl-2-methyl-2-pyrazinyl)propanone:  
mp 67°-68°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.7-1.8 (s, 6H),  
7.23-7.48 (m, 5H), 8.46-8.59 (m, 3H).

20 Anal. Calc. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O: C, 74.31; H, 6.24; N, 12.38  
Found: C, 74.22; H, 6.10; N, 12.23

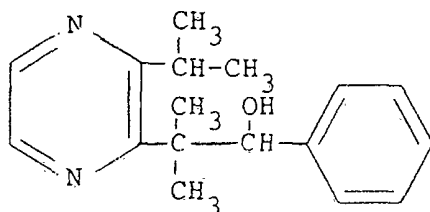
A solution of the prepared ketone (390 mg, 1.73 mmoles) in ether (100 ml) is stirred at  $-70^{\circ}\text{C}$  and treated with 2.23 mmoles) of MeLi in ether (2.23 ml). The reaction is quenched with MeOH after being stirred  
5 for 2 hours at  $-65^{\circ}\text{C}$ . The resultant mixture is concentrated and the residue is taken up in  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{Na}_2\text{SO}_4$ ) and filtered. Purification by centrifugal chromatography on silica gel with 95:4:1 hexanes/acetone/EtOH yields 221 mg  
10 (53%) of the desired product: mp  $99^{\circ}\text{-}100^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.37 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 5.68 (s, 1H), 7.21-7.34 (m, 5H), 8.48-8.54 (m, 3H).

Anal. Calc. for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$ : C, 74.35; H, 7.49; N, 11.56  
Found: C, 74.23; H, 7.61; N, 11.48

EXAMPLE XI

Preparation Of  
(R,S)-2-(1,1-Dimethyl-2-hydroxy-2-phenylethyl)-3-  
isopropylpyrazine

5



10 A solution of lithium diisopropylamide in  
ether is prepared as described in Example I from  
diisopropylamine (676 mg, 6.7 mmoles) and n-BuLi  
(6.6 mmoles) in 2.67 ml of hexane at -75°C. The  
15 resulting solution is warmed to 0°C and a solution of  
2,3-diisopropylpyrazine (1.0 g, 6.1 mmoles) in ether  
(2 ml) is added slowly and the reaction mixture is  
stirred under reflux for 2 hours. The mixture is then  
treated with benzaldehyde (0.78 g, 7.32 mmoles) as  
described in Example I.

Workup followed by purification using  
centrifugal chromatography and recrystallization from  
hexane affords 10.6 mg (0.64%) of (R,S)-  
2-(1,1-dimethyl-2-hydroxy-2-phenylethyl)-3-  
20 isopropylpyrazine: M.P. 128°-128.5°C; <sup>1</sup>H NMR  
(CDCl<sub>3</sub>) δ 1.25 (d, 3H, J = 7 Hz), 1.27 (s, 3H),  
1.30 (d, 3H, J = 7.0 Hz), 1.48 (s, 3H), 3.59 (heptet,  
1H, J = 7.0 Hz), 4.96 (br d, 1H, J = 3.3 Hz, CHOH),  
5.28 (br d, 1H, J = 3.3 Hz, CHOH), 7.2-7.4 (m, 5H),  
25 8.31 (d, 1H, J, J = 2.5 Hz), 8.48 (d, 1H, J = 2.5 Hz).

Anal. Calc. for C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O: C, 75.52; H, 8.20; N, 10.36  
Found: C, 75.31; H, 8.23; N, 10.30

EXAMPLE XII

This Example demonstrates first order rate constants for the pyrolysis of present invention pyrazine compounds in comparison with prior art pyrazine compounds.

The pyrolysis reactions are conducted in diglyme-d<sub>14</sub> (Merck Sharp & Dohme, Canada, Ltd.) that is dried over a molecular sieve. A 0.4 M solution of each of the pyrazines (0.5 ml) is placed in a thick-walled NMR tube, and the tubes are sealed. Kinetic runs are performed in a constant-temperature oil bath preheated to the desired temperature ( $170 \pm 0.8^\circ\text{C}$ ).

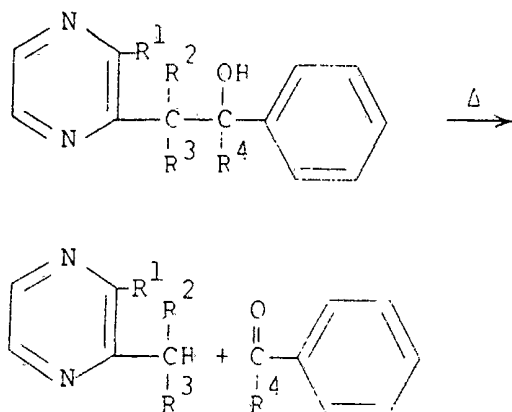
The progress of each pyrolysis is followed by NMR spectroscopy employing a method described in J. Org. Chem. 45, 999 (1980). Percentage compositions are calculated from integration of peaks of both reactants and products mainly in the aromatic regions. In each case the reaction proceeds smoothly with only the parent pyrazine and carbonyl product detected in the reaction mixture. First order rate constants are calculated and the comparative data are summarized in the Table.

The comparative data demonstrate that the heteroaromatic compounds of Examples VIII-X in accordance with the present invention pyrolyze at a significantly higher rate than known heteroaromatic compounds of related structure.

When a present invention heteroaromatic  
compound is utilized as a smoking composition  
flavorant-release additive, the fast rate of pyrolysis  
delivers a high yield of volatile pyrazine and  
5 carbonyl components which are effective for  
enhancement of the flavor and aroma of generated smoke.



TABLE



Example Compound	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	$k(\text{sec}^{-1}) \times 10$
(a) *	H	H	H	H	1.81
I	CH <sub>3</sub>	H	H	H	9.36
II	CH <sub>2</sub> CP <sub>3</sub>	H	H	H	9.49
III	CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	H	8.69
IV	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	H	9.06
V	C(CH <sub>3</sub> ) <sub>3</sub>	H	H	H	13.13
VI	H	CP <sub>3</sub>	H	H	5.44
VII	H	H	CP <sub>3</sub>	H	4.61
VIII	H	H	H	CP <sub>3</sub>	8.91
IX	H	CH <sub>3</sub>	CH <sub>3</sub>	H	53.77
X	H	P(CH <sub>3</sub> ) <sub>3</sub>	CH <sub>3</sub> (H)	CH <sub>3</sub>	18.57
		mixture of diastereoisomers			
	H	CH <sub>3</sub>	CH <sub>3</sub>	CP <sub>3</sub>	426.50

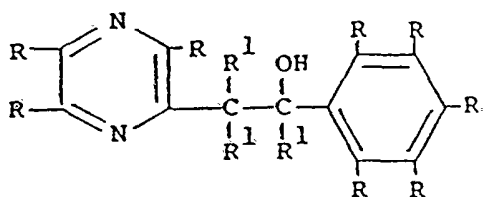
\*J. Org. Chem., 45, 999(1980).



8C29815A

The claims defining the invention are as follows:

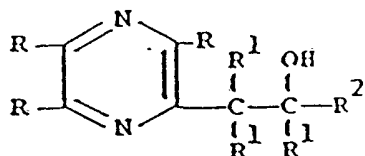
1. A pyrazine compound corresponding to the formula:



where R is hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group; and R<sup>1</sup> is hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group; with the proviso that at least two R<sup>1</sup> groups are C<sub>1</sub>-C<sub>8</sub> alkyl radicals.

2. 2-(1,1-Dimethyl-2-hydroxy-2-phenylethyl)-pyrazine.
3. 2-(1-Methyl-2-hydroxy-2-phenylpropyl)-pyrazine.
4. 2-(1,1-dimethyl-2-hydroxy-2-phenylpropyl) pyrazine.
5. 2-(1,1-Dimethyl-2-hydroxy-2-phenylethyl)-3-isopropylpyrazine.
6. 2-(2-Hydroxy-2-phenylethyl)-3-tertiary-butylpyrazine.
7. A smoking composition comprising an admixture of (1) combustible filler selected from natural tobacco, reconstituted tobacco and tobacco substitutes, and (2) a flavorant-release additive, comprising a pyrazine compound according to any of claims 1 to 6 in an amount between 0.0001 and 5 weight percent, based on the total weight of filler.

8. A smoking composition comprising an admixture of (1) combustible filler selected from natural tobacco, reconstituted tobacco and tobacco substitutes, and (2) a flavorant-release additive corresponding to the formula:



where R is hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group; R<sup>1</sup> is hydrogen or a C<sub>1</sub>-C<sub>8</sub> alkyl group; and R<sup>2</sup> is a C<sub>3</sub>-C<sub>12</sub> aromatic <sup>or heteroaromatic</sup> substituent; with the proviso that at least two R<sup>1</sup> groups are C<sub>1</sub>-C<sub>8</sub> alkyl radicals; which is present in an amount between 0.0001 and 5 weight percent based on the total weight of filler.

9. A smoking composition in accordance with claim 8 wherein R<sup>2</sup> is a phenyl radical.

10. A smoking composition in accordance with claim 8 wherein R<sup>2</sup> is a naphthyl radical.

11. A smoking composition in accordance with claim 8 wherein R<sup>2</sup> is a pyridyl radical.

12. A smoking composition in accordance with claim 8 wherein R<sup>2</sup> is a pyrazyl radical.

13. A smoking composition in accordance with claim 8 wherein R<sup>2</sup> is a thiazyl radical.

14. A smoking composition in accordance with claim



8 wherein R<sup>2</sup> is a furyl radical.

15. A smoking composition in accordance with claim 8, wherein R<sup>2</sup> is a thienyl radical.

16. A smoking composition, substantially as herein described with reference to any one of the Examples II to VI or VIII to X.

17. A method of preparing a smoking composition which comprises incorporating into natural tobacco, reconstituted tobacco or tobacco substitute between 0.0001 and 5 weight percent, based on composition weight, of a flavorant-release additive as defined in either claim 7 or claim 8.

DATED this 18th day of November 1991.

PHILIP MORRIS PRODUCTS INC.

By their Patent Attorneys:

CALLINAN LAWRIE

*Michael J. Houlahan.*

