PREPARATION OF *vic*-MERCAPTOISOPENTANOLS

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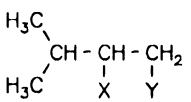
This paper describes the preparation of some mercaptoisopentanols: 2-mercapto-3-methyl-1-butanol (*I*), 1-mercapto-3-methyl-2-butanol (*II*), 3-mercapto-3-methyl-2-butanol (*III*) and the unsaturated analogue of compound *I* – 2-mercapto-3-methyl-2-buten-1-ol (*IV*). These compounds belong to the flavonoid group present in food responsible for deterioration of their gustatory properties.

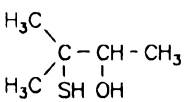
The presence of vicinal mercaptoalcohols[1,2] in foodstuffs bears responsibility for an onion or garlic-like aftertaste deteriorating thus their quality and therefore, research of these and even fragment compounds, study of their physiological and biological properties is of importance.

A new *vic*-mercaptoalcohol – 2-mercapto-3-methyl-1-butanol (*I*), the presence of which in beer causes an unpleasant onion-like aftertaste, was synthesized[2] in 1988 by a radical addition of hydrogen sulfide to 3-methyl-2-buten-1-ol in very low yield (7%). Further synthesis[3] starting from valine via diazonium salt afforded compound *I* in 78% yield.

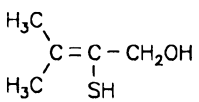
Synthesis of 1-mercapto-3-methyl-2-butanol (*II*) was described in connection with the preparation of oxazaphospholidines, thiazaphospholidines and oxythiaphospholanes, compounds with insecticide activity[4]. 3-Mercapto-3-methyl-2-butanol (*III*) is the main product in the reaction mixture with 2-methyl-3-mercapto-2-butanol (9 : 1) in the preparation of 1,3-oxathiolanes[5].



I, X = SH; Y = OH
II, X = OH; Y = SH

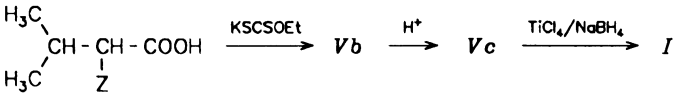


III

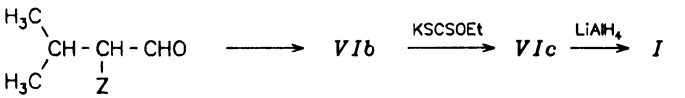


IV

According to our procedure, compound *I* was obtained from (±)-2-bromo-3-methylbutanoic acid and 3-methylbutanal (Scheme 1). 2-Bromo-3-methylbutanoic acid (*Vb*) reacted with potassium O-ethylxanthate in aqueous alcohol to give 2-mercapto-3-methylbutanoic acid (*Vc*) in 70% yield. The carboxyl group was reduced with $TiCl_4/NaBH_4$ (ref.[6]) in 1,2-dimethoxyethane to give compound *I* in 63% yield. The same compound was alternatively obtained from 3-methylbutanal (*VIa*) via the 2-iodo derivative[7] and potassium O-ethylxanthate followed by $LiAlH_4$ reduction in ether in 54% yield.



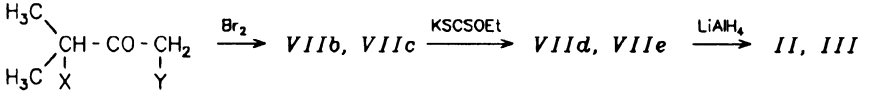
Va, Z = Br
Vb, Z = SCSOEt
Vc, Z = SH



VIa, Z = H
VIb, Z = I
VIc, Z = SCSOEt

SCHEME 1

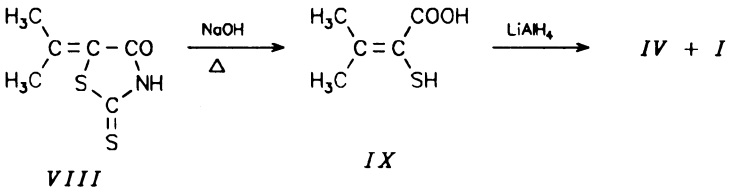
The mixture of isomers *II* and *III* was obtained from 3-methyl-2-butanone through 1-bromo- or 3-bromo-3-methyl-2-butanone[8] and potassium O-ethylxanthate; the intermediate was reduced with $LiAlH_4$ according to Djerassi[9] (Scheme 2).



VIIa, X = H; Y = H
VIIb, X = H; Y = Br
VIIc, X = Br; Y = H
VIId, X = H; Y = SCSOEt
VIIe, X = SCSOEt; Y = H

SCHEME 2

Compound *IV* was synthesized from acetone and rhodanine (Scheme 3) furnishing isopropylidenerhodanine[10] in basic medium in 70% yield. Base-catalyzed hydrolysis afforded 2-mercapto-3-methylbutenoic acid (*IX*) in 24% yield. Reduction of the latter with $LiAlH_4$ in ether gave the unsaturated thioalcohol *IV* in 17% yield and a small amount (3 – 7%) of thioalcohol *I* in addition to some, so far not identified compounds. Liberation of compound *IV* from the reduction complex is somehow complicated; column chromatography proved suitable but the yield is substantially lower.



VIII *IX*

SCHEME 3

EXPERIMENTAL

Melting points were determined with a Kofler micro hot-stage. ^1H NMR spectra of deuteriochloroform solutions (unless otherwise stated) containing tetramethylsilane as an internal reference were measured with a Tesla BS 587 A spectrometer operating at 80 MHz. Purity of products was monitored by means of gas chromatography on a GC apparatus (Hewlett–Packard) equipped with a dual flame-ionizing detector, 1.8 m × 4 mm column packed with 10% OV-101 over Chromosorb WHP (80 – 100 mesh, Hewlett–Packard); inlet temperature 200 °C, thermostat temperature 60 °C, 4 min isothermally, temperature gradient 8 °C min^{-1} up to 170 °C, FID temperature 220 °C, carrier gas (N_2) flow rate 35 ml min^{-1}.

3-Methyl-2-bromobutanoic acid (m.p. 42 – 44 °C), 3-methylbutanal (b.p. 90 °C), 3-methyl-2-butanone (b.p. 94 – 95 °C) and potassium O-methylxanthate (m.p. 210 °C, dec.), (Aldrich, U.S.A.); 2-iodo-3-methylpropanal (b.p. 68 – 70 °C/2 kPa), the 4 : 1 and alternatively the 3 : 2 mixtures of 1-bromo-3-methyl-2-butanone and 3-bromo-3-methyl-2-butanone (b.p. 80 – 85 °C/1.3 kPa) were prepared according to ref.[8] and ref.[9], respectively.

2-Mercapto-3-methylbutanoic Acid (*Vc*)

Potassium O-ethylxanthate (8.0 g, 50 mmol) was added to a well stirred mixture of 2-bromo-3-methylbutanoic acid (9.05 g, 50 mmol), and NaOH (2.2 g) in water (100 ml) during 15 min. More NaOH (2.2 g) was added after 24 h of stirring at room temperature and the mixture was then refluxed for 3 h. The cooled mixture (5 °C) was acidified with 1M-HCl and the aqueous layer was extracted with ether (5 × 25 ml). The combined ethereal extracts were dried with Na_2SO_4 overnight and worked up. Yield 4.7 g (70%) of the product distilled at 60 – 65 °C/1.3 kPa. For $C_5H_{10}O_2S$ (134.2) calculated: 44.75% C, 7.51% H, 23.89% S; found: 44.70% C, 7.40% H, 23.70% S. ^1H NMR: 1.05 d, 3 H (CH_3); 1.08 d, 3 H (CH_3); 2.01 d, 1 H (SH); 2.07 m, 1 H (CH); 3.18 dd, 1 H (CH–S); 10.12 bs, 1 H (COOH).

2-Mercapto-3-methyl-1-butanol (*I*)

Method A: Titanium tetrachloride (4.22 g, 22 mmol) was introduced into a stirred suspension of $NaBH_4$ (2.5 g) in 1,2-dimethoxyethane (100 ml) in argon atmosphere at 0 °C during 5 min. To the green preci-

pitate 2-mercapto-3-methylbutanoic acid (2.7 g, 20 mmol) was added at 0 °C within 15 min. The mixture was then stirred at room temperature for 48 h, poured on crushed ice (100 g), stirred for 30 min and the organic layer was separated. The aqueous layer was extracted with benzene (5 × 25 ml). Combined benzene extracts dried with Na_2SO_4 were filtered, the solvent was distilled off and the residue was distilled under reduced pressure. Yield 1.51 g (63%), b.p. 75 – 77 °C/1.7 kPa (ref.[2] b.p. 75 – 80 °C/1.7 kPa). ^{1}H NMR: 1.00 d, 3 H (CH_3); 1.03 d, 3 H (CH_3); 2.03 m, 1 H (CH); 1.28 d, 1 H (SH); 2.20 bs, 1 H (OH); 2.85 m, 1 H (CH–S); 3.45 dd, 1 H (CH_2OH); 3.82 dd, 1 H (CH_2OH).

Method B: Potassium O-ethylxanthate (4.0 g, 25 mmol) was added to a well stirred solution of 2-iodo-3-methylpropanal (4.25 g, 20 mmol) in aqueous 1,4-dioxane (50%, 50 ml) during 30 min. After additional 5 min stirring at ambient temperature the aqueous layer was extracted with ether (5 × 25 ml), the combined ethereal extracts were dried with Na_2SO_4, the solvent was removed and the residue was added to $LiAlH_4$ (1.6 g) in ether (100 ml) under argon during 2 h and stirred for 24 h. Excess of the reducing agent was decomposed with acetone and the content was acidified with 3M-H_2SO_4 after 2 h stirring. The separated ethereal layer was extracted with 10% KOH (5 × 15 ml), the aqueous layer was acidified with 1M-HCl at 5 °C, the product was taken into ether (5 × 25 ml), dried with Na_2SO_4 and distilled at 75 – 77 °C/1.7 kPa to give compound *I* (1.3 g, 54%).

1-Mercapto-3-methyl-2-butanol (*II*) and 3-Mercapto-3-methyl-2-butanol (*III*)

Potassium O-ethylxanthate (4.0 g, 25 mmol) in acetone (100 ml) was added to a vigorously stirred 4 : 1 mixture of *VIIb* and *VIIc* in acetone (50 ml). Sodium bromide separated during a 3 h stirring at room temperature was filtered off, acetone was removed under reduced pressure, the residue was added to $LiAlH_4$ (1.6 g) within 2 h and worked out as in the preceding case. Yield 1.4 g (58%) of a 3 : 1 mixture of *II* and *III* obtained by vacuum distillation at 72 – 80 °C/1.7 kPa. ^{1}H NMR *II*: 0.92 d, 3 H (CH_3); 0.96 d, 3 H (CH_3); 1.73 sept, 1 H (CH); 2.34 bs, 1 H (OH); 2.5 – 2.9 m, 2 H (CH_2); 3.32 m, 1 H (CH–O). *III*: 1.16, 1.24, 1.30 sss, 3 × 3 H (CH_3); 1.62 s, 1 H (SH); 3.55 m, 1 H (CH).

5-Isopropylidenerhodanine (*VIII*)

This compound was prepared according to ref.[10] in 70% yield, m.p. 195 °C. ^{1}H NMR ($(CD_3)_2SO$): 1.95 s, 3 H (CH_3); 2.33 s, 3 H (CH_3).

2-Mercapto-3-methyl-2-butenoic Acid (*IX*)

Compound *VIII* (7.0 g, 40 mmol) was heated in aqueous NaOH (25%, 25 mmol) at 80 °C for 30 min, cooled to 0 – 5 °C, acidified with 1M-HCl to pH 2 and the yellow precipitate (1.8 g, 24%) was filtered off. Crystallization from water afforded compound *IX*, m.p. 90 – 92 °C . ^{1}H NMR: 2.05 s, 3 H (CH_3); 2.21 s, 3 H (CH_3); 3.76 bs, 1 H (SH); 9.64 bs, 1 H (COOH).

2-Mercapto-3-methyl-2-buten-1-ol (*IV*)

Compound *IX* (2.6 g, 20 mmol) in ether (200 ml) was added to $LiAlH_4$ (1.6 g) in ether (100 ml) during 2 h and stirred for 48 h at ambient temperature. The excess of $LiAlH_4$ was decomposed by stirring with acetone at room temperature for 2 h and the mixture was acidified with 1M-H_2SO_4. The organic layer was separated, dried with Na_2SO_4 and the product was distilled under reduced pressure. Yield 0.4 g, b.p. 80 – 84 °C/1.7 kPa. ^{1}H NMR: 1.23 s, 1 H (SH); 2.00 s, 3 H (CH_3); 2.15 s, 3 H (CH_3); 3.69 q, 2 H (CH_2).

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