1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid and 1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid in Fruits

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1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid (THCA) and 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA), as two diastereoisomers (1*S*,3*S* and 1*R*,3*S*), occurred in commercial fruits. Citrus fruits exhibited the highest content; other fruits contained very low levels or none at all. The content of MTCA was as follows: orange, 0.35−2.47 μg/g; lemon, 0.15−2.05 μg/g; grapefruit, 1.12−8.37 μg/g; mandarin, 0.57−2.5 μg/g; banana, nd−0.74 μg/g; pear, nd−0.017 μg/g; grape, 0.01−0.22 μg/g, tomato, 0.05−0.25 μg/g; and apple, nd−0.012 μg/g). THCA, if present, usually occurred at <0.05 μg/g. Fruit ripening and softening during storage were accompanied with a significant increase of MTCA, in both pears and bananas. Those and previous results confirm that foods are an important source of tetrahydro-β-carbolines in humans.

Keywords: *Tetrahydro-β-carboline-3-carboxylic acid; tetrahydro-β-carbolines; β-carbolines; alkaloids; tryptophan; fruits; ripening; acetaldehyde*

INTRODUCTION

1,2,3,4-Tetrahydro-β-carbolines (THβCs) are naturally occurring tricyclic indole derivatives produced from indole-ethylamines and aldehydes or α-ketoacids through Pictet−Spengler condensation (Whaley and Govindachari, 1951). Similarly, 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids (THβC-3-COOHs) arise from a condensation between L-tryptophan and aldehydes. This latter reaction readily occurs in foods and is temperature and pH dependent (Herraiz and Ough, 1993).

Research in the past two decades has pointed out the occurrence of THβCs and β-carbolines (βCs) in biological tissues and fluids (Buckholtz, 1980; Airaksinen and Kari, 1981; Melchior and Collins, 1982; Myers, 1989; Rommelspacher et al., 1991). Those compounds might function as neuromodulators and have been increasingly studied in relation with alcoholism (Cohen and Collins, 1970; Tuomisto et al., 1982; Myers, 1989). Collins and co-workers have reported that *N*-methylated THβCs and βCs may act as endogenous neurotoxins (Collins and Neafsey, 1985; Matsubara et al., 1992). 1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (MTCA), the corresponding tryptophan−acetaldehyde condensation product, is a precursor of mutagenic *N*-nitroso compounds (Wakabayashi et al., 1983; Higashimoto et al., 1996) and may affect neuronal cell survival in vitro (Brenneman et al., 1993). Considering, altogether, a full delineation of the biological activity of this family of compounds is desirable and still needed to assign a particular biological effect, if any, to each specific compound.

We have reported the widespread presence of MTCA and 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (THCA) in commercial foods, alcoholic and nonalcoholic drinks, and fruit-derived products (Herraiz, 1996, 1997, 1998; Herraiz and Sanchez, 1997). Tetrahydro-β-carbolines have been mainly associated with fermentation and smoking products (Bosin et al., 1986; Adachi et al., 1991; Papavergou and Clifford, 1992; Herraiz et al., 1993; Herraiz and Ough, 1993, 1994; Herraiz, 1996; Sen et al., 1995; Gutsche and Herderich, 1997). However, THCA and MTCA have been lately found in fruit juices, purees, and jams (Herraiz, 1998). Those results suggest that both compounds are naturally occurring substances readily produced during food production, processing, and storage. Obviously, dietary sources should provide THβCs that may later accumulate in biological tissues and fluids.

This paper reveals, for the first time, the occurrence of tetrahydro-β-carboline-3-carboxylic acid (MTCA and THCA) in fruits. A brief discussion on the chemical and technological factors influencing their formation and biological implications is included.

MATERIALS AND METHODS

Reference Compounds and Samples. MTCA was purchased from Sigma (St. Louis, MO). The diastereoisomeric mixture of MTCA [1*S*,3*S*-MTCA and (−)-(1*R*,3*S*)-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid, 1*R*,3*S*-MTCA], THCA, and 1-ethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (ETCA) were obtained according to the method of Brossi et al. (1973). The stereochemistry of the isomers of MTCA has been established by Yamada and Akimoto (1969) and affirmed by Brossi et al. (1973). Data of NMR, MS, and GC/MS (trifluoroacetyl and methoxycarbonyl methyl ester derivatives) were consistent with the structures of the synthesized compounds (Herraiz and Ough, 1994; Herraiz and Sanchez, 1997; Herraiz, 1997).

Fruit samples (Table 1) from different origins (local and imported) were purchased locally between October 1998 and January 1999: pear (Bartlett, Ercolina, Blanquilla), banana (Cavendish, Corto), apple (Golden Delicious, Starking, Glouster, Granny Smith), grape (Muscat, Morada, Aledo), lemon (Eureka), grapefruit (Marsh, Star Ruby), orange (Navel, Navelina, Delta), mandarin (Clausellina, Minneola), melon (Galia, Torrelche), and peach (yellow and red types). Also, several bunches of pears (Blanquilla) and bananas (Cavendish) were stored at room temperature and analyzed over time. For that, different series of fruits were assayed along this work. Fruits

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Table 1. Content of 1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (1*S*,3*S*-MTCA and 1*R*,3*S*-MTCA) in Fruits

		SS-MTCA (μg/g)			*RS*-MTCA (μg/g)		
sample	*N*	mean	SD	range	mean	SD	range
grape	10	0.074	0.0548	0.012−0.174	0.021	0.016	nd[c]−0.05
apple	5	0.0028	0.0036	nd−0.009	0.0007	0.0016	nd−0.0035
melon	4	0.0131	0.0092	0.004−0.025	0.0038	0.0031	nd−0.0067
tomato	4	0.087	0.076	0.04−0.2	0.024	0.02	0.012−0.055
peach	4	0.0147	0.0111	nd-0.027	0.0042	0.0034	nd−0.008
lemon	4	0.65	0.62	0.11−1.55	0.21	0.20	0.037−0.501
grapefruit	7	3.27	2.0	0.84−6.56	0.91	0.52	0.28−1.81
orange	12	0.73	0.49	0.27−1.88	0.24	0.15	0.078−0.59
mandarin	7	0.8	0.55	0.44−1.96	0.28	0.141	0.13−0.55
banana							
control[a]	11	0.25	0.177	nd−0.52	0.086	0.070	nd−0.22
ripened[b]	11	1.205	0.460	0.62−1.88	0.436	0.146	0.25−0.59
pear							
control[a]	7	0.0068	0.0054	nd−0.017	nd		
ripened/soft[b]	7	0.17	0.049	0.105−0.226	0.047	0.015	0.034−0.066

[a] Commercial fruits when purchased were firm, hard, and slightly green. [b] Fruit after days of storage at room temperature. Pears are soft and juicy and bananas yellow-brown and tender but still firm. [c] nd, undetectable amount.

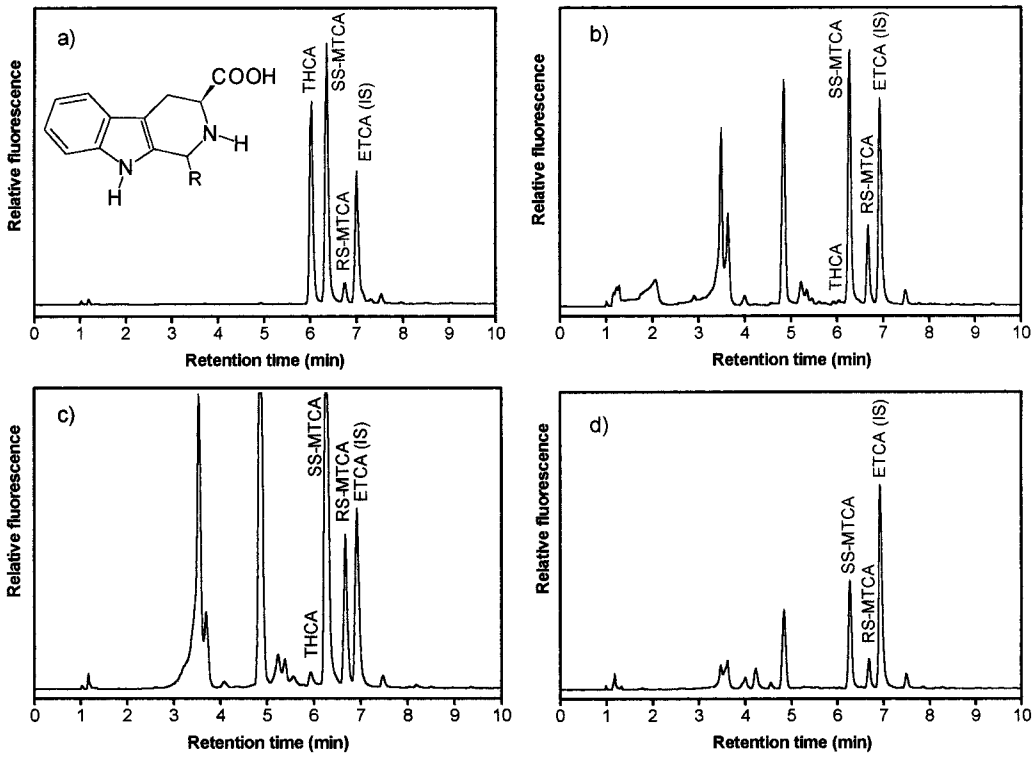

Figure 1. RP-HPLC chromatograms of standard tetrahydro-β-carbolines-3-carboxylic acid (a) and those isolated from orange (b), grapefruit (c), and lemon (d). The compounds are THCA, MTCA, which appears as two diastereoisomers (1*S*,3*S* and 1*R*,3*S*), and ETCA, used as internal standard. Chromatographic conditions are given under Materials and Methods. Fluorescence detection: $\lambda_{ex} = 270$ nm; $\lambda_{em} = 343$ nm.

were washed and peeled (except for grape, tomato, and peach) before analysis.

Isolation of THβC-3-COOHs. Free THβC-3-COOHs were isolated using SCX solid phase extraction following a previously described cleanup procedure (Adachi et al., 1991; Herraiz et al., 1993; Herraiz, 1996). (a) Fruit sample (5−8 g) was added with 10 mL of 0.6 M ClO_4H containing 1 mg/mL semicarbazide (Sigma) and then homogenized in an Ultra-turrax and centrifuged (5100*g*, 0−5 °C) for 10−15 min. An aliquot of supernatant (5.5 mL) was spiked with 0.5 mL of ETCA solution (5 mg/L), used as internal standard (IS), and slowly passed through benzenesulfonic acid SCX columns (Bond Elut, 500 mg/3 mL size; Varian, Harbor City, CA) using a vacuum manifold. Elution of THβC-3-COOHs from SCX columns was carried out as previously described (Herraiz, 1996) and subsequently injected into RP-HPLC.

Chromatographic Analysis. The analysis of THβC-3-COOHs by RP-HPLC and fluorescence detection was carried out as previously described (Herraiz, 1996). A 150 mm × 3.9 mm, 5 μm, Nova-Pak C_{18} column (Waters, Milford, MA) was used for separation. Chromatographic conditions were as follows: 50 mM ammonium phosphate buffer (pH 3) (buffer A) and 20% of A in acetonitrile (buffer B). The gradient was programmed from 0% (100% A) to 32% B in 8 min and then to 90% B at 18 min. The flow rate was 1 mL/min, the column temperature was 40 °C, and the injection volume was 20 μL. Fluorescent detection was set at 270 nm for excitation and at 343 nm for emission.

Quantitation was obtained from calibration curves (area ratio versus concentration) constructed from synthetic THCA and MTCA solutions analyzed through the entire procedure and using ETCA as an internal standard. The reliability of the analytical method has already been reported (Herraiz et al., 1993; Herraiz, 1996). Confirmation of the identity of isolated THβC-3-COOHs was established by HPLC retention times and coelution with authentic standards. Also, fluores-

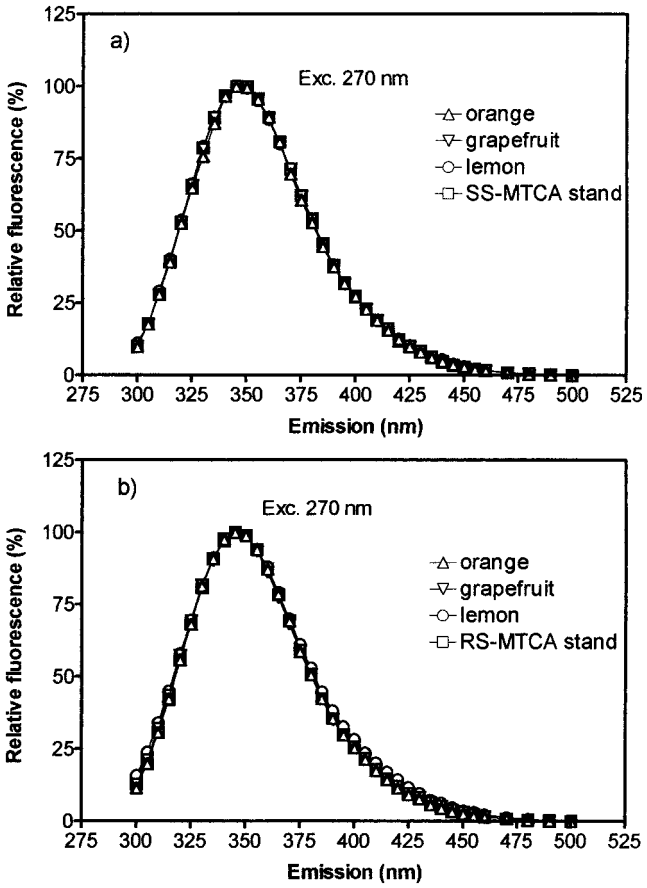

Figure 2. Normalized emission spectra of chromatographic peaks in orange, grapefruit, and lemon, and those of standards, when excitation is 270 nm: (a) 1*S*,3*S*-MTCA diastereoisomer; (b) 1*R*,3*S*-MTCA diastereoisomer.

cence spectra of the HPLC peaks were compared with those of reference compounds to ensure that quantified peaks correspond to those expected. For this, eluting peaks corresponding to TH*β*C-3-COOHs were trapped into the flow cell of the fluorescence detector by stopping the solvent pump, and excitation and emission spectra were monitored.

RESULTS

Chromatographic Analysis. In the past few years, we have studied the chemical characterization, formation, and occurrence of tetrahydro-*β*-carboline-3-carboxylic acid (THCA and MTCA) in many foods and alcoholic beverages by HPLC fluorescence and GC/MS (Herraiz et al., 1993; Herraiz, 1996, 1997; Herraiz and Sanchez, 1997). Recently, those compounds were reported in fruit-processed products (e.g., fruit juices, purees, and jams) (Herraiz, 1998). We wondered, then, if those compounds also occur in the whole fruit. As shown in Figure 1, fruit extracts obtained by SCX solid-phase extraction also gave chromatographic peaks of TH*β*C-3-COOHs. Fluorescence excitation and emission spectra of those peaks were very consistent with the ones from authentic standards (Figure 2). Moreover, the mass spectra obtained by GC/MS analysis (*N*-methoxycarbonyl-1,2,3,4-tetrahydro-*β*-carboline-3-carboxylic acid methyl ester derivatives) confirmed the presence of MTCA in oranges as it was previously done in orange juices (Herraiz, 1997; Herraiz and Sanchez, 1997) (results not shown).

Occurrence of TH*β*C-3-COOHs in Fruits. Fruits contained various amounts of TH*β*C-3-COOHs ranging from undetectable to several micrograms per gram in grapefruit. Table 1 lists the content of MTCA, the major tetrahydro-*β*-carboline, present as two diastereoisomers (1*S*,3*S*) and (1*R*,3*S*). Citrus fruits (grapefruit, lemon, orange, and mandarin) contained the highest levels of MTCA followed by bananas. In contrast, most samples of grape, peach, melon, tomato, pear, and apple contained undetectable or very small amounts of MTCA. Fruits showed very low or no THCA levels (usually in <0.05 μg/g, when found), except for a sample of mandarin that reached 0.5 μg/g.

Table 2. Effect of Storage Time at Room Temperature on the Content of TH*β*C-3-COOH in Pears and Bananas

	TH*β*C-3-COOH (μg/g)		
	days[a]	*SS*-MTCA	*RS*-MTCA
pear			
series A	0	0.008	
	13	0.16	0.047
	17	0.37	0.13
series B	0	0.0	0.0
	7	0.034	0.008
	13	0.16	0.05
	19	0.35	0.12
banana			
series A	0	0.49	0.17
	5	0.80	0.29
	13	1.61	0.58
series B	0	0.06	0.019
	7	0.77	0.29
	10	1.27	0.47
	13	1.35	0.5

[a] Days of storage at room temperature. Purchased fruits (0 days) were hard and slightly green. Pears become soft and juicy and bananas yellow-brown and tender when stored.

Interestingly, overripe and/or soft fruits seemed to contain more TH*β*C-3-COOHs. This assumption was evident from analyzed ripened pears and bananas, which notably increased MTCA compared to hard and slightly green mature fruits (Table 1). Subsequently, in an attempt to study this fact, several bunches of commercial hard-green pears and bananas were stored at room temperature. The content of MTCA observed in the fruits strongly increased during storage and ripening (Table 2). This is illustrated in Figure 3, which also shows the increase of free L-tryptophan along with MTCA in overripe and soft pears. The increasing trend of MTCA over time of storage was observed in all series studied during this work. Nevertheless, the absolute values of MTCA should be taken with caution because fruits at different stages of ripeness, variable harvest histories, different storage conditions, time of season, or even origin may influence the content of TH*β*C-3-COOHs in fruits and during fruit storage.

DISCUSSION

Those results reveal, for the first time, the occurrence of MTCA (diastereoisomers 1*S*,3*S* and 1*R*,3*S*) and THCA in some fruits. The level of MTCA found in fruits, especially citrus fruits, is noticeable. We have previously reported the occurrence of TH*β*C-3-COOH in fruit juices (0.04−13 μg/g) and fruit-derived products such as jams (0.2−3 μg/g) and purees (0.1−1.2 μg/g) (Herraiz, 1996, 1998). Among them, citrus products seemed to contain the highest content. With the result reported above, it should be expected that at least part of TH*β*C-3-COOHs could originate in the whole citrus fruit before processing into juices or purees.

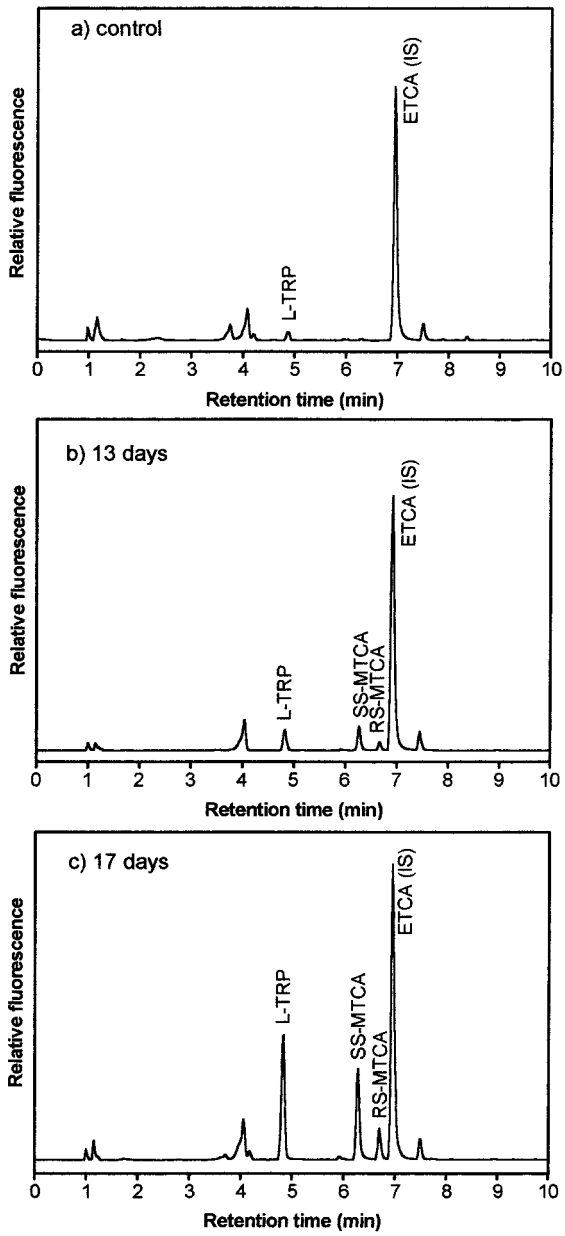

Figure 3. RP-HPLC chromatograms of THβC-3-COOHs and L-tryptophan in pears during storage at room temperature.

It is known that acetaldehyde and formaldehyde are natural constituents of many fruits and vegetables (Feron et al., 1991). Both aldehydes condensate with L-tryptophan in foods to provide THβC-3-COOHs (Herraiz and Ough, 1993; Herraiz, 1996, 1998). It is likely, then, that aldehydes (mainly acetaldehyde) released metabolically in the whole fruit react with L-tryptophan to provide THβC-3-COOHs through a Pictet−Spengler chemical condensation.

An interesting fact is that fruits appeared to release THβC-3-COOHs during storage. Indeed, as bananas ripened, becoming yellow and tender, and pears ripened, becoming soft and juicy, the amount of MTCA increased in both of them. MTCA rose with the storage time along with ripening and deterioration (softening) of fruits. An explanation is that both L-tryptophan and acetaldehyde metabolically released during storage and ripening reacted to give MTCA. Therefore, MTCA could be hypothetically regarded as a marker of fruit progress and quality and possibly be associated with ripening, softening, and deterioration. It is likely, however, that different factors such as the stage of ripeness, harvest and storage, season time, and fruit origin will make difficult the detection of any specific pattern.

The wide occurrence of THβC-3-COOHs in commonly ingested foods and beverages (Herraiz et al., 1993; Herraiz, 1996, 1998; this paper) strongly supports an intake of these substances in the diet (probably up to several milligrams per day). Those compounds have been found in sauces, wines, liquors, vinegars, bread, fermented dairy products, smoked fish, fruit-derived products, and now in citrus fruits. Their concentration ranged from traces to hundreds of milligrams per kilogram in soy sauce. Consequently, the diet along with a possible accumulation could partially explain their presence in tissues and biological fluids (Buckholtz, 1980; Myers, 1989; Rommelspacher et al., 1991; Adachi et al., 1991). In this regard, experiments in rats have shown absorption and accumulation of MTCA in organs (Ogawa et al., 1993). Although, as mentioned in the Introduction, some research has already been accomplished on the biological significance of THβCs and βCs, further additional work is needed for their complete delineation.

CONCLUSION

Tetrahydro-β-carboline-3-carboxylic acids (MTCA and THCA) occur in fruits ranging from undetectable amounts to 8.37 μg/g. Citrus fruits (orange, mandarin, grapefruit, and lemon) and bananas contained the highest amounts of MTCA, whereas grapes, apples, pear, tomato, peach, and melon showed very low or nondetectable amounts. Fruit ripening and softening during storage were accompanied with formation of MTCA, which might be regarded as a marker of the fruit progress and quality.

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