Perester Oxidation of (+)-Limonene to (−)-Carvone and Piperitenone

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(+)-Limonene was oxidized with *tert*-butyl perbenzoate or *tert*-butyl peracetate to an ester mixture which was hydrolyzed; the resulting alcohols were oxidized with chromic acid to (−)-carvone and piperitenone in 23 and 15% overall yields, respectively. The main product, optically pure (−)-carvone, was isolated by distillation. Products of oxidation at all allylic positions were isolated from the intermediate alcohol fraction.

Each year production of the citrus processing industry by-product, (+)-limonene, increases as more efficient means of cleaning waste streams are used. An estimated 80 million pounds per year of (+)-limonene is potentially recoverable from processed citrus fruit, but only about one-fourth of that amount is currently being recovered and marketed (Veldhuis, 1968). In order to expand markets for this monoterpene hydrocarbon by-product, methods for converting it to more valuable chemicals are needed.

Of the numerous chemical transformations of limonene reported (Verghese, 1968), only one reaction has been applied commercially. In it the principal ingredient in synthetic spearmint flavoring, (−)-carvone, is prepared from (+)-limonene and nitrosyl chloride (Bordenca et al., 1951; Derfer et al., 1966). (−)-Menthol, another commercially valuable oxidation product of (+)-limonene, has to be efficiently produced from it. Recently, we oxidized (+)-limonene with selenium dioxide–hydrogen peroxide and oxidized α-terpineol with *m*-chloroperbenzoic acid in efforts to obtain a single product more valuable than these abundant starting materials (Wilson and Shaw, 1973, 1975). Although some new hydroxy cyclic ethers were found, no one commercially valuable compound was obtained in high yield.

We now report the oxidation of (+)-limonene to (−)-carvone and piperitenone. Since piperitenone is an intermediate in menthol synthesis, this procedure has potential commercial application for synthesis of two important flavor chemicals, carvone and menthol.

EXPERIMENTAL SECTION

Mass spectra were determined with a Bendix Model 3012 Time-of-Flight or a Bell and Howell Model 21-490 mass spectrometer at 70 eV. Optical rotations of absolute ethanol solutions were determined with a Rudolf Model 62 polarimeter. Infrared spectra of thin liquid films were obtained with a Perkin-Elmer Model 137 Infracord. Synthesized compounds were identified by comparison of their infrared and mass spectra with those of authentic compounds.

Gas chromatographic (GC) separations were made by an F&M Model 700 gas chromatograph equipped with 0.20 in. × 20 ft stainless steel columns packed with 40% Carbowax 20M on 60–80 mesh Gas-Chrom P and a thermal conductivity detector at 275°. Temperature was programmed from 100 to 220° at 1°/min at a He flow rate of 100 ml/min. The injection port temperature was 245°. Reaction product percentages were determined from peak areas (height × width at half-height) of GC curves from crude reaction mixtures.

(+)-Limonene was distilled from Valencia orange essence oil, bp 45–50° (1.5 mmHg), $[\alpha]^{29}D$ 116.5° (*c* 1.24), and shown to be more than 99% pure by GC (Shaw and Coleman, 1971).

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Terpene Benzoate Esters. To 70 g (0.515 mol) of (+)-limonene and 1.0 g of cuprous bromide was added dropwise with stirring in 1 hr 100 g (0.516 mol) of *tert*-butyl perbenzoate (K&K Laboratories, Plainview, N.Y.) (Monson, 1971). (*Caution*! When the first 25 g of *tert*-butyl perbenzoate has been added, the reaction mixture should be blue-green. An explosion resulted when all perbenzoate was added before any color formed to indicate that reaction had begun.) The reaction mixture was heated at 82° oil bath temperature for 24 hr. The reaction was duplicated, and the two were combined. This was filtered into a 500-ml separatory funnel, and the filtrate was washed four times with 50-ml portions of saturated sodium carbonate and then two times with 50-ml portions of distilled water. Most of the unreacted limonene (35% recovery) was removed by distillation at 28° and 1.5 mmHg to afford 119 g of crude benzoate ester mixture which was shown by GC analysis to contain 11% limonene and 89% total benzoates.

Benzoate Ester Hydrolysis. To 166 g (0.67 mol) of crude benzoate ester mixture was added 500 ml of sodium hydroxide solution (58 g of NaOH in 500 ml of 1:1 methanol–water), and the solution was allowed to stand overnight. The resulting mixture was placed in a separatory funnel, and the upper oily layer was removed. The lower layer was extracted six times with 50-ml portions of diethyl ether, and the extracts added to the oily layer. The ethereal solution was washed three times with 50-ml portions of water. The ether was removed by a rotary film evaporator at 40° and 711 mmHg. The composition of the residual crude terpene alcohol mixture (Table I) was analyzed by GC and infrared and mass spectroscopy. Optical rotations, $[\alpha]^{23}D$ −185° (*c* 0.39) and $[\alpha]^{23}D$ −17.5° (*c* 0.27) were obtained for *trans*- and *cis*-carveol, respectively.

Chromic Acid Oxidation. To 92 g (0.60 mol) of crude terpene alcohol mixture in 500 ml of cold diethyl ether was added 350 ml of aqueous chromic acid [100 g (0.33 mol) of sodium dichromate dihydrate dissolved in 300 ml of water and 136 g (1.34 mol) of 97% sulfuric acid were mixed and the solution diluted to 500 ml]. The mixture which was stirred at ice bath temperature for 24 hr (Brown et al., 1971) was transferred to a separatory funnel, and the lower aqueous layer was withdrawn. The ethereal solution was concentrated by a rotary evaporator at 40° and 711 mmHg. Gas chromatographic analysis of the carbonyl mixture (Table II) showed 55% (−)-carvone, $[\alpha]^{23.5}D$ −68° (*c* 0.97) [lit. −62.45° (Simonsen, 1947)], and 40% piperitenone. Distillation at 65–70° and 70–74° at 1.2 mmHg afforded 33 g of (−)-carvone, $[\alpha]^{23.5}D$ −69° (*c* 1.16), and 3.0 g of a 1:1 mixture of (−)-carvone and piperitenone, respectively. The residue (ca. 45 g) still contained appreciable carvone and piperitenone in about a 1:1 ratio, as determined by GC analysis.

Terpene Acetate Esters. To 77 g (0.56 mol) of (+)-limonene and 1.0 g of cuprous bromide was added dropwise with stirring in 1 hr 100 g (0.56 mol) of 75% *tert*-butyl peracetate in benzene, and the reaction was carried out as described for the benzoate ester. Unreacted limonene, 38%,

Table I. Ester Hydrolysis Products

Hydrolysis product	GLC area % from Benzoate	GLC area % from Acetate	Optical rotation (deg) from Benzoate	Optical rotation (deg) from Acetate
trans-2,8-*p*-Menthadien-1-ol	Trace	Trace		
cis-2,8-*p*-Menthadien-1-ol	Trace	Trace		
1,4(8)-*p*-Menthadien-3-ol	17.0	9.0		
1,8-*p*-Menthadien-4-ol	2.0	5.0		–57.0
1(7),8-*p*-Menthadien-2-ol	10.0	4.0		–78.8
trans-1,8-*p*-Menthadien-6-ol (*trans*-carveol)	40.0	40.0	–185.0	–190.5
cis-1,8-*p*-Menthadien-6-ol (*cis*-carveol)	25.0	34.0	–17.5	–19.5
1,8-*p*-Menthadien-7-ol	3.0	2.5		
1,8-*p*-Menthadien-10-ol	3.0	2.5		
Limonene	Trace	6.0		

Table II. Carbonyls from Chromic Acid Oxidation of Terpene Alcohols

Compound	GLC area % from Benzoate	GLC area % from Acetate	Optical rotation (deg from) Benzoate	Optical rotation (deg from) Acetate
(–)-Carvone	55.0	57.0	–68.0	–67.0
Piperitenone	40.0	38.0	0.0	0.0
Unidentified	3.0	4.0		

Table III. Analysis of Acetate Esters

Compound	GLC area %	Optical rotation (deg)
1(7),8-*p*-Menthadienyl 2-acetate	12.0	
trans-1,8-*p*-Menthadienyl 2-acetate (*trans*-carvyl acetate)	42.0	–72.0
cis-1,8-*p*-Menthadienyl 2-acetate (*cis*-carvyl acetate)	25.0	–46.5
1,8-*p*-Menthadienyl 7-acetate	4.0	
1,8-*p*-Menthadienyl 10-acetate	4.0	
Limonene	12.0	

was recovered by distillation which left 119 g of crude acetate mixture. Chromatographic analysis (Table III) showed the mixture to contain 42% *trans*-carvyl acetate, $[\alpha]^{23.5}D$ −72° (*c* 0.97) [lit. −32.2° (Reitsema, 1953)], and 25% *cis*-carvyl acetate, $[\alpha]^{23.5}D$ −46.5° (*c* 0.86).

Acetate Ester Hydrolysis. To 119 g of crude acetate esters [ca. 84 g (0.43 mol) of *trans*- and *cis*-carvyl acetates] was added 100 ml of sodium hydroxide solution (58 g of NaOH in 500 ml of 1:1 methanol and water), and the mixture was treated as described for the hydrolysis of the benzoate esters. The yield of mixed terpene alcohols was 102 g. Chromatographic analysis showed that the mixture contained 40% *trans*-carveol, $[\alpha]^{23}D$ −190.5° (*c* 0.75), and 34% *cis*-carveol, $[\alpha]^{23}D$ −19.5° (*c* 0.51).

Chromic Acid Oxidation. The oxidation of 102 g (0.79 mol) of crude alcohol mixture in 500 ml of cold diethyl ether with 400 ml of aqueous dichromate at conditions described previously yielded 57% (−)-carvone, $[\alpha]^{23.5}D$ −67° (*c* 0.91), and 38% piperitenone (Table II). Distillation at 70–71° and 1.0 mmHg afforded 28 g of (−)-carvone, $[\alpha]^{23.5}D$ −62.0° (*c* 1.03), and distillation at 84–88° and 2.4 mmHg afforded 13.4 g of a 1:1 mixture of (−)-carvone and piperitenone. The residue contained appreciable (−)-carvone and piperitenone, as determined by GC analysis.

RESULTS AND DISCUSSION

(+)-Limonene was oxidized with *tert*-butyl perbenzoate or peracetate to a mixture of esters which were hydrolyzed, and the resulting alcohols were oxidized to a mixture consisting mostly of (−)-carvone and piperitenone. (−)-Carvone was recovered by distillation in 20–23% overall yield based on the (+)-limonene consumed. Piperitenone was present in ~15% overall yield, but was only partially separated by distillation.

In the perester oxidation reaction sequence products from oxidation at all allylic positions in (+)-limonene were identified. The benzoate ester mixture formed by oxidation with *tert*-butyl perbenzoate could not be separated into individual esters under the GC conditons used. However, separation was adequate to obtain a quantitative measure of total benzoates in the product mixture (see Experimental Section).

The acetate ester mixture was separated by GC. The major oxidation products, *trans*- and *cis*-carvyl acetates, comprised 67% of the reaction mixture, and 1(7),8-*p*-menthadienyl 2-acetate comprised 12% of the mixture (Table III). Other allylic oxidation products, 1,8-*p*-menthadienyl 7-acetate and 1,8-*p*-menthadienyl 10-acetate, were present in yields of 4% each.

Products of (+)-limonene oxidation at the remaining allylic positions were identified only after hydrolysis of the ester mixture to that of the corresponding alcohols. Table I shows GC analysis of the benzoate and acetate ester hydrolysates. In both reactions trace quantities of *cis*- and *trans*-2,8-*p*-menthadien-1-ol were found. These allylic alcohols can rearrange to 1,4(8)-*p*-menthadien-3-ol which was found in quantities of 17 and 9%, respectively, in the benzoate and acetate hydrolysates (Bain et al., 1959). Since the esters of 2,8-*p*-menthadien-1-ol or 2,4(8)-*p*-menthadien-3-ol (piperitenol) were not found, the precursor of piperitenol is not known. The yield of tertiary alcohol, 1,8-*p*-menthadien-4-ol, was 2–5%. 1(7),8-*p*-Menthadien-2-ol, 4–10% yield, probably contributed to the overall yield of carvone, to which it can convert by oxidation with rearrangement of the exocyclic 1(7) double bond. The epimeric 1(7)-8-dien-2-one was not isolated from the chromic acid oxidation mixture (see below). The major products, *trans*- and *cis*-carveol, accounted for 65 and 74% of the benzoate and acetate hydrolysates, respectively. The yields of the allylic oxidation products, 1,8-*p*-menthadien-7-ol and 1,8-*p*-menthadien-10-ol, were 2.5–3.0%.

Chromic acid oxidation of the crude ester hydrolysates afforded a mixture (Table II) containing about 56% (−)-carvone and 39% piperitenone. Distillation of the crude chromic acid oxidation products yielded a 1:1 carvone–piperitenone fraction and a (−)-carvone fraction which could probably have been increased by the use of a more efficient distillation column.

Thus, a straightforward three-step method has been developed for the preparation of the synthetic spearmint-flavoring ingredient, (−)-carvone. A second product, piperitenone, which is useful as an intermediate in the synthesis of menthol, was also produced in a good yield and partially purified.

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Olfactive Properties of a Number of Polysubstituted Pyrazines

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Alkoxyalkylpyrazines have previously been reported to be very potent naturally green smelling compounds. A number of this type of pyrazines have been identified in natural products. We have synthesized the following series of pyrazines: two monomethoxy- and four dimethoxy(di)alkylpyrazines; 2-methyl-, 2-methoxy-, 2-methylthio-, and 2-dimethylamino-3-isobutylpyrazine; 2-methylamino-3-methyl-, 2-dimethylamino-3(and 6)-methyl- and 2-dimethylamino-3(and 6)-isobutylpyrazine; four methoxyacetylalkylpyrazines and two methoxy-(α-hydroxyisopropyl)methylpyrazines. Odor descriptions are given and compared within each series. Odor threshold values of a number of these pyrazines are measured and presented together with threshold values of pyrazines reported in the literature.

The occurrence of pyrazine derivatives in natural products was indicated for the first time by Morin in 1888. Not before 1928, however, was it discovered that these types of compounds were useful aroma constituents. Then a patent was granted to Reichstein and Staudinger (1928); the use of pyrazines in combination with other compounds was claimed for the preparation of a synthetic coffee oil. After the introduction of advanced analytical methods in aroma research around 1960, it was found that pyrazines occur widely in natural products, particularly in roasted products like coffee, cocoa, and nuts.

The concentration of pyrazine derivatives in these products is often very low. However, their contribution to the odor complex may still be essential because many of them have very low threshold values.

Until 1969 only pyrazines with substituents consisting of carbon and hydrogen have been found. In this report we will pay attention to pyrazines with at least one substituent containing a heteroatom, viz. methoxy-, methylthio-, dimethylamino-, and acetylpyrazines.

In 1969 (a,b) Buttery et al. reported the isolation of 2-methoxy-3-isobutylpyrazine from green bell peppers. The extremely potent odor of this compound was shown to be characteristic for the aroma of bell peppers. Also in 1969 Bramwell et al. reported the identification of two alkoxypyrazines in the oil of galbanum, viz. 2-methoxy-3-*sec*-butylpyrazine and 2-methoxy-3-isobutylpyrazine. Apart from these two pyrazines Murray et al. (1970) showed the presence of 2-methoxy-3-isopropylpyrazine in green peas and in galbanum oil. In this oil Burrell et al. (1970) detected 2-methoxy-3-isopropyl-5-methylpyrazine, 2,6-dimethoxy-3-isopropyl-5-methylpyrazine, and some alkyl-substituted pyrazines.

Duprey and Janes (1971) reported the existence of 2-methoxy-3-isopropyl-, 2-methoxy-3-isobutyl-, and 2-methoxy-3-isopropyl-5-methylpyrazine in the oil of petit grain. Buttery and Ling (1973) have proven the presence of 2-methoxy-3-isopropylpyrazine in potatoes, while in potato sprouts 2-methoxy-3-ethylpyrazine is identified by Nursten and Sheen (1974).

Very recently an extensive review was published in this journal by Maga and Sizer (1973) concerning pyrazines identified in foods. Patent literature clearly shows the importance of pyrazines as flavor constituents or perfume components. An investigation of some essential oils in our laboratory (Timmer, 1973) revealed the occurrence of a number of polysubstituted mono- and dimethoxyalkylpyrazines, as well as methoxyacetyl- and methoxy-α-hydroxyisopropylpyrazines.

For an olfactive study we have synthesized some representatives of these classes of pyrazines, as well as a number of alkylaminopyrazines. Odor descriptions will be given. We measured the odor threshold values of some of these pyrazines. These figures will be given together with threshold values of pyrazines reported in the literature.

EXPERIMENTAL SECTION

Synthesis and Spectral Data. Descriptions of the syntheses as well as the infrared, mass spectral, and nuclear magnetic resonance (NMR) data of the pyrazines mentioned in this report have been deposited in the microfilm edition of this volume of the journal (see paragraph at end of paper).

Odor Evaluation. Descriptions of the olfactive properties were given by three expert perfumers. The compounds were smelled on blotters at appropriate dilutions in diethyl

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