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Some 4,5-Dialkylthiazoles with Potent Bell Pepper Like Aromas

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Five 4,5-dialkylthiazoles with potent bell pepper like aromas have been synthesized. The odor thresholds were measured and are reported. The most potent, 4-butyl-5-propylthiazole, had an odor threshold of 3 parts per 10^{12} parts of water. Odor thresholds are compared to some related 4,5-dialkylthiazoles. Mass and proton magnetic resonance spectral data are given. The compounds differ from previous bell pepper like aroma compounds in that they have no methoxy group.

The authors had previously found alkylthiazoles in potato products (Buttery and Ling, 1974) and in cooked beans (Buttery et al., 1975). In the course of the synthesis of some possible structures a number of very potent alkylthiazoles were discovered (Guadagni and Buttery, 1974) which had odor characters like that of bell peppers (*Capsicum annuum*). These compounds were of interest both from their possible use as flavoring compounds and also for the understanding of the relationship between chemical structure and odor potency and character. This relationship of bell pepper character and odor potency to chemical structure has been explored by a number of authors (Seifert et al., 1972; Pittet and Hruza, 1974; Parliment and Epstein, 1973).

EXPERIMENTAL SECTION

Materials. Aliphatic ketones were obtained from reliable commercial sources or synthesized by well-established methods.

Bromoketones. The method used was that of Catch et al. (1948). In cases where two isomeric bromoketones were formed they were not separated but taken through the thiazole synthesis, and the isomeric thiazoles were separated by gas-liquid chromatography (GLC).

Alkylthiazoles. These were all synthesized by the general method of Kurkijy and Brown (1952). The bromoketone was allowed to react with thioformamide

(formed in the reaction from formamide and P_2S_5). Yields were all satisfactory at about 50%. In the cases where a mixture of two isomeric bromoketones was used, the isomeric alkylthiazoles were separated by GLC using a 150 cm long \times 0.64 cm o.d. aluminum column packed with 80-100 mesh Chromosorb P coated with 15% Amine 220.

4-Butyl-5-propylthiazole was synthesized from 4-bromononan-5-one and thioformamide.

4-Butyl-5-methylthiazole and 4-ethyl-5-propylthiazole were formed from the condensation of a mixture of 2-bromoheptan-3-one and 4-bromoheptan-3-one with thioformamide. The thiazoles were readily separated by GLC and differentiated by mass and proton magnetic resonance spectra (1H NMR).

4-Butyl-5-ethylthiazole was formed from the condensation of 3-bromooctan-4-one (mixture with 5-bromooctan-4-one) with thioformamide. The 4-butyl-5-ethylthiazole was easily separated by GLC from the 4,5-di-propylthiazole also formed in the synthesis and differentiated by mass and 1H NMR spectra.

4-Ethyl-5-butylthiazole was synthesized from the condensation of 4-bromooctan-3-one (mixture with 2-bromooctan-3-one) with thioformamide. The 4-ethyl-5-butylthiazole was readily separated from the 4-pentyl-5-methylthiazole also formed in the synthesis by GLC and differentiated by mass and 1H NMR spectra.

Mass Spectra. These were measured using batch introduction on a Consolidated 21-620 cycloidal type mass spectrometer. Ionization voltage was 70 V.

Proton Magnetic Resonance Spectra. These were measured in $CDCl_3$ using a Varian HA-100 instrument.

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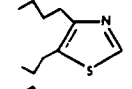
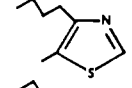
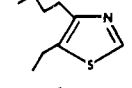
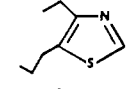
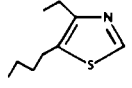
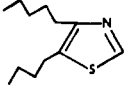
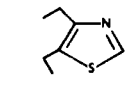
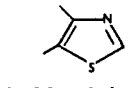
	COMPOUND	THRESHOLD PARTS PER 10 ¹² PARTS WATER
BELL PEPPER ODOR		I 3
		II 10
		III 20
		IV 60
		V 120
RELATED COMPOUNDS		VI 190
		VII 5100
		VIII 470,000

Figure 1. Odor thresholds of the bell pepper odor compounds and of some related compounds.

Odor Thresholds. Thresholds of the GLC purified compounds in water solution were determined as described previously (Guadagni et al., 1963) using Teflon bottles and tubing as containers for the odor solution.

RESULTS AND DISCUSSION

The syntheses of the 4,5-dialkylthiazoles were quite straightforward and followed general methods outlined for related compounds by previous workers (Kurkijy and Brown, 1952; Metzger and Koether, 1953). In the preparation of the bromoketones, used in the alkylthiazole synthesis, two isomeric bromoketones were usually formed. It was simpler to take the mixed bromoketones through the alkylthiazole synthesis and resolve the isomeric alkylthiazoles than to separate the bromoketones. The structures in each case were differentiated by ¹H NMR spectra. The mass spectral fragmentation patterns confirmed the ¹H NMR assignments.

Of the 4,5-dialkylthiazoles studied by the authors, five were judged (using thorough panel methods, cf. Guadagni et al., 1972) to have considerable bell pepper like character; these are listed in Figure 1 as 1 to 5 together with their odor thresholds. The odor thresholds of a number of other 4,5-dialkylthiazoles were also determined and some of these are listed in Figure 1 for comparison. As had been previously found with alkylmethoxy-pyrazines (Seifert et al., 1970) the odor threshold was relatively high for the 4,5-dialkylthiazoles when both alkyl groups were as short as one or two carbons. The odor threshold was the lowest when the alkyl group in the 4 position was butyl. With a chain length of 5 carbons in the 4 position, the odor threshold again increased.

Pittet and Hruza (1974) found that 4-isobutyl-5-methoxythiazole possessed a potent bell pepper aroma. From consideration of this and of the structures of other pyrazine and pyridine compounds they suggested a general structure for this high potency and character. In their general structure they thought that it was necessary to have a free hydrogen atom on the carbon α to the nitrogen

and on the other side of the nitrogen an isobutyl group in the α' position and a methoxy group in the β' position, i.e., as $-\text{CH}=\text{NC}(\text{isobutyl})=\text{C}(\text{OMe})-$. The structures of the most potent dialkylthiazoles in Figure 1 (compounds I, II, and III) fit the first two requirements reasonably well, having a normal butyl group instead of an isobutyl. However, these compounds do not, of course, fit the third requirement; they do not have any methoxy group. The third requirement then does not seem to be absolutely necessary. The role that the methoxy group plays, however, may be partly filled by the sulfur atom in the thiazole ring. An arrangement which covers more structures is $-\text{CH}=\text{NC}(\text{R})=\text{CX}-$ where R is a hydrocarbon chain about 4 carbons long and X is oxygen or sulfur. However, this arrangement does not fit some structures such as 2-methoxy-6-isobutylpyrazine which was reported by Parliment and Epstein (1973) to have an intense bell pepper aroma. With the above arrangements it is generally considered necessary that the nitrogen be in a ring although no study of a "straight" chain molecule, which otherwise fits the arrangement, has ever been made.

As far as the authors can determine, compounds I to V, in Figure 1, have not previously been reported in the literature although related compounds have been synthesized by Metzger and coworkers (cf. Metzger and Koether, 1953). The mass and ¹H NMR spectra of these compounds are listed below.

4-Butyl-5-propylthiazole (I) had a mass spectrum (two most intense ions every 14 mass units above m/e 34, intensities in parentheses) as follows: 41 (79), 45 (82); 53 (20), 55 (20); 69 (12), 71 (23); 77 (12), 85 (19); 98 (13), 99 (12); 112 (41), 113 (100); 126 (23), 127 (5); 140 (12), 141 (41); 168 (11); 183 (7). 4-Butyl-5-propylthiazole (I) had a ¹H NMR spectrum as follows: 100 MHz (CDCl_3) δ 0.88 (t, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.90 (t, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$) both overlapping together 6 H; 1.1–1.5 (m, 2, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.4–1.8 (m, 4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ and $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.57 (t, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.65 (t, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), both overlapping together (4 H); 8.36 (s, 1, H 2 pos.).

4-Butyl-5-methylthiazole (II) had a mass spectrum as follows: 41 (14), 45 (23); 53 (4), 59 (17); 69 (2), 71 (4); 85 (24), 86 (4); 98 (2), 99 (2); 112 (35), 113 (100); 126 (11), 127 (4); 140 (11), 141 (2); 154 (2), 155 (9). 4-Butyl-5-methylthiazole (II) had a ¹H NMR spectrum as follows: 100 MHz (CDCl_3) δ 0.92 (t, 3, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.2–1.8 (m, 4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.38 (s, 3, CH_3 5 pos.), 2.70 (t, 3, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 8.51 (s, 1, H 2 pos.).

4-Butyl-5-ethylthiazole (III) had a mass spectrum as follows: 39 (27), 45 (42); 53 (9), 59 (15); 65 (11), 71 (9); 77 (3), 85 (5); 98 (9), 99 (13); 112 (12), 113 (4); 126 (46), 127 (100); 140 (12), 141 (5), 154 (8), 155 (1); 168 (1), 169 (9). 4-Butyl-5-ethylthiazole (III) had a ¹H NMR spectrum: 100 MHz (CDCl_3) δ 0.93 (t, 3, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.27 (t, 3, $J = 7$ Hz, CH_2CH_3), 1.3–1.9 (m, 4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.71 (t, 2, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.80 (q, 2, $J = 7$ Hz, CH_2CH_3), 8.54 (s, 1, H 2 pos.).

4-Ethyl-5-propylthiazole (IV) has a mass spectrum as follows: 41 (16), 45 (18); 53 (5), 59 (15); 65 (9), 71 (5); 77 (3), 85 (7); 98 (11), 99 (12); 112 (9), 113 (7); 126 (100); 127 (15), 140 (32), 141 (4); 154 (2), 155 (28). 4-Ethyl-5-propylthiazole (IV) had the following ¹H NMR spectrum: 100 MHz (CDCl_3) δ 0.94 (t, 3, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.27 (t, 3, $J = 7$ Hz, CH_2CH_3), 1.4–1.8 (m, 2, $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.73 (q, 2, $J = 7$ Hz, CH_2CH_3), 2.74 (t, 2, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 8.55 (s, 1, H 2 pos.).

4-Ethyl-5-butylthiazole (V) had a mass spectrum as follows: 41 (33), 45 (38); 55 (8), 59 (19); 65 (11), 71 (7); 77

(3), 85 (7); 98 (13), 99 (11); 112 (19), 113 (6); 126 (100), 127 (14), 140 (23), 141 (5); 154 (3); 169 (15). 4-Ethyl-5-butylthiazole (V) had a ^1H NMR spectrum: 100 MHz (CDCl_3) δ 0.97 (t, 3, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.27 (t, 3, $J = 7$ Hz, CH_2CH_3), 1.5–1.8 (m, 4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.72 (q, 2, $J = 7$ Hz, CH_2CH_3), 2.77 (t, 2, $J = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 8.55 (s, 1, H 2 pos.).

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Volatile Heterocyclic Compounds in the Reaction of Glyoxal with Glycine

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The basic fraction of the volatiles from an equimolar glyoxal-glycine mixture heated under reflux for 4 hr was separated by gas chromatography. Carbonyls were converted to their 2,4-dinitrophenylhydrazones and separated by thin-layer chromatography. Individual components were isolated and analyzed by mass spectrometry, ultraviolet, visible, and infrared spectrophotometry. Six nitrogen-containing heterocycles (pyrazine, methyl-, 2,5-dimethyl-, 2,6-dimethyl-, and trimethylpyrazine, and 2-pyrrolaldehyde) were positively identified. Formaldehyde was found as the only carbonyl group containing reaction product. A possible precursor, aminoacetaldehyde, was synthesized and the formation mechanism of pyrazines and pyrrole was presented.

During the past few years numerous heterocyclic nitrogen-containing compounds, namely pyrazines and pyrroles, have been reportedly isolated from various food and model systems. Reviews on pyrazines, their chemistry, reactions, occurrences in foods, and importance in the roasted or cooked flavor of many foods, have been recently published by Cheeseman and Werstiuk (1972) and by Maga and Sizer (1973). Some important model systems employing simple carbonyls, carbohydrates, their derivatives, amino acids, and proteins are listed in Table III. The role of carbohydrate degradation or lipid decomposition on the formation of pyrazines has been well documented (Maga and Sizer, 1973; Koehler and Odell, 1970; Wang and Odell, 1972). The formation of pyrroles in foods as well as in model systems has been greatly neglected and most attempts at the formation of these compounds have taken the form of reporting their occurrence in the flavor of various heated and toasted foods.

In food chemistry, glyoxal is known as a degradation product of sugars (Hodge, 1967; Gotlieb and Markakis, 1968; Fagerson, 1969), ascorbic acid (Osthoff, 1966), and

lipids (Enders et al., 1962; Cobb and Day, 1965; Bala et al., 1968; Wang and Odell, 1972). This α -dicarbonyl compound reacts with α -amino acids to produce carbon dioxide and aldehydes with one less carbon atom through Strecker degradation (Schonberg and Moubacher, 1952; Plechan and Mardasev, 1953; Fujimaki et al., 1971; Chuyen et al., 1972; Velíšek et al., 1972). Acetaldehyde was identified in the reaction of glyoxal with alanine (Neuberg and Kobel, 1927) and isovaleraldehyde in the reaction with leucine (Fujimaki et al., 1968). Glyoxal was also used as a model compound in the Strecker degradation of numerous α -amino acids. Carbon dioxide evolution was observed in its reaction with glycine (Fujimaki et al., 1971; Chuyen et al., 1972) and this compound was also detected as the only reaction product by Rizzi (1972). On the other hand, Bengelsdorf (1953) and Kamata and Sakurai (1957) observed only the formation of brown high molecular weight pigments.

Koehler and Odell (1970) have found that glyoxal produced pyrazine when heated with ammonium hydroxide or asparagine. Some methylpyrazine was also formed indicating that secondary recombinations and rearrangements occurred.

The present study was undertaken as a part of a series of studies of flavor-significant compounds produced in simple model systems and concerned the identification of

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