Structure-odour relation in homologous series of alkane-1,1-dithiols and dithio(hemi)acetals

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Abstract

Twenty 1,1-dithioalkane derivatives were synthesized including ten compounds structurally derived from acetaldehyde and the ten corresponding compounds structurally derived from propanal. Compounds included ethane-1,1-dithiol and propane-1,1-dithiol as basic structures and their methyl, ethyl, and propyl derivatives 1-(methylsulfanyl)ethane-1-thiol, 1-(ethylsulfanyl)ethane-1-thiol, 1-(propylsulfanyl)-ethane-1-thiol, 1,1-bis(methylsulfanyl)ethane, 1-(ethylsulfanyl)-1-(methylsulfanyl) ethane, 1-(methylsulfanyl)-1-(propylsulfanyl)ethane, 1,1-bis(ethylsulfanyl)ethane, 1-(ethylsulfanyl)-1-(propylsulfanyl)ethane, 1,1-bis(propylsulfanyl)ethane, 1-(methyl-sulfanyl) propane-1-thiol, 1-(ethylsulfanyl)propane-1-thiol, 1-(propylsulfanyl)propane-1-thiol, 1,1-bis(methylsulfanyl)propane, 1-(methylsulfanyl)-1-(ethylsulfanyl)propane, 1-(methylsulfanyl)-1-(propylsulfanyl)propane, 1,1-bis(ethylsulfanyl)propane, 1-(ethyl-sulfanyl)-1-(propylsulfanyl)propane, and 1,1-bis(propylsulfanyl)propane. GC-O analyses revealed onion-like odour qualities for the majority of the compounds and additional fruity notes for some higher homologues. Thresholds showed a clear tendency towards higher values with increasing alkyl chain length, particularly the dithiohemiacetals showed consistently lower thresholds than the dithioacetals.

Introduction

1,1-Dithioalkane derivatives such as alkane-1,1-dithiols, dithiohemiacetals, and dithioacetals (Figure 1) have scarcely been reported in food so far. One of the rare exceptions is durian, the fruit of the Southeast Asian tropical rainforest tree *Durio zibethinus.* Durian is famous for its strong and penetrating odour which combines fruity notes with a strong sulfury, oniony smell. The latter was recently assigned to a series of 1,1-dithio compounds and some short-chain alkanethiols [1,2]. The odour-active 1,1-dithio compounds in durian were all structurally related to acetaldehyde and propanal as carbonyl component and hydrogen sulfide, methanethiol, ethanethiol, and propane-1-thiol as thio component. This prompted us to synthesize all possible 1,1-dithio compounds available from these building blocks and have a closer look at the relation of their structure to their odour properties.

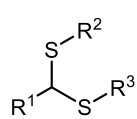

Figure 1: General structure of alkane-1,1-dithiols (R^1 = alkyl; R^2, R^3 = H), dithiohemiacetals (R^2 = H; R^1, R^3 = alkyl), and dithioacetals (R^1, R^2, R^3 = alkyl)

Experimental

Syntheses

Compounds **1-6**, **8**, **12**, and **13** were synthesized as detailed in [1].

Synthesis of 1-(methylsulfanyl)-1-(propylsulfanyl)ethane (**7**) was accomplished by adding $CsCO_3$ (820 mg, 25 mmol) and Bu_4NI (930 mg, 2.5 mmol) in anhydrous DMF

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(13 ml) under Ar to **2** (270 mg, 2.5 mmol). After stirring (1 h, RT), PrBr (338 mg, 2.75 mmol) was added dropwise at 0 °C. After further stirring (1 h, RT), water (30 ml) was added and the mixture was extracted with DCM (3 × 30 ml). Combined solvent extracts were washed with water (3 × 30 ml) and brine (30 ml) and dried. The solvent was evaporated and the product was purified by flash chromatography [1] to give 145 mg of **7** in 97% purity (GC-FID) and with 37% yield.

Synthesis of 1-(ethylsulfanyl)-1-(propylsulfanyl)ethane (**9**) was done by adding **4** (272 mg, 2 mmol) to a mixture of aqueous NaOH (10 M, 0.2 ml) and MeOH (5 ml) at 0 °C. After stirring (5 min), EtI (2.4 mmol, 0.2 ml) was added and stirring was continued (2 h, RT). MeOH was removed (Vigreux column), water (20 ml) was added, and the mixture was extracted with Et_2O (3 × 20 ml). Combined extracts were washed with brine (60 ml) and dried. The solvent was evaporated and the product was purified by flash chromatography [1] to afford 155 mg of **9** (85% purity, 40% yield).

Synthesis of 1,1-bis(propylsulfanyl)ethane (**10**), 1,1-bis(ethylsulfanyl)propane (**18**), and 1,1-bis(propylsulfanyl)propane (**20**) was achieved from the corresponding aldehydes and alkanethiols by applying the approach detailed for **8** in [1]. Yields were 1.31 g (73%) (**10**), 1.31 g (79%) (**18**), and 1.29 g (67%) (**20**), all in 99% purity.

Propane-1,1-dithiol (**11**) and 1-(propylsulfanyl)propane-1-thiol (**14**) were synthesized by adding propanal (2.9 g, 50 mmol), PrSH (3.8 g, 50 mmol), and acetate buffer (5.4 M, pH 5, 40 ml) to a mixture of $Na_2S \cdot 9\,H_2O$ (12 g, 50 mmol) and DCM (20 ml) at -60 °C under Ar. After stirring (3 h at -60 °C, then 3 d at RT), the organic layer was separated and the aqueous phase was extracted with DCM (50 ml). Combined extracts were washed with water (100 ml), dried and the solvent was evaporated. Vacuum distillation (60 °C, 5 kPa) afforded 230 mg of **11** (90% purity, 3.8% yield). DCM (50 mL) was added to the residue, the mixture was washed with aqueous Na_2CO_3 (5%, 50 ml), dried, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography. Elution with pentane afforded 330 mg of **14** in 99 % purity (GC-FID).

1,1-bis(Methylsulfanyl)propane (**15**) was synthesized from Me_2S_2 (1.32 g, 21.3 mmol) and propanal (1.24 g, 21.3 mmol) by the approach detailed for **5** [1], resulting in 500 mg product (97% purity, 17% yield).

The approach detailed above for **9** was also used to synthesize 1-(ethylsulfanyl)-1-(methylsulfanyl)propane (**16**) from **13** (180 mg, 1.2 mmol), 10 M NaOH solution (0.1 ml, 1 mmol) and MeI (0.1 ml, 1.6 mmol), 1-(methylsulfanyl)-1-(propylsulfanyl)propane (**17**) from **14** (150 mg, 1 mmol), 10 M sodium hydroxide solution (0.1 ml, 1 mmol) and MeI (0.1 ml, 1.6 mmol), as well as 1-(ethylsulfanyl)-1-(propylsulfanyl)propane (**19**) from **14** (150 mg, 1 mmol), 10 M sodium hydroxide solution (0.1 ml, 1 mmol) and EtI (0.1 ml, 1.6 mmol). Yields were 42 mg (22%) in 93% purity (**16**), 50 mg (30%) in 95% purity (**17**), and 62 mg (34%) in 98% purity (**19**).

Odour threshold values (OTVs) in air

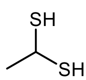
These were determined by aroma extract dilution analysis using (2*E*)-dec-2-enal as internal standard [3,4]. Results of two panellists were averaged by calculating the geometrical mean of the individual thresholds.

Results and discussion

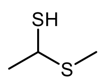
In total, 1,1-dithio compounds were synthesized. Ten compounds were derived from acetaldehyde as carbonyl component (Figure 2) and ten compounds were derived from propanal as carbonyl component (Figure 3). Each series started from the 1,1-dithiol, i.e.

ethane-1,1-dithiol (**1**) and propane-1,1-dithiol (**11**). Then the structure was modified by adding alkyl groups of increasing length, namely methyl, ethyl, and propyl to both of the two sulfur atoms. In doing so, for each of the two carbonyl compounds, four homologues series resulted, each including four members.

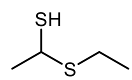
For the acetaldehyde derivatives (Figure 2), the first homologues series consisted of ethane-1,1-dithiol (**1**) and the three 1-(alkylsulfanyl)ethane-1-thiols 1-(methylsulfanyl)ethane-1-thiol (**2**), 1-(ethylsulfanyl)ethane-1-thiol (**3**), and 1-(propylsulfanyl)ethane-1-thiol (**4**). In this series, all compounds exhibited an onion-like smell and rather low odour thresholds. Thresholds decreased from **1** to **3** and increased from **3** to **4**, with **4** showing the highest threshold value in the series.



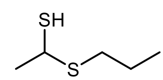
(1)*
onion-like
0.29 ng/L



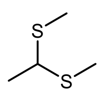
(2)*
onion-like
0.20 ng/L



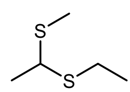
(3)*
onion-like
0.15 ng/L



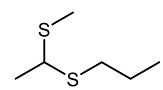
(4)*
onion-like
0.40 ng/L



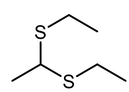
(5)*
onion-like
0.88 ng/L



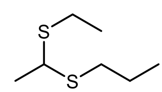
(6)*
onion-like, fruity
1.9 ng/L



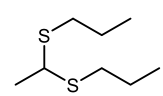
(7)
onion-like
9.7 ng/L



(8)*
onion-like, fruity
1.9 ng/L



(9)
onion-like, fruity
9.6 ng/L



(10)*
onion-like, fruity
18 ng/L

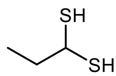
Figure 2: Structures, odour qualities as perceived during GC-O, and OTVs of 1,1-dithioethane derivatives; asterisks indicate compounds found among the odour-active compounds in durian [1]

The second homologues series of acetaldehyde derivatives consisted of 1-(methylsulfanyl)ethane-1-thiol (**2**) and the three 1-(methylsulfanyl)-1-(alkylsulfanyl)ethanes 1,1-bis(methylsulfanyl)ethane (**5**), 1-(ethylsulfanyl)-1-(methylsulfanyl)ethane (**6**), and 1-(methylsulfanyl)-1-(propylsulfanyl)ethane (**7**). Thresholds increased in this series, odour qualities were described as onion-like, but **6** showed an additional fruity note.

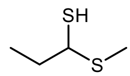
In the third homologues series of acetaldehyde derivatives, including 1-(ethylsulfanyl)ethane-1-thiol (**3**) and the three 1-(ethylsulfanyl)-1-(alkylsulfanyl)ethanes 1-(ethylsulfanyl)-1-(methylsulfanyl)ethane (**6**), 1,1-bis(ethylsulfanyl)ethane (**8**), and 1-(ethylsulfanyl)-1-(propylsulfanyl)ethane (**9**), thresholds again increased with increasing carbon number and fruity notes were prevalent, though the onion-like note dominated.

The fourth homologues series of acetaldehyde derivatives consisted of 1-(propylsulfanyl)ethane-1-thiol (**4**) and the three 1-(propylsulfanyl)-1-(alkylsulfanyl)ethanes

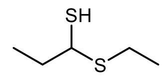
1-(methylsulfanyl)-1-(propylsulfanyl)ethane (**7**), 1-(ethylsulfanyl)-1-(propylsulfanyl)-ethane (**9**), and 1,1-bis(propylsulfanyl)ethane (**10**). All compounds showed onion-like odours, but the higher homologues **9** and **10** additionally exhibited fruity notes and thresholds increased by trend.



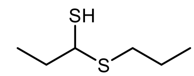
(11)
onion-like
0.67 ng/L



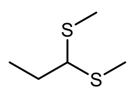
(12)*
onion-like
0.15 ng/L



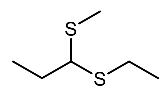
(13)*
onion-like, fruity
0.24 ng/L



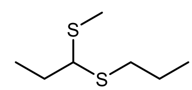
(14)
onion-like, fruity
0.31 ng/L



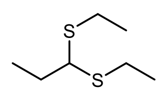
(15)
onion-like, fruity
4.7 ng/L



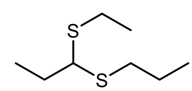
(16)
onion-like, fruity
14 ng/L



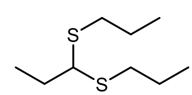
(17)
fruity, fatty
13 ng/L



(18)
onion-like, fruity
7.3 ng/L



(19)
onion-like
11 ng/L



(20)
onion-like
27 ng/L

Figure 3: Structures, odour qualities as perceived during GC-O, and OTVs of 1,1-dithiopropane derivatives; asterisks indicate compounds found among the odour-active compounds in durian [1]

In summary, all analysed acetaldehyde derivatives showed an onion-like odour, but an additional fruity note was prevalent in the higher homologues. Thresholds showed a tendency towards higher values with increasing chain length. Similar observations were made with the propanal derivatives (Figure 3). The comparison of the propanal derivatives with the respective acetaldehyde derivatives showed a tendency towards slightly higher thresholds in the propanal derivatives. For both, acetaldehyde and propanal derivatives, the dithiohemiacetals (**1-4** and **11-14**) showed consistently lower thresholds than the dithioacetals (**5-10** and **15**-**20**).

References

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