Convenient Synthesis of Various Substituted Homotaurines from Alk-2-enamides

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Various substituted homotaurines (= 3-aminopropane-1-sulfonic acids) **6** were readily synthesized in satisfactory to good yields *via* the *Michael* addition of thioacetic acid to alk-2-enamides **3** (→ **4**), followed by $LiAlH_4$ reduction (→ **5**) and performic acid oxidation (*Scheme 1*). The configuration of '*anti*'-disubstituted homotaurine '*anti*'-**6h** was deduced from the 3-(acetylthio)alkanamide (= *S*-(3-amino-1,2-dimethyl-3-oxopropyl) ethanethioate)'*anti*'-**4h** formed in the *Michael* addition, which was identified *via* the *Karplus* equation analysis, and confirmed by X-ray diffraction analysis. The current route is an efficient method to synthesize diverse substituted homotaurines, including 1-, 2-, and *N*-monosubstituted, as well as 1,2-, 1,*N*-, 2,*N*-, and *N*,*N*-disubstituted homotaurines (*Table*).

Introduction. – Homotaurine, *i.e.*, 3-amino-1-propanesulfonic acid (3APS), also called tramiprosate, shows biological activities as a neuroprotective compound and amyloid antagonist and was a candidate drug for treating *Alzheimer*'s disease [1]. Moreover, calcium 3-(acetamido)propanesulfonate (acamprosate) is one of the few medications for the prevention of alcohol relapse in detoxified alcohol-dependent patients in several countries [2]. Both homotaurine and substituted homotaurine derivatives are considered as bioisosteres of γ-aminobutyric acid (GABA = 3-amino-butanoic acid) [3], which is of great importance as a specific inhibitor of impulse transmission in the central nervous system [4]. Therefore, several methods for the synthesis of substituted homotaurines have been developed.

The 1-carboxyhomotaurine was prepared from methyl 2,4-dibromobutanoate *via* displacement of Br-C(2) with thioacetic acid (= ethanethioic *S*-acid) in the presence of diisopropylethylamine and oxidation with H_2O_2 in AcOH, and subsequent substitution of Br-C(4) with NaN_3, acidic hydrolysis, and hydrogenation [5]. Various 1-substituted homotaurines were synthesized from α,β-unsaturated nitriles by the *Michael* addition with thioacetic acid, reduction with $LiAlH_4$, and oxidation with performic acid [6], or from *S*-(*N*-phthalimidomethyl) xanthate and different olefins *via* radical addition and subsequent oxidation with performic acid [7]. The 2-methylhomotaurine was first synthesized as a competitive antagonists of the GABA receptor *via* addition of methacrolein (= 2-methylprop-2-enal) with $NaHSO_3$ and subsequent reductive amination under hydrogenation conditions [8]. The 2-phenylhomotaurine was prepared from phenyl styrenesulfonate *via* addition of nitromethane in the presence of MeONa

and subsequent catalytic hydrogenation and hydrolysis [9][10]. The 2-(4-chlorophenyl)homotaurine was considered as important antagonist of GABA and synthesized from 2-(4-chlorophenyl)acrylonitrile (=2-(4-chlorophenyl)prop-2-enenitrile) *via* addition with $NaHSO_3$ and subsequent reduction [11], *via* the O_2-catalyzed radical addition of $NaHSO_3$ to 2-(4-chlorophenyl)allylamine or their *N*-phthalyl derivatives [12–14]. The 3-carboxyhomotaurine was prepared *via* hydrolysis of 2-(2,5-dioxoimidazolidin-4-yl)ethanesulfonic acid [15] or *via* oxidation of homocysteine with peroxy acid [16]. The 3-substituted homotaurines were synthesized *via* the *Horner–Wadsworth–Emmons* reaction of *N*-protected α-aminoalkanals and ethyl (diethoxyphosphoryl)methanesulfonate in the presence of BuLi and subsequent hydrogenation and deprotection [17][18]. Ring-opening reactions of substituted propane-1,3-sultones with NH_3 or with NaN_3 followed by reduction were applied for the synthesis of variously substituted homotaurines [19]. Reduction of 4-oximino/imino-substituted 1,2,3,4-tetrahydronaphthalene-2-sulfonic acids gave rise to 4-(alkyl)amino-1,2,3,4-tetrahydronaphthalene-2-sulfonic acids, which are regarded as 1,3-disubstituted homotaurines [20]. The 3-nitroalkanesulfonic acids, the precursors of 1,3-disubstituted homotaurines, were obtained *via* addition of aryl methanesulfonates to nitroolefins in the presence of BuLi [21]. In addition, a cyclic substituted homotaurine, considered as a 1,3-disubstituted homotaurine, was synthesized *via Diels–Alder* reaction of cyclopentadiene and *N*-sulfinylcarbamate and subsequent basic hydrolysis and performic acid oxidation [22]. Recently, *cis*- and *trans*-2-(aminomethyl)cyclopropane-1-sulfonic acids were synthesized *via* diazo ester addition to olefins as key step as conformationally restricted GABA analogues serving as pharmacological tools to study GABA receptor subtypes [4][23]. Despite of these synthetic methods for substituted homotaurines, no general and versatile method has been developed.

Recently, we focused on the synthesis of various aminoalkanesulfonic acids. Structurally diverse substituted taurines were prepared from nitroalkenes *via Michael* addition with sodium *O*-ethyl xanthate or thioacetic acid and subsequent oxidation and reduction [24][25]. We hope to extend our method to the synthesis of substituted homotaurines from alk-2-enamides as starting materials, which are commercially available or can be prepared readily from various commercially available alk-2-enoic acids. Although α,β-unsaturated nitriles have been applied in the synthesis of substituted homotaurines, they can only be used in the preparation of 1-substituted homotaurines. Herein, we present a general synthesis of substituted homotaurines from alk-2-enamides *via Michael* reaction with thioacetic acid, reduction, and performic acid (=methaneperoxoic acid) oxidation.

Results and Discussion. – Alk-2-enamides **3b**–**3d**, **3f**, **3h**, and **3i** were prepared from the corresponding alk-2-enoic acids **1b**–**1d**, **1f**, **1h**, and **1i** (*Scheme 1, Table*), whereas prop-2-enamide (**3a**) and 2-methylprop-2-enamide (**3e**) were commercially available. Thus, alk-2-enoic acids **1** were treated with $SOCl_2$ to afford alk-2-enoyl chlorides **2**, which were directly treated with aqueous NH_3 solution to give rise to the corresponding alk-2-enamides **3** in satisfactory to good yields (*Table*). The 2-phenylprop-2-enoic acid (**1f**) polymerized favorably when it was refluxed with $SOCl_2$. The polymerization was inhibited when 0.5 equiv. of benzoquinone was added to the reaction mixture (*Table*, *Entry 6*). Alk-2-enoic chlorides **2a**, **2b**, and **2e** reacted with benzylamine in the presence

of Et_3N to produce *N*-benzylalk-2-enamides **3g**, **3j**, and **3k**, respectively, in excellent yields (*Entries 7*, *10*, and *11*). *N*,*N*-Dibenzylprop-2-enamide (**3l**) was obtained in good yield *via* aminolysis of prop-2-enyl chloride (**2a**) with dibenzylamine in the presence of Et_3N (*Entry 12*). Alk-2-enamides **3a**–**3g** were selected as the representatives of aliphatic and aromatic 2-, 3-, and *N*-monosubstituted prop-2-enamides, while alk-2-enamides **3h**–**3l** were designed as examples of 2,3-, 3,3-, 2,*N*-, 3,*N*-, and *N*,*N*-disubstituted prop-2-enamides.

Scheme 1. *Synthesis of Substituted Homotaurines* **6**

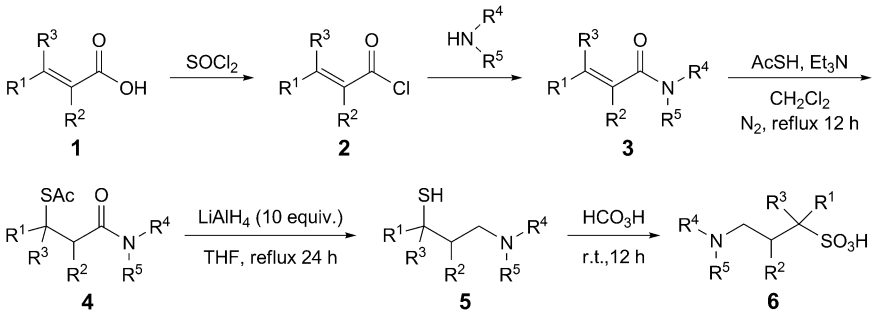


Table. *Synthesis of Substituted Homotaurines* **6** *from Alk-2-enamides* **3**

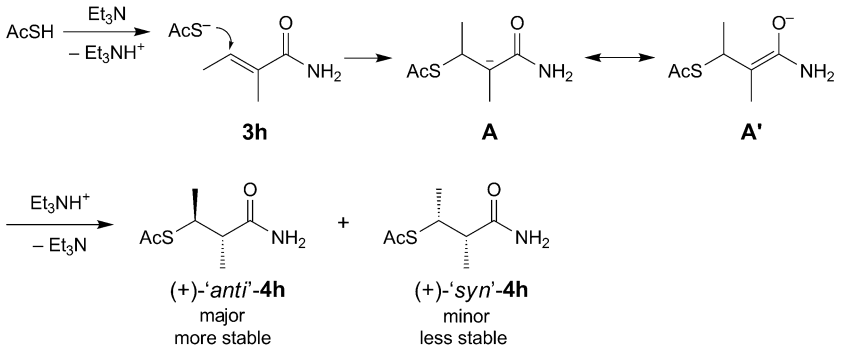
Entry	R^1	R^2	R^3	R^4	R^5	**1**	**3**	Yield [%]		
								3	**4**	**6**[a])
1	H	H	H	H	H	**1a**	**3a**	–	94	22[b])
2	Me	H	H	H	H	**1b**	**3b**	50	78	67
3	Pr	H	H	H	H	**1c**	**3c**	89	83	84
4	Ph	H	H	H	H	**1d**	**3d**	70	–	
5	H	Me	H	H	H	**1e**	**3e**	–	95	70
6	H	Ph	H	H	H	**1f**	**3f**	64[c])	70	74
7	H	H	H	Bn	H	**1a**	**3g**	94	94	63
8	Me	Me	H	H	H	**1h**	**3h**	77	75[d])	51[e])
9	Me	H	Me	H	H	**1i**	**3i**	43	–	
10	Me	H	H	Bn	H	**1b**	**3j**	96	88	91
11	H	Me	H	Bn	H	**1e**	**3k**	98	95	94
12	H	H	H	Bn	Bn	**1a**	**3l**	75	77	76

[a]) Overall yield from thioacetate **4**. [b]) Overall yield was obtained from **4a** *via* *N*-Cbz protected 3-aminopropane-1-thiol (**7**) after the reduction. [c]) 0.5% Equiv. of benzoquinone was added to the mixture. [d]) '*Anti*'/'*syn*' = 10 : 1. [e]) Yield of '*syn*'-**6h** from '*syn*'-**4h**.

Although both thioacetic acid and sodium *O*-ethyl xanthate can serve as good nucleophiles in the *Michael* addition with electron-deficient nitroolefins and can be converted to aminoalkanesulfonic acids, thioacetic acid shows higher efficiency in the *Michael* addition with nitroolefins in the synthesis of substituted taurines [24][25]. Thus, thioacetic acid was selected as a sulfur-containing nucleophile in our synthesis of substituted homotaurines. The *Michael* addition of thioacetic acid and alk-2-enamides **3** has been explored previously [26]. Considering the solubility of alk-2-enamides **3**, the

instability of thioacetic acid in air, and the reversibility of the *Michael* addition reaction at higher temperature, the *Michael* addition of thioacetic acid and **3** was conducted in refluxing CH_2Cl_2 in the presence of a catalytic amount of Et_3N under N_2 for 12 h, affording the corresponding 2-(acetylthio)alkanamides (= *S*-(3-amino-1,2-dimethyl-3-oxopropyl) ethanethioates) **4** in good to excellent yields (*Table*), except for cinnamamide (=(2*E*)-3-phenylprop-2-enamide; **3d**) and 3-methylbut-2-enamide (**3i**), which did not undergo the *Michael* addition due to favorable *E*1cb elimination and steric hindrance, respectively (*Table*, *Entries 4* and *9*). It is supported by the fact that 3-unsubstituted prop-2-enamides **3a**, **3e**, **3g**, and **3k** afforded the adducts in higher yields than the corresponding 3-substituted prop-2-enamides **3b**, **3c**, **3h**, and **3j** (*Entries 1 vs. 2* and *3*, *5 vs. 8*, and *6 vs. 4*). For 2-methylbut-2-enamide (**3h**), a mixture of '*anti*'- and '*syn*'-**4h** was obtained in a ratio 10:1 (^{1}H-NMR) (*Scheme 2*). The relative configurations of the adducts **4h** were assigned on the basis of the reaction mechanism and their ^{1}H-NMR data. Thioacetate undergoes the *Michael* addition with **3h** to generate an intermediate **A**, which is protonated to afford '*anti*'-**4h** as major product and '*syn*'-**4h** as minor isomer due to their stability (*Scheme 2*).

Scheme 2. *Diastereoselectivity in the* Michael *Addition of (2*E*)-2-Methylbut-2-enamide* (**3h**) *and Thioacetic Acid in the Presence of Et_3N*



The two H-atoms at C(2) and C(3) in '*anti*'-**4h** are in the '*anti*' (antiperiplanar) position, while they are in the *gauche* (syndinal) position in '*syn*'-**4h**. According to the *Karplus* equation, the coupling constant between these two H-atoms in '*anti*'-**4h** should be larger than that in '*syn*'-**4h**. ^{1}H-NMR Spectroscopic analysis indicates that the coupling constants are 6.8 Hz for the major isomer '*anti*'-**4h** and 4.4 Hz for the minor isomer '*syn*'-**4h**. To verify the assignment of the relative configuration, the major product was recrystallized from AcOEt/hexanes and subjected to single-crystal X-ray diffraction analysis[1]). The results revealed that the major product is '*anti*'-**4h** (*Fig.*).

To realize the *Michael* addition of thioacetic acid and cinnamamide (**3d**), the reaction was carried out in THF, a slightly higher boiling solvent, for a longer time (18 h), but no product was observed. The more electron-rich sulfur-containing

[1]) CCDC-920579 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

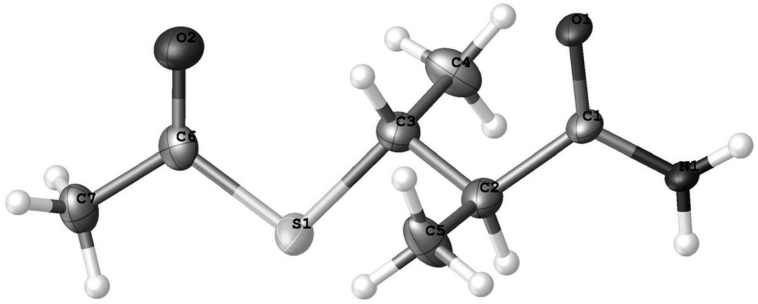


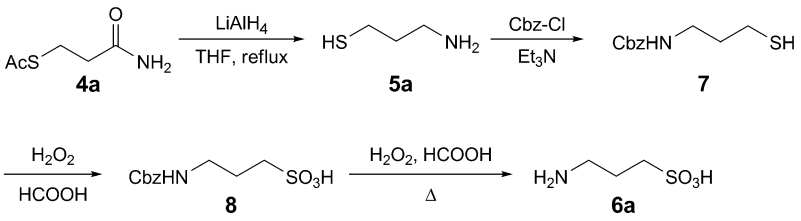
Fig. 1. *ORTEP Representation of the molecular structure of* 'anti'-**4h**

nucleophile sodium *O*-ethyl xanthate was also attempted in the *Michael* addition with **3d** in both refluxing THF and in AcOH at 60°. No reaction occurred in both cases. The results indicate that **3d**, a 3-arylprop-2-enamide, is inert in the *Michael* addition.

The 3-(acetylthio)alkanamides **4** were then reduced with $LiAlH_4$ in dry THF to give the corresponding 3-aminoalkane-1-thiols **5**. For complete reduction, 10 equiv. of $LiAlH_4$ were required. Insufficient reduction resulted in the formation of 3-mercaptoalkanamides, revealing that the acetylthio group was reduced predominately. After usual workup, the crude thiols **5** were oxidized to afford substituted homotaurines **6** in acceptable to excellent overall yields, except for **6a**, because it could not be extracted from the aqueous solution (*Scheme 1, Table*).

Analogously to a previous report [6], 3-(acetylthio)prop-2-enamide (**4a**) was reduced to **5a**, which was converted to the less hydrophilic benzyl *N*-(3-mercaptopropyl)carbamate (**7**) in 16% overall yield (*Scheme 3*). If the crude **7** was directly oxidized with performic acid, **6a** was obtained in 22% overall yield from **4a**. Oxidation of pure **7** with performic acid gave rise to *N*-[(benzyloxy)carbonyl]homotaurine (**8**) in 55% yield and **6a** in 8% yield if the solvent was removed at a temperature below 45°, while it gave **6a** in 64% yield if the solvent was evaporated above 45° (*Scheme 3*), as observed in the synthesis of substituted taurines [27].

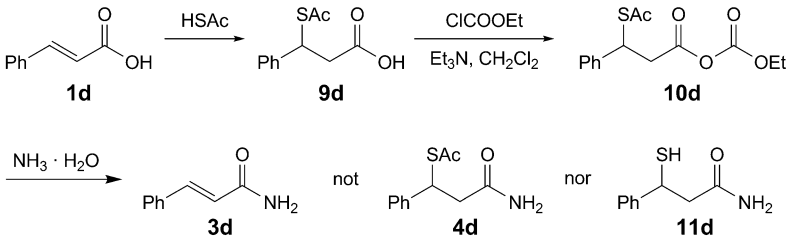
Scheme 3. *Synthesis of Homotaurine* (**6a**) *and* N-*Cbz-Protected Homotaurine* **8**



The above method cannot be used to prepare 3-aryl-3-(acetylthio)propanamides. Considering that alk-2-enoic acids should be better *Michael* acceptors than the corresponding alk-2-enamides, we hoped to introduce the sulfur moiety first *via* the *Michael* addition of alk-2-enoic acids and thioacetic acid and then to convert the 3-(acetylthio)alkanoic acids to 3-(acetylthio)alkanamides. As expected, cinnamic acid (**1d**) reacted with thioacetic acid in benzene to give 3-(acetylthio)-3-phenylpropanoic

acid (**9d**) in 76% yield (*Scheme 4*). However, 3-methylbut-2-enoic acid (**1i**) did not undergo the *Michael* addition with thioacetic acid either. To convert **9d** to 3-(acetylthio)-3-phenylpropanamide (**4d**) under mild conditions, it was treated with ethyl carbonochloridate in the presence of Et_3N to give the mixed anhydride **10d**. The latter was *in situ* treated with NH_3. Unfortunately, cinnamamide (**3d**) was obtained in 87% yield instead of **4d** (*Scheme 4*). It is believed that a reverse *Michael* addition reaction, an *E*1cb elimination, occurred during ammonolysis.

Scheme 4. *Attempt to Synthesize 3-(Acetylthio)cinnamamide* (**4d**) *from Cinnamic Acid* (**1d**)



Conclusion. – A new protocol was developed successfully for the synthesis of substituted homotaurines from alk-2-enoic acids. Substituted homotaurines were prepared from alk-2-enamides *via Michael* addition with thioacetic acid, reduction with $LiAlH_4$, and oxidation with performic acid. The relative configuration of '*anti*'-1,2-disubstituted homotaurine was deduced from the 3-(acetylthio)alkanamide formed in the *Michael* addition, which was assigned on the basis of the *Karplus* equation analysis and confirmed by X-ray diffraction determination. The presented method can be used to synthesize 1-alkyl-, 2-alkyl-, 2-aryl-, *N*-substituted, 1,2-, 1,*N*-, 2,*N*-, and *N,N*-disubstituted homotaurines from readily available alk-2-enamides or alk-2-enoic acids as starting materials.

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Experimental Part

General. Thioacetic acid, prop-2-enamide (**3a**), and 2-methylprop-2-enamide (**3e**) were commercially available. THF was heated to reflux over Na and diphenyl ketone until the color of the mixture became blue, and was freshly distilled prior to use; CH_2Cl_2 was heated to reflux over CaH_2 and freshly distilled prior to use. TLC: glass plates pre-coated with silica gel *YT257–85* (10–40 μm); visualization with UV light or I_2. Column chromatography (CC): silica gel *zcx II* (SiO_2; 200–300 mesh) petroleum ether/AcOEt (*v*/*v*) eluent. M.p.: *Yanaco-MP-500* melting-point apparatus; uncorrected. IR Spectra: *Nicolet-Avatar-330-FT-IR* spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Varian-300-plus* (300 MHz) or *Bruker-AV-400* (400 MHz) spectrometer; in $CDCl_3$ with Me_4Si as internal standard or in D_2O for homotaurines (with HCOOH as an internal standard at δ(C) 166.3; δ in ppm, coupling constants *J* in Hz. HR-MS: *Agilent-LC/MSD-TOF* mass spectrometer; in *m*/*z*.

1. *Alk-2-enamides* **3b–3d**, **3f**, **3h**, *and* **3i**: *General Procedure.* A soln. of alk-2-enoic acid (40 mmol) in $SOCl_2$ (3.6 ml, 5.95 g, 50 mmol) was stirred at r.t. for 4 h. After evaporation of the excess $SOCl_2$, the residue was added dropwise to 25% aq. NH_3 soln. (30 ml) under stirring at 0°, and the mixture was stirred

at r.t. for 30 min. Then, the soln. was extracted with AcOEt (3×30 ml), the combined org. phases dried (Na_2SO_4) and concentrated and the colorless crystalline product recrystallized from AcOEt/petroleum ether: alk-2-enamide as colorless crystals. The anal. data of **3b–3d** and **3f–3l** were identical to those earlier reported (**3b** [28], **3c** [29], **3d** [30], **3f** [31], **3h** [32] and **3i** [32]).

2. N-*Benzylalk-2-enamides* **3g** *and* **3j–3l**: *General Procedure.* A soln. of alk-2-enoic acid (100 mmol) in $SOCl_2$ (8.5 ml, 13.89 g, 110 mmol) was stirred at r.t. for 12 h. The mixture was distilled to collect the alk-2-enoyl chloride. To a soln. of benzylamine (5.5 g, 51.3 mmol) or dibenzylamine (10.12 g, 51.3 mmol) and Et_3N (7.5 ml, 5.20 g, 51.3 mmol) in dried CH_2Cl_2 (30 ml) was added dropwise alk-2-enoyl chloride (34.2 mmol) under stirring at 0°. The resulting soln. was stirred at r.t. for 2 h, then washed with sat. NaCl soln. (3×10 ml), and dried (Na_2SO_4). After evaporation of the solvent, the residue was subjected to CC: *N*-benzylalk-2-enamide as colorless crystals. The anal. data of *N*-benzylxalk-2-enamides **3g** and **3j–3l** were identical to those earlier reported (**3g** and **3j** [33], **3k** [34], and **3l** [35]).

3. S-*(3-Amino-3-oxopropyl) Ethanethioates* **4**: *General Procedure.* To a boiling soln. of Et_3N (10 drops) and alk-2-enamide (20 mmol) in dried CH_2Cl_2 (30 ml) was added thioacetic acid (1.8 ml, 1.90 g, 25 mmol), dropwise under N_2. The resulting soln. was heated under reflux for 12 h. After evaporation of the solvent, the residue was subjected to CC or recrystallization to afford the desired product.

S-*(3-Amino-3-oxopropyl) Ethanethioate* (**4a**): CC (petroleum ether/AcOEt 1:2). Colorless crystals. Yield 2.76 g (94%). M.p. 96° ([36]: 82–83°). ^{1}H-NMR (300 MHz): 5.90 (br. *s*, 1 H of NH_2); 5.71 (br. *m*, 1 H of NH_2); 3.13 (*t*, $J = 6.9$, CH_2S); 2.55 (*t*, $J = 6.9$, $COCH_2$); 2.34 (*s*, Me).

S-*(3-Amino-1-methyl-3-oxopropyl) Ethanethioate* (**4b**): CC (petroleum ether/AcOEt 1:2): White wax. Yield 2.51 g (78%). IR: 3349 (NH), 3195 (NH), 1670 (CO). ^{1}H-NMR (400 MHz): 6.16 (br. *s*, 1 H of NH_2); 6.00 (br. *s*, 1 H of NH_2); 3.87 (*ddq*, $J = 6.0, 8.0, 6.8$, CH); 2.61 (*dd*, $J = 6.0, 14.4$, 1 H of CH_2); 2.44 (*dd*, $J = 8.0, 14.4$, 1 H of CH_2); 2.32 (*s*, COMe); 1.39 (*d*, $J = 6.8$, Me). ^{13}C-NMR (100 MHz): 195.8; 173.0; 42.5; 36.0; 30.5; 20.4. HR-MS-ESI: 162.0578 ($[M+H]^+$, $C_6H_{11}NO_2S^+$; calc. 162.0583).

S-*(3-Amino-3-oxo-1-propylpropyl) Ethanethioate* (**4c**): CC (petroleum ether/AcOEt 1:2). Colorless crystals. Yield 3.50 g (83%). M.p. 73–74.5°. IR: 3391 (NH), 3197 (NH), 1686 (CO), 1651 (CO). ^{1}H-NMR (400 MHz): 5.80 (br. *s*, 1 H of NH_2); 5.66 (br. *s*, 1 H of NH_2); 3.81–3.74 (*m*, CH); 2.59 (*dd*, $J =$ 6.4, 15.2, 1 H of $COCH_2$); 2.52 (*dd*, $J = 7.2, 15.2$, 1 H of $COCH_2$); 2.33 (*s*, COMe); 1.76–1.58 (*m*, CH_2); 1.51–1.32 (*m*, CH_2); 0.91 (*t*, $J = 7.2$, Me). ^{13}C-NMR (100 MHz): 196.2; 172.9; 41.8; 41.1; 36.1; 30.7; 20.2; 13.6. HR-MS-ESI: 212.0719 ($[M+H]^+$, $C_8H_{15}NO_2S^+$; calc. 212.0721).

S-*(3-Amino-2-methyl-3-oxopropyl) Ethanethioate* (**4e**) [37]: Recrystallized from EtOH/Et_2O. Colorless crystals. Yield 3.06 g (95%). M.p. 84–86°. IR: 3381 (NH), 3190 (NH), 1687 (CO), 1656 (CO). ^{1}H-NMR (400 MHz): 6.19 (br. *s*, 1 H of NH_2); 5.96 (br. *s*, 1 H of NH_2); 3.11 (*dd*, $J = 6.8, 13.6$, 1 H of CH_2); 2.95 (*dd*, $J = 6.8, 13.6$, 1 H of CH_2); 2.53 (*ddq*, $J = 6.8, 6.8, 6.8$, CH); 2.34 (*s*, COMe); 1.24 (*d*, $J =$ 6.8, Me). ^{13}C-NMR (100 MHz): 196.1; 177.0; 40.7; 32.4; 30.5; 17.3.

S-*(3-Amino-3-oxo-2-phenylpropyl) Ethanethioate* (**4f**): CC (petroleum ether/AcOEt 1:1). Colorless crystals. Yield 3.09 g (70%). M.p. 116–117°. IR: 3389 (NH), 3184 (NH), 1691 (CO), 1655 (CO). ^{1}H-NMR (400 MHz): 7.36–7.27 (*m*, 5 arom. H); 5.91 (br. *s*, 1 H of NH_2); 5.62 (br. *s*, 1 H of NH_2); 3.67 (*dd*, $J = 6.4, 8.4$, CH); 3.44 (*dd*, $J = 8.4, 13.6$, 1 H of CH_2); 3.27 (*dd*, $J = 6.4, 13.6$, 1 H of CH_2); 2.30 (*s*, Me). ^{13}C-NMR (100 MHz): 196.1; 174.0; 138.2; 128.9; 127.9; 127.8; 52.1; 32.0; 30.5. HR-MS-ESI: 224.0736 ($[M+H]^+$, $C_{11}H_{13}NO_2S^+$; calc. 224.0740).

S-*{3-Oxo-3-[(phenylmethyl)amino]propyl} Ethanethioate* (**4g**): Recrystallized from Et_2O. Colorless crystals. Yield 4.46 g (94%). M.p. 80–80.5°. IR: 3290 (NH), 1692 (CO), 1637 (CO). ^{1}H-NMR (400 MHz): 7.36–7.26 (*m*, 5 arom. H); 5.87 (br. *s*, NH); 4.44 (*d*, $J = 5.6$, CH_2); 3.16 (*t*, $J = 6.8$, CH_2S); 2.52 (*t*, $J = 6.8$, $COCH_2$); 2.31 (*s*, Me). ^{13}C-NMR (100 MHz): 196.1; 170.4; 138.0; 128.6; 127.7; 127.5; 43.6; 36.1; 30.5; 24.9. HR-MS-ESI: 238.0888 ($[M+H]^+$, $C_{12}H_{15}NO_2S^+$; calc. 238.0896).

S-*[(1*RS*,2*RS*)-3-Amino-1,2-dimethyl-3-oxopropyl] Ethanethioate* ('*anti*'-**4h**): Recrystallized from AcOEt/petroleum ether. Colorless crystals. Yield 2.63 g (75%). M.p. 136–138°. IR: 3356 (NH), 3111 (NH), 1685 (CO), 1655 (CO). ^{1}H-NMR (400 MHz): 5.69 (br. *s*, NH_2); 3.76 (*dq*, $J = 6.8, 6.8$, CHS); 2.52 (*dq*, $J = 6.8, 6.8$, CHCO); 2.33 (*s*, MeCO); 1.37 (*d*, $J = 6.8$, Me); 1.24 (*d*, $J = 6.8$, Me). ^{13}C-NMR (100 MHz): 195.2; 176.3; 45.5; 42.0; 30.7; 19.0; 15.6. HR-MS-ESI: 176.0733 ($[M+H]^+$, $C_7H_{13}NO_2S^+$; calc. 176.0740).

S-*[(1*RS,*2*RS*)-3-Amino-1,2-dimethyl-3-oxopropyl] Ethanethioate* ('*syn*'-**4h**): Data from '*syn*'/'*anti*'-**4h** after the recrystallization of '*anti*'-**4h** (see above). Colorless oil. Yield 0.26 g (7.5%). IR: 3356 (NH), 3111 (NH), 1685 (CO), 1655 (CO). ^{1}H-NMR (400 MHz): 5.82 (br. *s*, NH_2); 3.82 (*dq*, *J* = 4.4, 6.8, CHS); 2.63 (*dq*, *J* = 4.4, 6.8, CHCO); 2.33 (*s*, MeCO); 1.30 (*d*, *J* = 6.8, Me); 1.17 (*d*, *J* = 6.8, Me). ^{13}C-NMR (100 MHz): 196.5; 176.2; 44.7; 41.9; 30.6; 16.7; 12.9. HR-MS-ESI: 176.0735 ($[M+H]^+$, $C_7H_{13}NO_2S^+$; calc. 176.0740).

S-*{1-Methyl-3-oxo-3-[(phenylmethyl)amino]propyl} Ethanethioate* (**4j**): CC (petroleum ether/AcOEt 2:1). White crystals. Yield 4.42 g (88%). M.p. 60–61° ([38]: 65–66°). IR: 3276 (NH), 1682 (CO), 1644 (CO). ^{1}H-NMR (400 MHz): 7.35–7.27 (*m*, 5 arom. H); 5.99 (br. *s*, NH); 4.44 (*d*, *J* = 5.6, ArCH_2); 3.87 (*ddq*, *J* = 6.4, 7.6, 6.8, CH); 2.58 (*dd*, *J* = 6.4, 14.4, 1 H of CH_2); 2.45 (*dd*, *J* = 7.6, 14.4, 1 H of CH_2); 2.27 (*s*, COMe); 1.39 (*d*, *J* = 6.8, Me). ^{13}C-NMR (100 MHz): 195.8; 169.8; 138.1; 128.6; 127.8; 127.5; 43.5; 43.3; 36.5; 30.6; 20.6.

S-{*2-Methyl-3-oxo-3-[(phenylmethyl)amino]propyl*} *Ethanethioate* (**4k**): CC (petroleum ether/AcOEt 2:1). Yellow oil ([38]: M.p. 60°). Yield 4.77 g (95%). IR: 3296 (NH), 1692 (CO), 1650 (CO). ^{1}H-NMR (400 MHz): 7.35–7.27 (*m*, 5 arom. H); 6.09 (br. *s*, NH); 4.43 (*d*, *J* = 5.6, ArCH_2); 3.11 (*dd*, *J* = 8.0, 13.6, 1 H of CH_2); 2.96 (*dd*, *J* = 6.0, 13.6, 1 H of CH_2); 2.46 (*ddq*, *J* = 6.0, 8.0, 7.2, CH); 2.29 (*s*, COMe); 1.23 (*d*, *J* = 7.2, Me). ^{13}C-NMR (100 MHz): 196.1; 174.1; 138.2; 128.6; 127.7; 127.4; 43.5; 41.5; 32.7; 30.5; 17.4.

S-*{3-[Bis(phenylmethyl)amino]-3-oxopropyl} Ethanethioate* (**4l**): CC (petroleum ether/AcOEt 5:1). Yellow oil. Yield: 5.04 g (77%). IR: 1688 (CO), 1650 (CO). ^{1}H-NMR (400 MHz): 7.37–7.12 (*m*, 10 arom. H); 4.60 (*s*, CH_2); 4.42 (*s*, CH_2); 3.22 (*t*, *J* = 6.8, CH_2S); 2.74 (*t*, *J* = 6.8, $COCH_2$); 2.29 (*s*, Me). ^{13}C-NMR (100 MHz): 195.9; 171.2; 137.0; 136.0; 128.8; 128.5; 128.2; 127.5; 127.3; 126.2; 49.6; 48.2; 33.2; 30.4; 24.8. HR-MS-ESI: 328.1362 ($[M+H]^+$, $C_{19}H_{21}NO_2S^+$; calc. 328.1366).

4. *Substituted Homotaurines* **6**: *General Procedure.* To a suspension of $LiAlH_4$ (1.52 g, 40 mmol) in dried THF (30 ml) was added a soln. of **4** (4 mmol) in dried THF (5 ml), dropwise under stirring at 0°. The resulting mixture was heated under reflux for 24 h and then cooled to 0°. The excess $LiAlH_4$ was carefully quenched with H_2O (10 ml) under stirring at r.t. After filtration, the filtrate was extracted with CH_2Cl_2 (3 × 10 ml), the combined org. phase dried (Na_2SO_4) and concentrated, and the residual yellow oil dissolved in HCOOH (10 ml). To the soln. was added a mixture of HCOOH (10 ml) and 30% H_2O_2 soln. (5 ml), dropwise under stirring at r.t. After stirring for 12 h and removal of the solvent, the residue was crystallized from MeOH/Et_2O to give the substituted homotaurine.

4-Aminobutane-2-sulfonic Acid (**6b**): Colorless solid. Yield 410 mg (67%). M.p. 281–283° ([39]: 288–289°). IR: 3448 (br., NH, OH), 1257 (SO), 1167 (SO). ^{1}H-NMR (400 MHz, D_2O): 3.16–3.04 (*m*, CH_2N); 2.94 (*ddq*, *J* = 6.4, 6.4, 6.9, CH); 2.12 (*ddt*, *J* = 6.9, 14.8, 6.4, 1 H of CH_2); 1.82 (*ddt*, *J* = 6.8, 14.8, 6.4, 1 H of CH_2); 1.25 (*d*, *J* = 6.9, Me). ^{13}C-NMR (100 MHz, D_2O): 53.0; 37.3; 29.2; 14.6.

1-Aminohexane-3-sulfonic Acid (**6c**): Colorless crystals. Yield 608 mg (84%). M.p. 230–234°. IR: 3407 (br., NH, OH), 1255 (SO), 1163 (SO). ^{1}H-NMR (400 MHz, D_2O): 3.13 (*t*, *J* = 8.0, CH_2N); 2.82 (*tt*, *J* = 4.8, 7.6, CH); 2.08–1.92 (*m*, CH_2); 1.82–1.73 (*m*, 1 H of CH_2); 1.53–1.39 (*m*, CH_2); 1.37–1.28 (*m*, 1 H of CH_2); 0.85 (*t*, *J* = 7.2, Me). ^{13}C-NMR (100 MHz, D_2O): 57.5; 37.5; 31.5; 27.2; 19.5; 13.2. HR-MS-ESI: 182.0849 ($[M+H]^+$, $C_6H_{15}NO_3S^+$; calc. 182.0581).

3-Amino-2-methylpropane-1-sulfonic Acid (**6e**): Colorless crystals. Yield 428 mg (70%). M.p. 234–238° ([8]: 260–265°). IR: 3451 (br. NH, OH), 1280 (SO), 1176 (SO). ^{1}H-NMR (400 MHz, D_2O): 3.15 (*dd*, *J* = 6.0, 13.2, 1 H of CH_2S); 2.93 (*dd*, *J* = 6.8, 14.4, 1 H of CH_2N); 2.90 (*dd*, *J* = 6.8, 13.2, 1 H of CH_2S); 2.87 (*dd*, *J* = 6.0, 14.4, 1 H of CH_2N); 2.37–2.26 (*m*, CH); 1.10 (*d*, *J* = 6.8, Me). ^{13}C-NMR (100 MHz, D_2O): 54.7; 44.2; 28.7; 17.0.

3-Amino-2-phenylpropane-1-sulfonic Acid (**6f**) [10]: Colorless crystals. Yield 636 mg (74%). M.p. 220–225° (dec.). IR: 2960 (br., NH, OH), 1180 (SO), 1142 (SO). ^{1}H-NMR (400 MHz, D_2O): 7.40–7.30 (*m*, 5 arom. H); 3.53 (*dd*, *J* = 5.2, 12.8, 1 H of CH_2S); 3.46–3.38 (*m*, CH); 3.28 (*dd*, *J* = 6.4, 14.4, 1 H of CH_2N); 3.24 (*m*, 1 H of CH_2S); 3.22 (*dd*, *J* = 6.4, 14.4, 1 H of CH_2N). ^{13}C-NMR (100 MHz, D_2O): 134.7; 129.4; 128.9; 58.6; 30.3; 16.8.

3-[(Phenylmethyl)amino]propane-1-sulfonic Acid (**6g**): Colorless crystals. Yield 577 mg (63%). M.p. 241–243° ([40]: 302–303°). IR: 3452 (br., NH, OH), 1245 (SO), 1184 (SO). ^{1}H-NMR (400 MHz, D_2O):

7.42 (*s*, 5 arom. H); 4.17 (*s*, PhCH_2); 3.15 (*t*, *J* = 7.2, CH_2S); 2.91 (*t*, *J* = 7.2, CH_2N); 2.06 (*quint.*, *J* = 7.2, CH_2). ^{13}C-NMR (100 MHz, D_2O): 130.6; 129.8; 129.7; 129.3; 51.1; 47.9; 45.7; 21.3.

*(2*RS*,3*RS*)-4-Amino-3-methylbutane-2-sulfonic Acid* ('*anti*'-**6h**): Yellow oil. Yield 341 mg (51%). IR: 2976 (br., NH, OH), 1205 (SO), 1030 (SO). ^{1}H-NMR (400 MHz, D_2O): 3.27 (*dd*, *J* = 5.6, 13.2, 1 H of CH_2N); 2.96 (*dq*, *J* = 2.8, 7.2, CHS); 2.82 (*dd*, *J* = 8.4, 13.2, 1 H of CH_2N); 2.42 (*dddq*, *J* = 2.8, 5.6, 8.4, 7.2, CH); 1.21 (*d*, *J* = 7.2, Me); 1.05 (*d*, *J* = 7.2, Me). ^{13}C-NMR (100 MHz, D_2O): 58.5; 41.2; 32.3; 15.4; 9.8. HR-MS-ESI: 168.0682 ($[M+H]^+$, $C_5H_{13}NO_3S^+$; calc. 168.0689).

4-[(Phenylmethyl)amino]butane-2-sulfonic Acid (**6j**) [19]: Colorless crystals. Yield 885 mg (91%). M.p. 251–253°. IR: 3431 (br., NH, OH), 1210 (SO), 1161, (SO). ^{1}H-NMR (400 MHz, D_2O): 7.44–7.39 (*m*, 5 arom. H); 4.17 (*s*, PhCH_2); 3.16 (*t*, *J* = 8.0, CH_2N); 2.91 (*ddq*, *J* = 6.8, 6.8, 6.8, CH); 2.18–2.09 (*m*, 1 H of CH_2); 1.90–1.80 (*m*, 1 H of CH_2); 1.22 (*d*, *J* = 6.8, Me). ^{13}C-NMR (100 MHz, D_2O): 130.6; 129.8; 129.7; 129.3; 53.1; 51.1; 44.8; 27.9; 14.6.

2-Methyl-3-[(phenylmethyl)amino]propane-1-sulfonic Acid (**6k**): Colorless crystals. Yield 914 mg (94%). M.p. 265–267°. IR: 3435 (br., NH, OH), 1209 (SO), 1179 (SO). ^{1}H-NMR (400 MHz, D_2O): 7.42 (*s*, 5 arom. H); 4.18 (*d*, *J* = 2.4, PhCH_2); 3.20 (*dd*, *J* = 6.8, 12.8, 1 H of CH_2S); 2.97 (*dd*, *J* = 6.8, 12.8, 1 H of CH_2S); 2.91 (*dd*, *J* = 6.8, 14.4, 1 H of CH_2N); 2.86 (*dd*, *J* = 5.6, 14.4, 1 H of CH_2N); 2.37 (*ddddq*, *J* = 5.6, 6.8, 6.8, 6.8, 6.8, CH); 1.07 (*d*, *J* = 6.8, Me). ^{13}C-NMR (100 MHz, D_2O): 130.5; 129.9; 129.7; 129.3; 55.0; 51.9; 51.5; 27.8; 17.6. HR-MS-ESI: 244.1005 ($[M+H]^+$, $C_{11}H_{17}NO_3S^+$; calc. 244.1007).

3-[Bis(phenylmethyl)amino]propane-1-sulfonic Acid (**6l**): Yellow oil. Yield 970 mg (76%). IR: 3424 (br., OH), 1215 (SO), 1151 (SO). ^{1}H-NMR (400 MHz, D_2O): 7.45–7.32 (*m*, 10 arom. H); 4.22 (*s*, 2 CH_2); 3.16 (*t*, *J* = 8.1, CH_2N); 2.75 (*t*, *J* = 7.2, CH_2N); 2.11 (*tt*, *J* = 7.2, 8.1, CH_2). ^{13}C-NMR (100 MHz, D_2O): 131.0; 130.2; 129.4; 128.9; 57.1; 51.1; 47.9; 19.2. HR-MS-ESI: 320.1313 ($[M+H]^+$, $C_{17}H_{21}NO_3S^+$; calc. 320.1315).

5. N-*Cbz-Protected Homotaurine* **8** *and Homotaurine* **6a**. *Method A:* To a suspension of $LiAlH_4$ (1.52 g, 40 mmol) in dried THF (30 ml) was added a soln. of **4a** (588 mg, 4 mmol) in dried THF (5 ml), dropwise under stirring at 0°. The resulting soln. was heated to reflux for 24 h and then cooled to 0°. The excess $LiAlH_4$ was carefully quenched with H_2O (10 ml) under stirring at r.t. After filtration, benzyl carbonochloridate (1.36 g, 8 mmol) and Et_3N (2.20 g, 20 mmol) were added to the filtrate. The resulting mixture was stirred at r.t. for 12 h. After evaporation of the solvent, the residue was subjected to CC: **7** (144 mg, 16%). To a soln. of **7** (338 mg, 1.5 mmol) in HCOOH (10 ml) was added a mixture of HCOOH (10 ml) and 30% H_2O_2 soln. (5 ml), dropwise under stirring at r.t. After stirring for 12 h and evaporation of the solvent below 45°, the residue was crystallized from MeOH/H_2O to give **8** (224 mg, 55%); from the mother liquor, **6a** (17 mg, 8%) was obtained. If the solvent was evaporated above 45° after the reaction, **6a** was obtained in 64% yield (134 mg).

Method B: Thioacetate **4a** (588 mg, 4 mmol) was reduced with $LiAlH_4$ and treated with benzyl carbonochloridate as described above. After evaporated of the solvent, the residue, crude **7**, was oxidized directly to afford **6a** (123 mg, 22% overall yield from **4a**).

Phenylmethyl N-*(3-Sulfanylpropyl)carbamate* (**7**): Colorless crystals. M.p. 91–92° ([6]: 91–92°). ^{1}H-NMR (400 MHz): 7.34–7.26 (*m*, 5 arom. H); 5.08 (*s*, PhCH_2); 3.29 (*q*, *J* = 6.8, CH_2N); 2.70 (*t*, *J* = 6.8, CH_2S); 1.90 (*quint.*, *J* = 6.8, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): 156.4; 136.5; 128.4; 128.1; 66.6; 39.6; 35.8; 29.3.

3-{[(Phenylmethoxy)carbonyl]amino}propane-1-sulfonic Acid (**8**) [41]: Colorless crystals. M.p. 90–91°. IR: 3427 (br., NH, OH), 1732 (CO), 1325 (SO), 1167 (SO). ^{1}H-NMR (400 MHz): 7.43–7.30 (*m*, 5 arom. H); 5.30 (*s*, PhCH_2); 3.82 (*t*, *J* = 6.8, CH_2S); 3.34 (*t*, *J* = 6.8, CH_2N); 2.39 (*quint.*, *J* = 6.8, CH_2). ^{13}C-NMR (100 MHz): 150.8; 135.0; 128.5; 128.4; 127.9; 68.6; 49.4; 45.2; 18.6.

3-Aminopropane-1-sulfonic Acid (= Homotaurine; **6a**): Colorless crystals. M.p. 292–294° ([39]: 294–295°). ^{1}H-NMR (400 MHz, D_2O): 3.08 (*t*, *J* = 7.6, CH_2S), 2.94 (*t*, *J* = 7.6, CH_2N), 2.04 (*quint.*, *J* = 7.6, CH_2).

6. *3-(Acetylsulfanyl)-3-phenylpropanoic Acid* (**9d**): To a refluxing soln. of cinnamic acid (**1d**; 2.964 g, 20 mmol) in benzene (40 ml) was added thioacetic acid (2.1 ml, 2.28 g, 30 mmol), dropwise under stirring. The resulting soln. was heated to reflux for 4 h. After evaporation of the solvent, the residue was subjected to CC: **9d** (3.40 g, 76%). Colorless oil ([42]: M.p. 95–96°). ^{1}H-NMR (400 MHz): 7.32–7.24 (*m*,

5 arom. H); 5.03 (*dd*, *J* = 6.8, 8.4, CH); 3.29 (*d*, *J* = 6.8, 1 H of CH_2); 3.27 (*d*, *J* = 8.4, 1 H of CH_2); 2.30 (*s*, Me).

7. *Mixed Anhydride of* **9d** *and Subsequent Ammonolysis.* To a soln. of **9d** (3.392 g, 15 mmol) and Et_3N (2.2 ml, 1.52 g, 15 mmol) in dried CH_2Cl_2 (30 ml) was added ethyl carbonochloridate (1.5 ml, 1.63 g, 15 mmol), dropwise under stirring at 0°. The resulting soln. was stirred for 30 min to generate the mixed anhydride **10d**, which was directly treated with 25% aq. NH_3 soln. (4 ml). The mixture was stirred for 2 h. The org. phase was separated, the aq. phase extracted with AcOEt (3 × 25 ml), the combined org. phase washed with sat. NaCl soln. (3 × 25 ml) and dried (Na_2SO_4), the solvent evaporated, and the residue subjected to CC: *cinnamamide (=(2*E*)-3-phenylprop-2-enamide* (**3d**; 1.92 g, 87%). Colorless crystals. M.p. 152–153° ([28]: 148–151°). ^{1}H-NMR (400 MHz): 7.65 (*d*, *J* = 15.6, CH); 7.52–7.36 (*m*, 5 arom. H); 6.47 (*d*, *J* = 15.6, COCH); 5.84 (br. *s*, NH_2).

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