Synthesis and Crystal Structure of 3,3,6,6-Tetramethylmorpholine-2,5-dione, and Its 5-Monothioxo and 2,5-Dithioxo Derivatives

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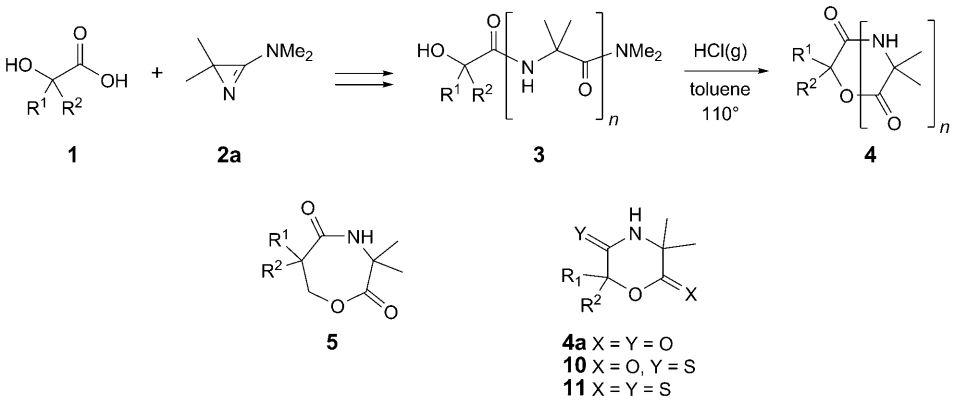
The synthesis of 3,3-dimethylmorpholine-2,5-diones **4a** was achieved conveniently *via* the 'direct amide cyclization' of the linear precursors of type **3**, which were prepared by coupling of 2,2-dimethyl-2*H*-azirin-3-amines **2** with 2-hydroxyalkanoic acids **1**. Thionation of **4a** with *Lawesson*'s reagent yielded the corresponding 5-thioxomorpholin-2-ones **10** and morpholine-2,5-dithiones **11**, respectively, depending on the reaction conditions. The structures of **3aa**, **4aa**, **10a**, and **11a** were established by X-ray crystallography. All attempts to prepare S-containing morpholine-2,5-dione analogs or thiomorpholine-2,5-diones by cyclization of corresponding S-containing precursors were unsuccessful and led to various other products. The structures of some of them have also been established by X-ray crystallography.

Introduction. – In the last 30 years, we have demonstrated that the 'direct amide cyclization' [1] is a useful method for the synthesis of cyclodepsipeptides, which contain α,α-disubstituted α-amino acids, *e.g.*, α-aminoisobutyric acid (Aib) [2]. The combination with the 'azirine/oxazolone method' [3] for the preparation of the linear precursors offers a convenient and efficient access to this class of compounds. For example, the reaction sequence starting with an α-hydroxy acid **1** and azirine **2a** yielding compound **3** ($n=1$), followed by repeated hydrolysis and azirine coupling, and finally cyclization leads to cyclodepsipeptides of type **4** with 6-, 9-, 12-, and 15-membered rings [1b] (*Scheme 1*). Analogously, 16- and 19-membered cyclodepsipeptides are accessible from β-hydroxy acids [4]. Furthermore, cyclodepsipeptides with an alternating sequence of α-hydroxy and α,α-disubstituted α-amino acids can be prepared by coupling segments of type **3**, followed by 'direct amide cyclization' [1c][5].

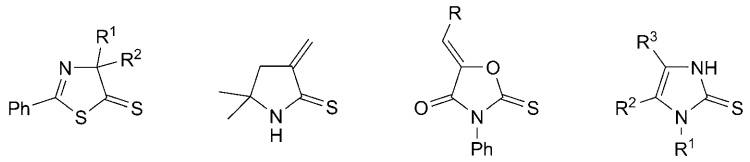
The synthesis and stability of morpholine-2,5-diones (**4a**), which are the smallest cyclodepsipeptides, was studied already 60 years ago [6]. But only in the last couple of years have these compounds attracted increasing interest as natural products [7], biologically active compounds [8], and particularly as monomers of biodegradable polymers [9]. There are three types of cyclization leading to **4a**, *i.e.*, lactonization, lactamization, and cyclization of *N*-(2-bromoacetyl)glycine sodium salts (for reviews, see [10]). In the case of α,α-disubstituted glycines, a very simple and efficient protocol is the 'direct amide cyclization' of **3** ($n=1$) [1b]. Surprisingly, all attempts to prepare the analogous seven-membered 1,4-oxazepane-2,5-diones **5** by the same method failed, and only the 14-membered cyclodimers were obtained [11].

[1]) Stay at the University of Zürich, 09.2000 – 09.2001.
[2]) Diploma thesis, University of Zürich, 2000.

Scheme 1



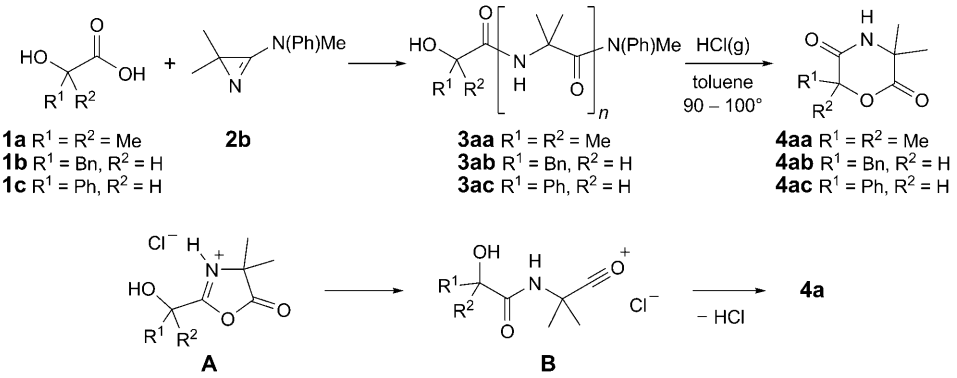
In connection with our interest in heterocyclic thiones, *e.g.*, 1,3-thiazole-5(4*H*)-thiones **6** [12], 5,5-dimethyl-3-methylidenpyrrolidine-2-thione (**7**) [13], 5-benzylidene-3-phenylrhodanine (**8**) [14], and 1*H*-imidazole-2-thiones **9** [15], we became interested in thioxo analogs of morpholine-2,5-diones. Therefore, we studied various reactions toward the only scarcely known mono- and dithioxomorpholines of type **10** and **11**. Besides attempted cyclizations of thioxo derivatives of **3a** ($n=1$), the stepwise thionation of **4a** with *Lawesson*'s reagent [16] to yield 5-thioxomorpholin-2-ones **10** and morpholine-2,5-dithiones **11** was investigated.



Results and Discussion. – *Synthesis and Thionation of Morpholine-2,5-diones.* The reaction of α-hydroxy acids **1a**–**1c** with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**2b**) in MeCN at 0° → room temperature led to the diamides **3aa**–**3ac** in 95–96% yield (*Scheme 2*), in accordance with the general reactivity of 2*H*-azirin-3-amines [3a]. In comparison with the reactions of the corresponding 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amines [17], the reaction times were longer, but the yields were higher. The structures of the products have been established by their spectroscopic data and, in the case of **3aa**, by X-ray crystallography (*Fig. 1*).

The conformation of **3aa** is as expected for peptides containing Aib [19]: the torsion angles ϕ (C(2)–C(3)–N(4)–C(5)) and ψ (N(1)–C(2)–C(3)–N(4)) of the Aib unit are $-46.1(3)$ and $-49.0(3)°$, respectively, *i.e.*, close to the values for helical peptide structures (*e.g.*, *ca.* -47 and $-57°$ for the α-helix). Both amide groups are almost planar (C(3)–C(2)–N(1)–C(7): 178.6(2)°; C(3)–N(4)–C(5)–C(6): $-175.8(2)°$),

Scheme 2



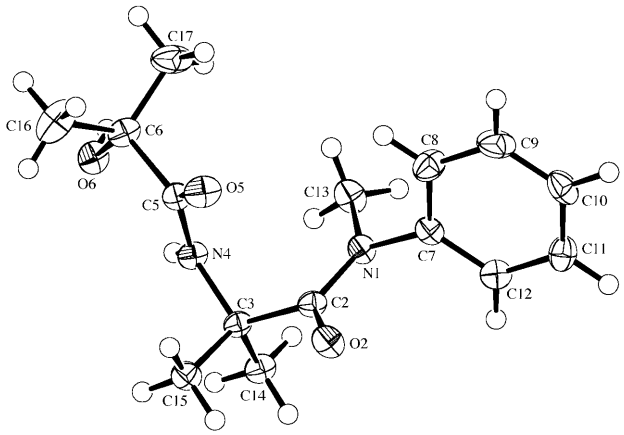


Fig. 1. *ORTEP Plot* [18] *of the molecular structure of* **3aa** (50% probability ellipsoids, arbitrary numbering of the atoms)

but the orientation of the Ph ring at N(1) is nearly orthogonal to the plane of the amide group (C(2)–N(1)–C(7)–C(8): −99.9(2)°). The N(4)–H group forms an intramolecular H-bond with the O(6)-atom of the OH group, thereby forming a five-membered loop with a graph set motif [20] of *S*(5). As a result, the torsion angle N(4)–C(5)–C(6)–O(6) is 9.5(3)°. The OH group forms an intermolecular H-bond with the amide O(5)-atom of a neighboring molecule, thereby linking the molecules into one-dimensional chains which run parallel to the [100] direction and have a graph set motif of *C*(5).

The cyclization of **3aa**–**3ac** to give the morpholine-2,5-diones **4aa**–**4ac** was performed according to the protocol described in [1b]: a stirred suspension[3]) of the diamides in dry toluene was heated to 90–100°, and a stream of dry HCl gas was

[3]) At the reaction temperature of *ca.* 100°, the diamides of type **3a** ($n=1$) were dissolved.

bubbled through the solution for 10–30 min. After removing the precipitated *N*-methylaniline hydrochloride and purification of the product by crystallization or chromatography, **4aa**–**4ac** [1b] were obtained in 61, 27, and 22% yield, respectively (*Scheme 2*)[4]). The elucidation of the structures was based on the spectroscopic[5]) and analytical data, and, in the cases of **4aa** (*Fig. 2*, *a*) and **4ab** [21], the structures were confirmed by X-ray crystallography.

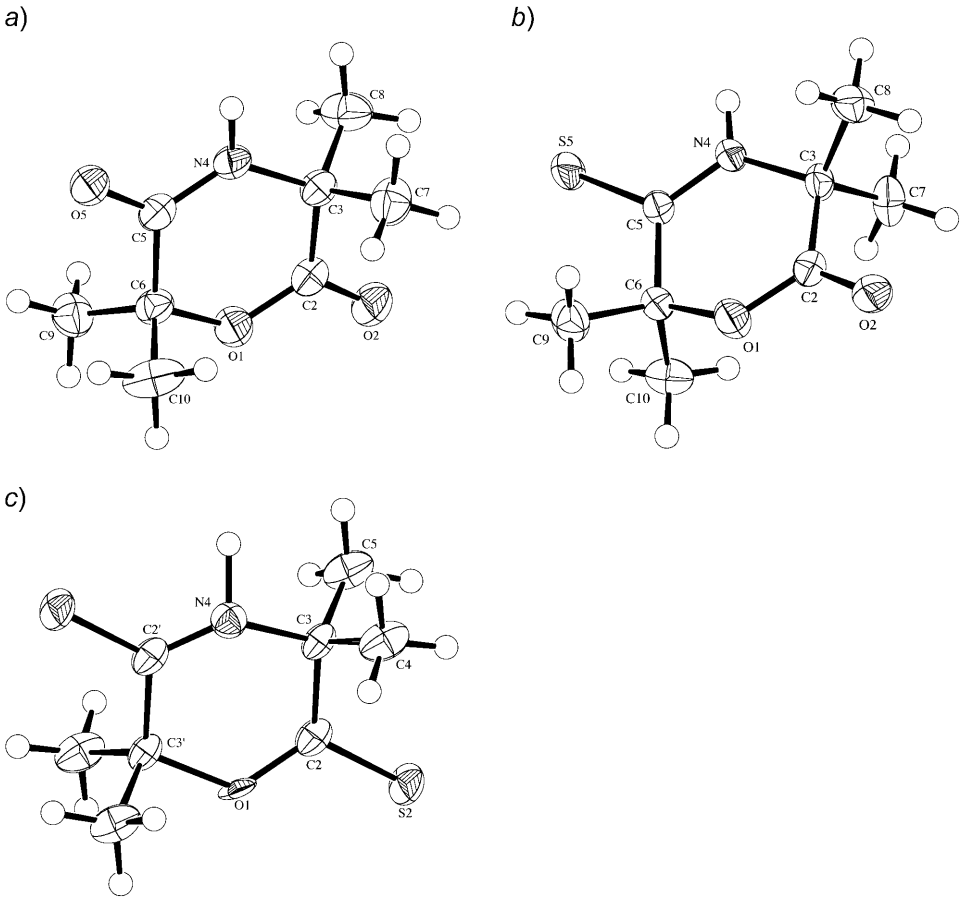


Fig. 2. *ORTEP Plots* [18] *of the molecular structures of* a) **4aa**, b) **10a** (polymorph 1), *and* c) **11a** (50% probability ellipsoids, arbitrary numbering of the atoms)

Conceivable intermediates for the acid-catalyzed cyclization of **3** to **4** are shown in *Scheme 2* (see also [1b]). In analogy to previously described 'direct amide cyclizations', we propose that the first step is the formation of a 1,3-oxazol-5(4*H*)-one **A** [2].

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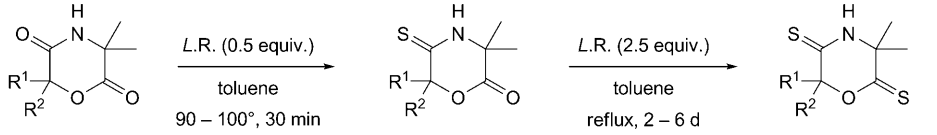
[4]) The cyclization of the corresponding *N*,*N*-dimethyl derivatives **3** ($n = 1$) yielded the morpholin-2,5-diones **4aa**–**4ac** in 87, 30, and 75% yield, respectively [1b].

[5]) The previously reported ^{13}C chemical shift of C(2) of **4ac** proved to be incorrect. The signals of the two C=O groups appear at 169.1 and 165.3 ppm (*Table 1*).

Whereas, in analogous intermediates with a longer tether between the oxazolone ring and the nucleophilic group, the attack at C(5) may occur directly, this seems not possible in the present case. Therefore, the ring opening to give the acylium ion **B**, which cyclizes *via* formation of the lactone group, is a likely process.

The thionation of morpholine-2,5-diones **4aa**–**4ac** with 0.5 equiv. *Lawesson*'s reagent (*L.*R.; 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide) in toluene at 90–100° for 20–30 min gave the thiolactams **10a**–**10c**, respectively, in 68–98% yield as the sole products (*Scheme 3*). The observed selectivity confirms the generally known reactivity of C=O compounds on thionations with *L.*R. [16], *i.e.*, thionations of amides (lactams) are faster than those of esters (lactones). The structures have been deduced from the spectroscopic data. The most characteristic differences to those of **4aa**–**4ac**, in addition to elemental analyses, are the missing C=O absorption at *ca.* 1680 cm^{-1} in the IR spectrum and the absorption of C(5)=S at 193–200 ppm in the ^{13}C-NMR spectrum (*Table 1*). Furthermore, X-ray crystal-structure determinations were performed in the cases of **10a** (*Fig. 2*, *b*) and **10b** [21].

Scheme 3



4aa $R^1 = R^2 = Me$
4ab $R^1 = Bn$, $R^2 = H$
4ac $R^1 = Ph$, $R^2 = H$

10a $R^1 = R^2 = Me$
10b $R^1 = Bn$, $R^2 = H$
10c $R^1 = Ph$, $R^2 = H$

11a $R^1 = R^2 = Me$
11b $R^1 = Bn$, $R^2 = H$

*L.*R. = *Lawesson*'s reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide)

Table 1. *Characteristic Spectroscopic Data of Compounds* **4a**, **10**, *and* **11**

Compound	IR (KBr) [cm^{-1}][a])		^{13}C-NMR ($CDCl_3$) [ppm]		EI-MS $M^{+\cdot}$ [m/z (%)]
	C(2)=O	C(5)=O	C(2)	C(5)	
4aa	1743 (1750)	1677 (1680)	170.2	169.8	172 (100)[b])
4ab	1746 (1748)	1686 (1680)	169.5	166.2	233 (18) [1b]
4ac	1747 (1740)	1682 (1690)	169.1	165.3	219 (19) [1b]
10a	1738	–	169.4	200.5	188 (100)[b])
10b	1749	–	168.3	193.7	249 (100)
10c	1742	–	169.7	192.7	235 (100)
12a	–	–	216.8	199.9	203 (7)
12b	–	–	215.2	193.3	265 (4)

[a]) Values in brackets from [1b]. [b]) CI-MS (NH_3): $[M+1]^+$.

The thionation of the lactone group of **10a** and **10b** has been achieved under more drastic conditions [22]: suspensions of **10a** and **10b**, and 2.5 equiv. of *L.*R. in toluene were heated to reflux for 2–6 d leading to morpholine-2,5-dithiones **11a** and **11b** in 49 and 28% yield, respectively, as yellow crystalline materials. Again, the structures have

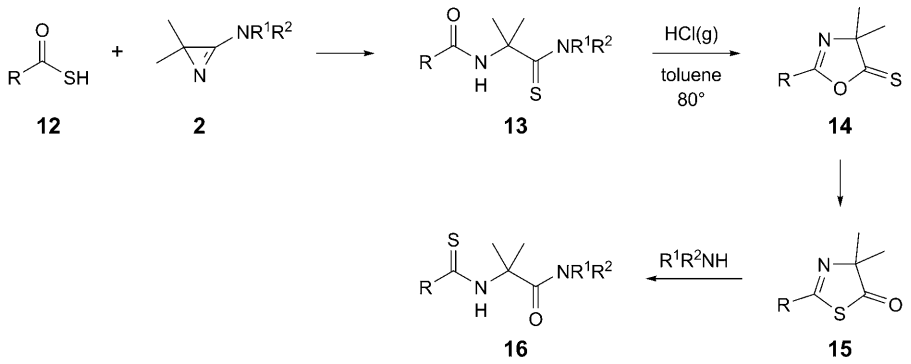
been determined on the basis of the spectroscopic data (*Table 1*) and confirmed by X-ray crystal-structure determinations (**11a** (*Fig. 2,c*), **11b** [21]).

The six-membered rings of **4aa** and **10a** (polymorph 1) have a conformation midway between that of a highly flattened boat and a twist-boat, where C(6) shows the most significant deviation from the ring plane. The N(4)–H group forms an intermolecular H-bond with the amide O(5)-atom and the S(5)-atom, respectively, of a neighboring molecule. This interaction forms closed loops, thereby linking pairs of molecules into centrosymmetric dimers, which have a graph set motif [20] of $R_2^2(8)$ (for a similar structure, see [21]). In another crystallization of **10a**, a second polymorph was obtained, in which two symmetry-independent molecules are in the asymmetric unit. The six-membered ring in each molecule has a flattened boat conformation. The N–H group in molecule A forms an intermolecular H-bond with the S-atom of a neighboring molecule A. This interaction forms closed loops, thereby linking pairs of molecules of type A into centrosymmetric dimers, which have a graph set motif of $R_2^2(8)$. The molecules of type B form the same type of centrosymmetric dimers.

In the dithione **11a**, the molecule sits across a crystallographic center of inversion. Thus, the O-atom and NH group are necessarily disordered in the model with equal site occupation factors of 0.5. The proximity of the N- and O-atoms in the model makes it difficult to accurately refine their positions. Therefore, some of the bond lengths involving these atoms are only approximate, and a reliable analysis of the ring conformation is not achievable. The N(4)–H group forms an intermolecular H-bond with the S(2)-atom of a neighboring molecule. This interaction links the molecules into infinite one-dimensional chains, which run parallel to the [101] direction and have a graph set motif of $C(5)$. The centrosymmetric disorder in the molecules results in disorder also of these chains, which run in one direction in one orientation of the disorder and in the opposite direction in the alternate disordered orientation.

Attempted Cyclizations of S-Containing Diamides. In the past, we have shown that the reaction of 2*H*-azirin-3-amines of type **2** with thio acids **12** leads to monothiodiamides **13** with a terminal thioamide group [23] (*Scheme 4*). Under acidic conditions, the latter cyclize to 1,3-oxathiazole-5(4*H*)-thiones **14**, which undergo a spontaneous isomerization to yield 1,3-thiazol-5(4*H*)-ones **15**. Treatment of **15** with Me_2NH gave the

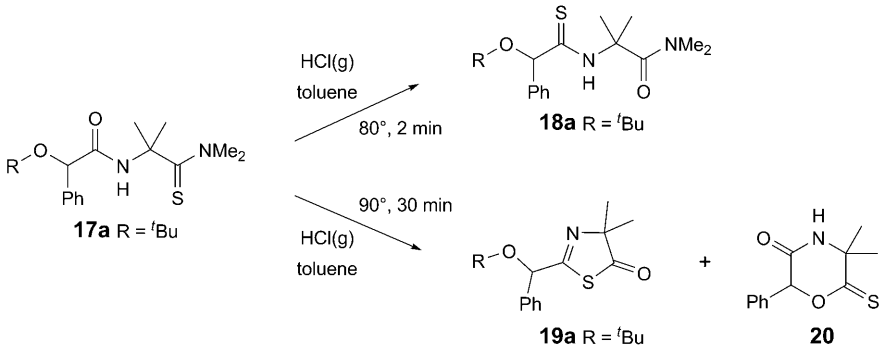
Scheme 4



monothiodiamides of type **16** ($R^1 = R^2 = Me$). Under modified conditions, a one-pot isomerization **13** → **16** was elaborated. This reaction sequence was used for the selective synthesis of Aib-containing endothiopeptides [23d][24].

In [23d], we described the acid-catalyzed reactions of compounds **17** (R = ^{t}Bu, THP (= tetrahydro-2*H*-pyran-2-yl)). Whereas the treatment of a solution of **17a** (R = ^{t}Bu) in dry toluene at 80° with HCl gas for 2 min gave the isomeric product **18a** in 53% yield, an analogous reaction (30 min, 90°) led to a mixture of 1,3-thiazol-5(4*H*)-one **19a** (60%) and 2-thioxomorpholin-5-one **20** (6%; *Scheme 5*). The latter was obtained in 30% yield *via* deprotection of the THP derivative **17b** (R = THP) and subsequent acid-catalyzed cyclization (toluene, 90°, HCl gas).

Scheme 5



With these results in mind, we attempted to synthesize S-analogues of morpholine-2,5-diones *via* acid-catalyzed cyclization of suitable S-containing precursors. In a first experiment, the crude THP-protected mandelic thioacid **21** was reacted with azirine **2b** to give the desired monothiodiamide **22** in 52% yield (*Scheme 6*). As an unexpected minor product (20%), **23** was obtained, the structure of which was established by X-ray crystallography (*Fig. 3*). Since the space group is centrosymmetric, the crystals are racemic. The amide NH group forms an intramolecular H-bond with O(7) of the carbonate group, thereby forming a five-membered ring with a graph set motif of $S(5)^6$).

Deprotection of **22** to give **24** was achieved in quantitative yield by treatment with pyridinium *para*-toluenesulfonate (PPTS) in EtOH (*Scheme 6*). With the aim of preparing the 2-thioxomorpholin-5-one **20** (*Scheme 5*), HCl gas was bubbled through a solution of **24** in dry toluene at 100–110° for 20 min, leading to a complex mixture of products. Chromatographic workup gave, in addition to 33% of the starting material **24**, three isomeric products in *ca.* 26, 12, and 6% yield, with the mass of the expected **20** (ESI-MS: *m*/*z* 236 ($[M+1]^+$)). Unfortunately, the spectroscopic data of the two main isomers do not fit those of **20**, and the structures of the products are not known so far.

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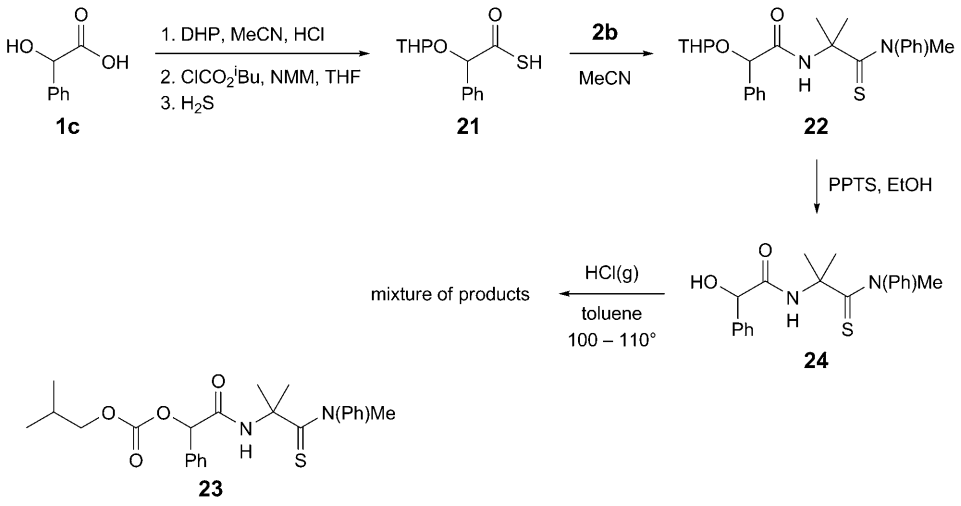
6) The formation of **23** may be explained *via* the exchange of the THP protecting group for the (isobutyloxy)carbonyl group in the conversion of mandelic acid (**1c**) to **21** or an incomplete THP protection of **1c** and its twofold reaction with $ClCO_2{}^i$Bu and *N*-methylmorpholine (NMM, see below).

Scheme 6



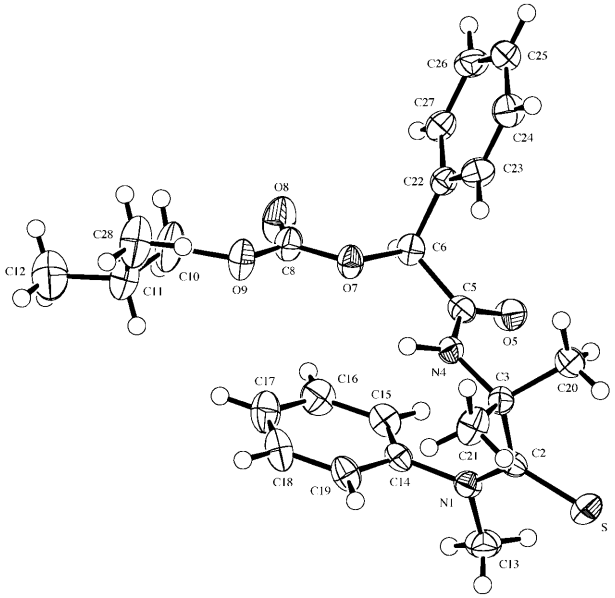
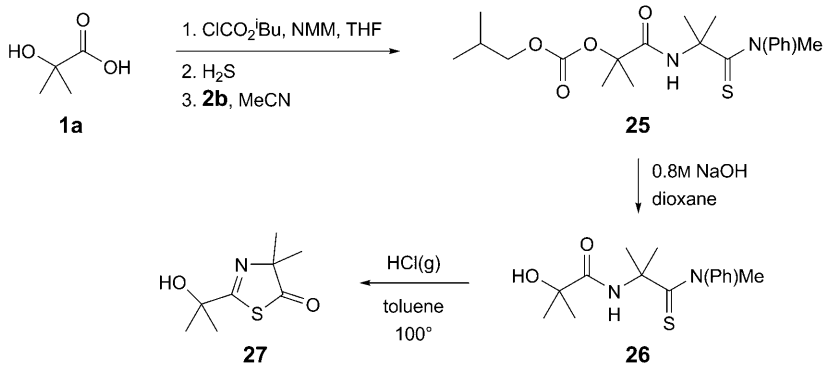


Fig. 3. *ORTEP Plot* [18] *of the molecular structure of* **23** (50% probability ellipsoids, arbitrary numbering of the atoms)

In a similar reaction as shown in *Scheme 6*, the conversion of 2-hydroxyisobutyric acid (**1a**) to the O-protected monothiodiamide **25** was achieved in 92% yield (*Scheme 7*). In this case, the protection of the OH group and the activation of the carboxylic function of **1a** were accomplished simultaneously by treatment with

Scheme 7



$ClCO_2{}^{i}Bu$ and NMM. Deprotection of the OH group with 0.8M NaOH in dioxane yielded **26** (85%), the precursor for the cyclization, whose structure was established by X-ray crystallography (*Fig. 4*).

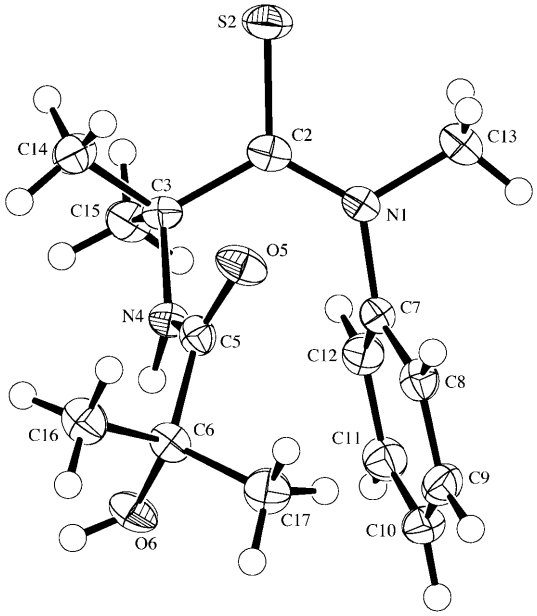


Fig. 4. *ORTEP Plot* [18] *of the molecular structure of one of the three independent molecules of* **26** (50% probability ellipsoids, arbitrary numbering of the atoms)

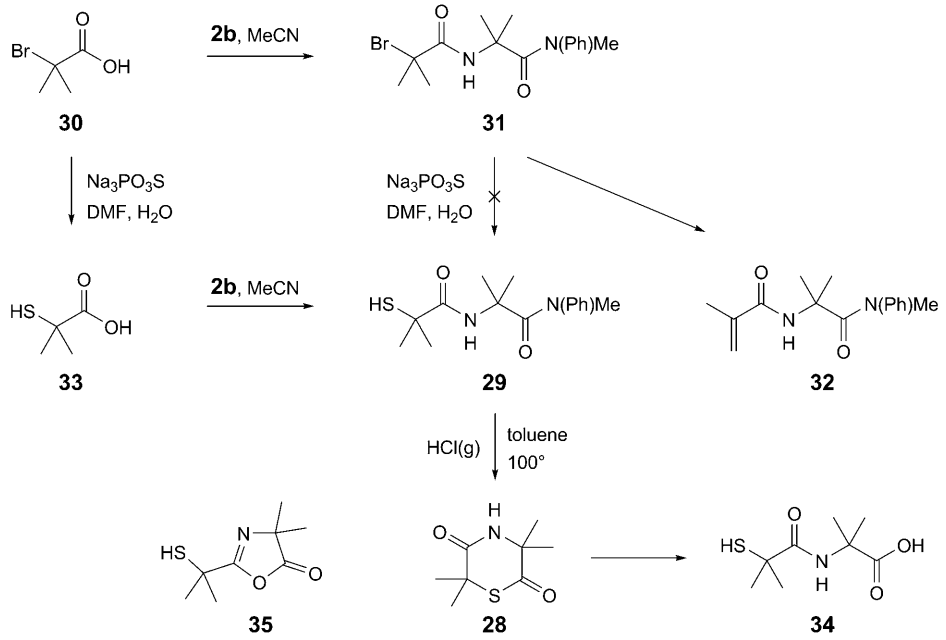
There are three symmetry-independent molecules of **26** in the asymmetric unit, but their conformations differ only very slightly, the main difference being slightly different orientations of the Ph ring. In each molecule, the amide NH group forms an intramolecular H-bond with the O-atom of the OH group, thereby creating a five-membered loop with a graph set motif of $S(5)$. The OH group forms an intermolecular

H-bond with the amide O-atom of a neighboring symmetry-independent molecule and thereby links the three independent molecules into infinite one-dimensional chains. These chains run parallel to the [110] direction and are composed of repeating $\cdots A \cdots B \cdots C \cdots$ units, which produce a tertiary graph set motif of $C_3^3(15)$.

The cyclization of **26** under the usual conditions of the 'direct amide cyclization', *i.e.*, by bubbling dry HCl gas through a suspension of **26** in toluene at 100°, led also to a complex mixture of products, and chromatographic workup gave, unexpectedly, the 1,3-thiazol-5(4*H*)-one **27** in 20% yield (*Scheme 7*). In addition, traces of **10a** (*Scheme 3*) were detected, but none of the desired 3,3,6,6-tetramethyl-2-thioxomorpholin-5-one of type **20**. The formation of **27** may be rationalized by the cyclization of **26** to give the corresponding 1,3-oxazole-5(4*H*)-thione and subsequent rearrangement to **27** as shown in *Scheme 4*.

To prepare thiomorpholine-2,5-dione **28** *via* acid-catalyzed cyclization of **29**, 2-bromoisobutyric acid (**30**) was reacted with **2b** to afford **31** in 97% yield (*Scheme 8*). The replacement of Br with the SH group was attempted by treatment of **31** with Na_3PO_3S according to the method described in [25]. Unfortunately, no **29** was obtained, and the only product, isolated in 28% yield as colorless plates, was **32**. Most likely, it was formed from **31** by elimination of HBr.

Scheme 8



The structure of **32** was established by X-ray crystallography (*Fig. 5,a*). The space group is non-centrosymmetric, but achiral. The NH group forms an intermolecular H-bond with the amide O(5)-atom of a neighboring molecule, thereby linking the

molecules into infinite one-dimensional chains, which run parallel to the [001] direction and have a graph set motif of $C(4)$.

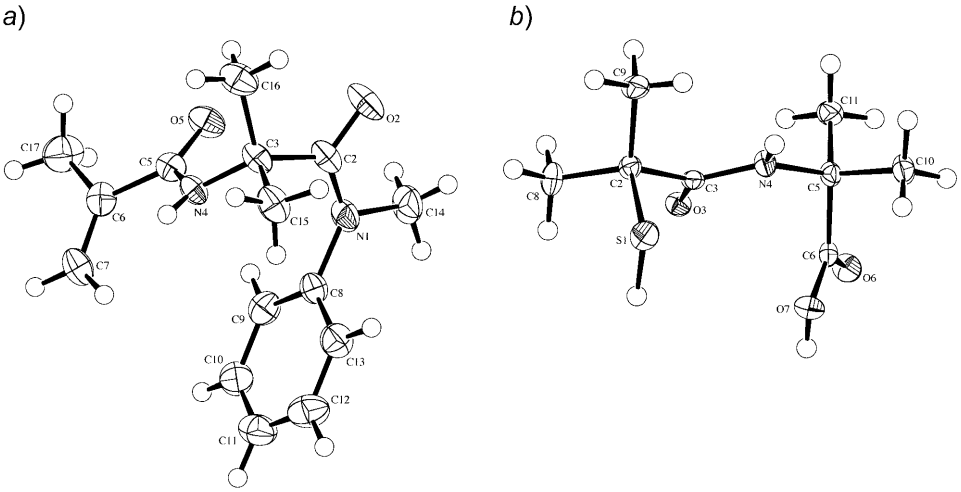


Fig. 5. *ORTEP Plots* [18] *of the molecular structures of* a) **32** *and* b) **34** (50% probability ellipsoids, arbitrary numbering of the atoms)

Finally, the sulfanyl diamide **29** was obtained in 95% yield from the reaction of 2-sulfanylisobutyric acid (**33**) [25] with **2b** in MeCN at room temperature (*Scheme 8*). Unfortunately, the conversion of the Br compound **30** to the sulfanyl derivative **33** was achieved in only 22% yield and was the yield-limiting step (see [25]). The cyclization of **29** was attempted under the conditions of the 'direct amide cyclization', *i.e.*, a stream of dry HCl gas was bubbled through a suspension of **29** in toluene at 100° for 15 min. After usual workup, the crude solid product, which was assumed to be **28**, was purified by chromatography to give the sulfanyl acid **34** in 60% yield (*Scheme 8*).

The unexpected structure of the product was again established by X-ray crystallography (*Fig. 5*, *b*). The carboxylic OH group forms an intermolecular H-bond with the amide O(3)-atom of a neighboring molecule. This interaction links pairs of molecules across a center of inversion into dimers, which have a graph set motif of $R_2^2(7)$. The SH group forms an intermolecular H-bond with the C=O O(6)-atom of the COOH group of the same neighboring molecule and so forms a second set of links between the H-bonded dimers. This latter interaction has a graph set motif of $R_2^2(8)$. The amide NH group is not involved in any H-bonding interactions.

The formation of **34**, which is the product of the hydrolysis of the terminal amide group of **29**, may be explained *via* the acid-catalyzed intramolecular condensation to give the 1,3-oxazol-5(4*H*)-one **35** (*Scheme 8*) and subsequent hydrolytic ring opening. This reaction sequence, *i.e.*, the selective cleavage of the terminal amide group in Aib peptides, is generally observed by treatment of peptides of type **29** with acids in aqueous media [17][26]. It is the basis of the 'azirine/oxazolone method' in peptide synthesis. On the other hand, it has been shown that, under anhydrous conditions, the formed 1,3-oxazol-5(4*H*)-ones are stable and can be isolated [23a]. Therefore, it may

be assumed that **34** is the product of the hydrolytic ring opening of the desired thiomorpholine-2,5-dione **28**, which, in analogy to the synthesis of morpholine-2,5-diones **4** (*Scheme 2*), is formed from **29** *via* **35** (*Scheme 8*).

In conclusion, a convenient synthesis of 3,3-dimethylmorpholine-2,5-diones was elaborated by a combination of the 'azirine/oxazolone method' and the 'direct amide cyclization'. The corresponding 5-monothioxo and 2,5-dithioxo derivatives are accessible *via* stepwise thionation with *Lawesson*'s reagent. On the other hand, attempted cyclizations of S-containing linear precursors were not successful and led to mixtures of products. Whereas 1,3-oxazol-5(4*H*)-ones of type **A** (*Scheme 2*) under acidic conditions are prone to undergo the ring enlargement to give 3,3-dimethylmorpholine-2,5-diones **4**, the corresponding 1,3-thiazol-5(4*H*)-ones of type **27** (*Scheme 7*) are stable under the conditions of the 'direct amide cyclization' and do not show any tendency for a ring-enlargement reaction.

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Experimental Part

1. *General.* Solvents were purified by standard procedures. TLC: aluminium sheets, silica gel *60* F_{254} (SiO_2; *Merck*). Prep. TLC: glass plates, SiO_2 *60* F_{254} (2 mm; *Merck*). Column chromatography (CC): SiO_2 C-*560* (0.04–0.063 mm; *Uetikon-Chemie*). Medium-pressure liquid chromatography (MPLC): *LiChroprep Si 60*, 15–25 μm (*Merck*); column: *Kron-Lab 4/98-Pro*, 480 × 30 mm or *Labomatic*, 380 × 20 mm. M.p.: *Mettler-FP-5* or *Büchi B-450* apparatus; uncorrected. IR Spectra: *Perkin-Elmer 781* or *Perkin-Elmer Spectrum one* FT-IR spectrophotometer; in KBr unless otherwise stated; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker-AC-300* or *Bruker-ARX-300* instrument (300 and 75.5 MHz, resp.), in $CDCl_3$; multiplicity of C-atoms from DEPT spectra; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Finnigan MAT-90*, *Finnigan SSQ-700* (EI and CI), or *Finnigan TSQ-700* instrument (ESI); in *m*/*z* (rel. %). Elemental analyses were performed by the Mikroanalytisches Laboratorium des Organisch-chemischen Instituts der Universität Zürich (*Elementar Vario EL* instrument).

General Procedure 1 (*GP 1*). *Coupling of 2*H-*Azirin-3-amines with Carboxylic and Thiocarboxylic Acids.* To a stirred soln. of the acid in MeCN at 0°, *2,2,*N-*trimethyl*-N-*phenyl-2*H-*azirin-3-amine* (**2b**) was added dropwise. The mixture was stirred at r.t. for 2–22 h, and then diluted with Et_2O. The precipitate was filtered off and purified by chromatography or recrystallization.

General Procedure 2 (*GP 2*). *Direct Amide Cyclization.* A stirred suspension of a dipeptide in dry toluene was heated up to 90–100° under N_2. A strong stream of dry HCl gas was bubbled through the soln. for 10–30 min at the chosen temp. The resulting soln. was purged with N_2 for 30 min to remove remaining HCl, the toluene was evaporated, and THF/Et_2O 1:1 (10 ml) was added to the residue. After 30 min of stirring at r.t., the precipitated Me(Ph)NH·HCl was removed by filtration, followed by evaporation of the solvent, to yield a solid crude product, which was purified by chromatography.

General Procedure 3 (*GP 3*). *Monothionation with* Lawesson's *Reagent* (*L.*R.). A stirred suspension of 1 equiv. of a morpholine-2,5-dione **4** and 0.5 equiv. of *L.*R. in dry toluene was heated to 90–100°, until a clear soln. was obtained. Then, the soln. was heated to reflux for 30 min. By cooling the mixture to r.t., remaining *L.*R. precipitated and was removed by filtration. After evaporation of the toluene, the residue was purified by CC.

General Procedure 4 (*GP 4*). *Dithionation with* Lawesson's *Reagent* (*L.*R.). A stirred suspension of 1 equiv. of a 5-thioxomorpholin-2-one **10** and 2.5 equiv. of *L.*R. in dry toluene was heated to reflux for 2–6 d. By cooling the mixture to r.t., remaining *L.*R. precipitated and was removed by filtration. After evaporation of the toluene, the residue was purified by CC.

2. *Starting Materials.* Compound **2b** was prepared according to [27]. All other chemicals were commercially available.

3. *Azirine Coupling with 2-Hydroxy Acids.* 3.1. *2-(2-Hydroxy-2-methylpropanamido)*-N-*phenyl*-N,*2-dimethylpropanamide* (**3aa**). According to *GP 1:* 270.7 mg (4.8 mmol) of *2-hydroxyisobutyric acid* (**1a**) in MeCN (20 ml), 836.5 mg (4.8 mmol) of **2b**, stirring for 2 h at r.t. The product was purified by CC (SiO_2; CH_2Cl_2/MeOH 20:1) and recrystallized from MeCN. Yield: 1.2 g (95%). Colorless needles. M.p. 131–134°. IR: 3359*s*, 3059*w*, 3009*w*, 2992*m*, 2974*m*, 2930*s*, 1637v*s*, 1595*s*, 1525*s*, 1498*s*, 1463*m*, 1454*m*, 1399*s*, 1367*s*, 1357*s*, 1262*m*, 1226*m*, 1196*s*, 1180*m*, 1161*w*, 1126*s*, 1089*s*, 1070*m*, 1025*w*, 992*m*, 966*m*, 773*m*, 709*s*, 641*m*, 616*m*. ^{1}H-NMR: 7.40–7.24 (*m*, 5 arom. H); 7.15 (br. *s*, NH); 3.28 (*s*, MeN); 1.47, 1.35 (2*s*, 2 Me_2C). ^{13}C-NMR: 175.2, 173.4 (2*s*, 2 C=O); 144.7 (*s*, arom. C); 129.4, 128.2, 127.9 (3*d*, 5 arom. CH); 73.2, 57.9 (2*s*, 2 Me_2*C*); 41.4 (*q*, MeN); 27.4, 26.1 (2*q*, 2 *Me*$_2$C). ESI-MS: 579 (8, $[2\,M+Na]^+$), 301 (100, $[M+Na]^+$). Anal. calc. for $C_{15}H_{22}NO_3$ (278.40): C 64.73, H 7.97, N 10.10; found: C 64.83, H 8.10, N 10.37.

Recrystallization from MeCN by slow evaporation of the solvent yielded colorless needles suitable for the X-ray crystal-structure determination.

3.2. *2-(2-Hydroxy-3-phenylpropanamido)*-N-*phenyl*-N,*2-dimethylpropanamide* (**3ab**). According to *GP 1:* 408 mg (2.5 mmol) of DL-phenyllactic acid (**1b**) in MeCN (20 ml), 472 mg (2.7 mmol) of **2b**, stirring for 22 h at r.t. Purified by CC (SiO_2; CH_2Cl_2/Et_2O 6:1). Yield: 773 mg (92%). Colorless needles. M.p. 127–128°. IR: 3440*s*, 3324*s*, 2985*w*, 2932*w*, 1640v*s*, 1593*m*, 1527*s*, 1494v*s*, 1454*m*, 1394*s*, 1374*m*, 1285*m*, 1262*w*, 1206*m*, 1093*s*, 740*w*, 709*s*, 630*w*. ^{1}H-NMR: 7.43–7.14 (*m*, 10 arom. H); 6.46 (br. *s*, NH); 3.98–3.89 (*m*, PhCH$_2$C*H*); 3.25 (*s*, MeN); 3.05, 2.81 (*AB*-like, PhC*H*$_2$CH); 2.13 (*d*, *J* = 5, OH); 1.442, 1.439 (2*s*, Me_2C). ^{1}H-NMR (CD_3OD): 7.42–7.15 (*m*, 10 arom. H); 4.00–3.80 (*m*, PhCH$_2$C*H*); 3.21 (*s*, MeN); 3.03–2.75 (*AB* of *ABX*, J_{AB} = 13.8, J_{AX} = 7.7, J_{BX} = 4.0, PhC*H*$_2$CH); 1.39, 1.38 (2*s*, Me_2C). ^{13}C-NMR: 172.8, 171.2 (2*s*, 2 C=O); 144.8, 136.7 (2*s*, 2 arom. C); 129.5, 129.3, 128.4, 127.7, 126.8 (5*d*, 10 arom. CH); 72.9 (*d*, PhCH$_2$*C*H); 57.6 (*s*, Me_2*C*); 40.3 (*t*, Ph*C*H$_2$); 41.3 (*q*, MeN); 26.9, 26.1 (2*q*, *Me*$_2$C). ^{13}C-NMR (CD_3OD): 174.9 (*s*, 2 C=O); 146.2, 138.9 (2*s*, 2 arom. C); 130.8, 130.4, 129.0, 128.8, 128.5, 127.3 (6*d*, 10 arom. CH); 73.6 (*d*, PhCH$_2$*C*H); 58.2 (*s*, Me_2*C*); 41.5 (*t*, Ph*C*H$_2$); 41.3 (*q*, MeN); 27.0, 26.7 (2*q*, *Me*$_2$C). ESI-MS: 703 (20, $[2\,M+Na]^+$), 363 (12, $[M+Na]^+$), 341 (40, $[M+H]^+$), 234 (100).

3.3. *2-(2-Hydroxy-2-phenylacetamido)*-N-*phenyl*-N,*2-dimethylpropanamide* (**3ac**). According to *GP 1:* 152 mg (1 mmol) of DL-*mandelic acid* (**1c**) in MeCN (6 ml), 192 mg (1.1 mmol) of **2b** in MeCN (8 ml), stirring for 3 h at r.t. Yield: 310 mg (95%). Colorless needles. M.p. 149–150°. IR: 3340v*s*, 3060*w*, 3030*w*, 3010*w*, 2981*w*, 2914*w*, 1645v*s*, 1594*m*, 1520v*s*, 1492v*s*, 1455*m*, 1392*s*, 1373*m*, 1362*m*, 1373*w*, 1362*m*, 1327*m*, 1268*m*, 1227*m*, 1204*w*, 1190*w*, 1090*s*, 1066*m*, 744*w*, 710*s*, 697*m*. ^{1}H-NMR (CD_3OD): 7.42–7.20 (*m*, 10 arom. H); 4.18 (*s*, PhC*H*); 3.15 (*s*, MeN); 1.47, 1.45 (2*s*, Me_2C). ^{13}C-NMR (CD_3OD): 175.0, 174.0 (2*s*, 2 C=O); 145.4, 141.5 (2*s*, 2 arom. C); 130.4, 129.3, 129.0, 128.8, 128.5, 127.9 (6*d*, 10 arom. CH); 75.1 (*s*, Ph*C*H); 58.3 (*s*, Me_2*C*); 41.2 (*q*, MeN); 26.8, 26.6 (2*q*, *Me*$_2$C).

4. *Direct Amide Cyclization.* 4.1. *3,3,6,6-Tetramethylmorpholine-2,5-dione* (**4aa**) [1b]. According to *GP 2:* 500 mg (1.8 mmol) of **3aa** in dry toluene (100 ml), 90°, HCl gas for 30 min. The product was purified by CC (SiO_2; CH_2Cl_2/Et_2O 2:1) and recrystallized from toluene. Yield: 187 mg (61%). Colorless crystals. M.p. 139–140°. IR: 3354*s*, 3202*w*, 3073*w*, 2987*m*, 2932*m*, 1743v*s*, 1677*s*, 1643*s*, 1528*m*, 1472*s*, 1444*s*, 1385*w*, 1369*m*, 1326*s*, 1228*s*, 1201*m*, 1154v*s*, 988*m*, 859*m*, 692*w*. ^{1}H-NMR: 6.82 (br. *s*, NH); 1.75, 1.70 (2*s*, 2 Me_2C). ^{13}C-NMR: 170.2, 169.8 (2*s*, 2 C=O); 82.9 (*s*, C(6)); 56.3 (*s*, C(3)); 29.4, 27.0 (2*q*, 2 *Me*$_2$C). CI-MS (NH_3): 172 (100, $[M+H]^+$). Anal. calc. for $C_8H_{13}NO_3$ (171.20): C 56.13, H 7.65, N 8.18; found: C 55.91, H 7.57, N 8.23.

Recrystallization from toluene by slow evaporation of the solvent yielded colorless needles suitable for the X-ray crystal-structure determination.

4.2. *6-Benzyl-3,3-dimethylmorpholine-2,5-dione* (**4ab**) [1b][21]. According to *GP 2:* 2.19 g (6.44 mmol) of **3ab** in dry toluene (300 ml), 100°, HCl gas for 15 min. The product was purified by CC (SiO_2; CH_2Cl_2/Et_2O 6:1) and recrystallized from Et_2O. Yield: 407 mg (27%). Colorless needles. M.p. 164–165°. IR: 3190*s*, 3066*s*, 2920*s*, 1746v*s*, 1686v*s*, 1498*s*, 1429v*s*, 1388*s*, 1360*s*, 1340*s*, 1283v*s*, 1204*s*, 1160v*s*, 1072v*s*, 1045*s*, 1004*s*, 932*w*, 908*w*, 820*m*, 767*m*, 740v*s*, 693v*s*. ^{1}H-NMR: 7.34–7.24 (*m*, 5 arom. H); 5.13 (*dd*, *J* = 5.2, 4.5, PhCH$_2$C*H*); 3.37–3.24 (*AB* of *ABX*, J_{AB} = 14.4, J_{AX} = 5.2, J_{BX} = 4.5, PhC*H*$_2$CH); 1.49, 1.02 (2*s*, Me_2C). ^{13}C-NMR: 169.5, 166.2 (2*s*, 2 C=O); 134.7 (*s*, arom. C); 130.4, 128.7, 127.4 (3*d*, 5 arom. CH); 79.2 (*d*, C(6)); 55.5 (*s*, C(3)); 41.5 (*t*, Ph*C*H$_2$); 29.0, 27.9 (2*q*, *Me*$_2$C). CI-MS (NH_3): 252 (14), 251 (100, $[M+NH_4]^+$), 234 (15, $[M+H]^+$).

4.3. *6-Phenyl-3,3-dimethylmorpholine-2,5-dione* (**4ac**) [1b]. According to *GP 2:* 326 mg (1 mmol) of **3ac** in dry toluene (50 ml), 100°, HCl gas for 10 min. The product was recrystallized from Et_2O/pentane 1:2. Yield: 48 mg (22%). Colorless needles. M.p. 197–198°. IR: 3187*s*, 3083*s*, 3001*s*, 2975*s*, 2929*s*, 1747v*s*, 1682v*s*, 1607v*s*, 1501*s*, 1458v*s*, 1441v*s*, 1415v*s*, 1388*s*, 1372*s*, 1355*m*, 1316v*s*, 1301v*s*, 1284v*s*, 1211*m*, 1163v*s*, 1079*m*, 1042v*s*, 1011*s*, 931*m*, 911*m*, 859*s*, 806v*s*, 752v*s*, 697v*s*. ^{1}H-NMR: 7.43–7.30 (*m*, 5 arom. H); 5.84 (*s*, PhC*H*); 1.54, 1.30 (2*s*, Me_2C). ^{13}C-NMR: 169.1, 165.3 (2*s*, 2 C=O); 133.3 (*s*, arom. C); 128.2, 127.9, 125.2 (3*d*, 5 arom. CH); 78.9 (*d*, C(6)); 54.5 (*s*, C(3)); 27.6, 27.3 (2*q*, *Me*$_2$C).

5. *Thionation with* Lawesson's *Reagent.* 5.1. *3,3,6,6-Tetramethyl-5-thioxomorpholin-2-one* (**10a**). According to *GP 3:* 150 mg (0.876 mmol) of **4aa**, 177 mg (0.438 mmol) of *Lawesson*'s reagent (*L.*R.), dry toluene (10 ml), 90°, 30 min. Purification by CC (SiO_2; CH_2Cl_2/Et_2O 2:1). Yield: 164 mg (95%). Colorless crystals. M.p. 174–175°. IR: 3166*m*, 3041*m*, 3005*m*, 2996*m*, 2977*m*, 1738v*s*, 1557*s*, 1462*s*, 1440*m*, 1421*s*, 1378*w*, 1365*m*, 1329*s*, 1204*m*, 1184*m*, 1143*m*, 1051*s*, 982*s*, 966*m*, 826*m*, 668*m*, 658*w*. ^{1}H-NMR: 8.15 (br. *s*, NH); 1.84, 1.65 (2*s*, 2 Me_2C). ^{13}C-NMR: 200.5 (*s*, C(5)); 169.4 (*s*, C(2)); 82.8 (*s*, C(6)); 56.4 (*s*, C(3)); 29.3, 27.0 (2*q*, 2 *Me*$_2$C). CI-MS: 188 (100, $[M+H]^+$). Anal. calc. for $C_8H_{13}NO_2S$: (187.26): C 51.31, H 6.99, N 7.48, S 17.12; found: C 51.38, H 6.47, N 7.31, S 17.24.

Recrystallization from toluene by slow evaporation of the solvent yielded colorless prisms suitable for the X-ray crystal-structure determination. A second recrystallization, also from toluene, yielded crystals of a second polymorph.

5.2. *6-Benzyl-3,3-dimethyl-5-thioxomorpholin-2-one* (**10b**) [21]. According to *GP 3:* 276 mg (1.19 mmol) of **4ab**, 240 mg (0.59 mmol) of *L.*R., dry toluene (15 ml), 100°, 30 min. Purification by CC (SiO_2; CH_2Cl_2/pentane 3:2), recrystallized from CH_2Cl_2/Et_2O. Yield: 281 mg (96%). Colorless needles. M.p. 174–175°. IR: 3286v*s*, 3067*m*, 3033*m*, 3002*m*, 2956*w*, 1749v*s*, 1552v*s*, 1497*m*, 1469*s*, 1454*s*, 1437*m*, 1414*s*, 1386v*s*, 1373*m*, 1279v*s*, 1170v*s*, 1103*s*, 1074*s*, 1028*s*, 1009v*s*, 972*w*, 953*w*, 893*m*, 785*m*, 761*s*. ^{1}H-NMR: 7.35–7.24 (*m*, 5 arom. H); 5.55 (*t*-like, $J = 4.7$, PhCH$_2$C*H*); 3.65–3.48 (*AB* of *ABX*, $J_{AB} = 14.2$, $J_{AX} = 4.7$, $J_{BX} = 4.6$, PhCH_2CH); 1.58, 0.81 (2*s*, Me_2C). ^{13}C-NMR: 193.7 (*s*, C(5)); 168.3 (*s*, C(2)); 134.2 (*s*, 1 arom. C); 130.8, 128.8, 127.8 (3*d*, 5 arom. CH); 85.5 (*d*, C(6)); 57.3 (*s*, C(3)); 41.7 (*t*, Ph*C*H$_2$); 28.8, 27.0 (2*q*, *Me*$_2$C). EI-MS: 250 (14), 249 (100, M^+), 205 (15), 147 (11), 130 (23), 115 (26), 91 (51). Anal. calc. for $C_{13}H_{15}NO_2S$: (249.33): C 62.62, H 6.06, N 5.62, S 12.86; found: C 62.51, H 6.13, N 5.56, S 12.70.

5.3. *6-Phenyl-3,3-dimethyl-5-thioxomorpholin-2-one* (**10c**). According to *GP 3:* 90 mg (0.4 mmol) of **4ac**, 80 mg (0.2 mmol) of *L.*R., dry toluene (5 ml), 90–100°, 20 min. Purification by prep. TLC (SiO_2; CH_2Cl_2/pentane 3:2), recrystallized from toluene. Yield: 66 mg (68%). Colorless needles. M.p. 198–199°. IR: 3149*s*, 3027*s*, 2918*s*, 1742v*s*, 1548v*s*, 1499*m*, 1462v*s*, 1411v*s*, 1366*m*, 1327v*s*, 1305*s*, 1267*s*, 1204*s*, 1178*s*, 1119*s*, 1078*m*, 1010v*s*, 912*m*, 828*m*, 780*m*, 743v*s*, 695v*s*, 656*s*. ^{1}H-NMR ((D$_6$)DMSO): 7.45–7.38 (*m*, 5 arom. H); 4.58 (*s*, PhC*H*); 1.58, 1.43 (2*s*, Me_2C). ^{13}C-NMR ((D$_6$)DMSO): 192.7 (*s*, C(5)); 169.7 (*s*, C(2)); 137.1 (*s*, 1 arom. C); 128.7, 128.2, 127.8 (3*d*, 5 arom. CH); 84.7 (*d*, C(6)); 56.3 (*s*, C(3)); 26.5, 26.3 (2*q*, *Me*$_2$C). EI-MS: 236 (14), 235 (100, M^+), 134 (34), 107 (42), 105 (10), 101 (11), 100 (37), 86 (16), 84 (26), 77 (19).

5.4. *3,3,6,6-Tetramethylmorpholine-2,5-dithione* (**11a**). According to *GP 4:* 100 mg (0.53 mmol) of **10a**, 539 mg (1.34 mmol) of *L.*R., dry toluene (7 ml), reflux for 6 d. Purification by CC and prep. TLC (SiO_2; hexane/AcOEt 1:1), recrystallized from hexane/AcOEt 1:1. Yield: 49 mg (49%). Yellow crystals. M.p. 156–158°. IR: 3248*m*, 3165*s*, 3046*m*, 2974*m*, 2928*m*, 1742*w*, 1560v*s*, 1528*m*, 1465*s*, 1418*s*, 1361*m*, 1318v*s*, 1279*s*, 1185*m*, 1142*m*, 1109v*s*, 1044*s*, 967*m*, 907*m*, 819*m*, 762*m*, 654*m*, 599*m*. ^{1}H-NMR: 8.65 (br. *s*, NH); 1.82, 1.72 (2*s*, 2 Me_2C). ^{13}C-NMR: 216.8 (*s*, C(2)); 199.9 (*s*, C(5)); 91.4 (*s*, C(6)); 64.9 (*s*, C(3)); 32.9, 30.0 (2*q*, 2 *Me*$_2$C). EI-MS: 203 (7, M^+), 175 (21), 143 (58), 110 (9), 100 (11), 86 (100), 85 (21), 75 (21). Anal. calc. for $C_8H_{13}NOS_2$: (203.33): C 47.26, H 6.44, N 6.89, S 31.54; found: C 47.14, H 6.46, N 6.61, S 31.30.

Recrystallization from toluene by slow evaporation of the solvent yielded colorless prisms suitable for the X-ray crystal-structure determination.

5.5. *6-Benzyl-3,3-dimethylmorpholine-2,5-dithione* (**11b**) [21]. According to *GP 4:* 95 mg (0.38 mmol) of **10b**, 384 mg (0.95 mmol) of *L.*R., dry toluene (10 ml), reflux for 2 d. Purification by prep. TLC (SiO_2; CH_2Cl_2/hexane 1:1). Yield: 28 mg (28%). Yellow solid. M.p. 123–124°. IR: 3151*m*, 3031*s*, 2945*s*, 1752*w*, 1656*w*, 1570*s*, 1496*m*, 1467*m*, 1454*m*, 1435*m*, 1385*s*, 1351*m*, 1246*s*, 1215*s*, 1177*s*, 1152*s*, 1131*s*, 1093*m*, 1070*m*, 1035*m*, 1014*m*, 973*s*, 947*s*, 908*m*, 703*s*. ^{1}H-NMR: 8.61 (br. *s*, NH); 7.37–7.23 (*m*, 5

arom. H); 5.52 (*dd*, *J* = 5.6, 4.4, PhCH$_2$C*H*); 3.72–3.54 (*AB* of *ABX*, J_{AB} = 14.4, J_{AX} = 5.6, J_{BX} = 4.4, PhC*H*$_2$); 1.65, 1.16 (2*s*, Me$_2$C). ^{13}C-NMR: 215.2 (*s*, C(2)); 193.3 (*s*, C(5)); 134.4 (*s*, 1 arom. C); 130.8, 128.7, 127.6 (3*d*, 5 arom. CH); 87.2 (*d*, C(6)); 64.3 (*s*, C(3)); 41.2 (*t*, PhCH$_2$); 32.4, 31.6 (2*q*, *Me*$_2$C). EI-MS: 265 (4, M^+), 205 (21), 147 (20), 115 (39), 91 (51), 65 (14), 58 (100). CI-MS (NH_3): 266 (100, $[M+H]^+$), 234 (14), 232 (12), 208 (23), 206 (45). Anal. calc. for $C_{13}H_{15}NOS_2$: (265.39): C 58.83, H 5.69, N 5.28, S 24.16; found: C 58.71, H 5.45, N 5.03, S 24.02.

6. *Synthesis of Monothiodiamides and Attempted Acid-Catalyzed Cyclizations.* 6.1. *Synthesis of* N-*[1-Methyl-1-(*N-*methyl*-N-*phenylthiocarbamoyl)ethyl]-2-phenyl-2-[(tetrahydro-2*H*-pyran-2-yl)oxy]acetamide* (**22**). To a suspension of **1c** (304 mg, 2 mmol) in dry MeCN (5 ml) at 0° were added 3,4-dihydro-2*H*-pyrane (DHP; 195 mg, 2.3 mmol) and 0.04 ml of a 2M aq. HCl. The mixture was stirred for 3 h at r.t., the solvent was evaporated, and the residue was dried *in vacuo* to give crude THP-protected mandelic acid as a mixture of two diastereoisomers. ^{1}H-NMR: 7.51–7.30 (*m*, 5 arom. H); 5.23, 5.21 (2*s*, PhC*H*); 4.91, 4.58 (2*t*, CH of THP); 3.98–3.43 (2*m*, 1 CH$_2$ of THP); 1.90–1.26 (*m*, 3 CH$_2$ of THP). ^{13}C-NMR: 176.8, 175.6 (2*s*, C=O); 136.2, 135.6 (2*s*, 1 arom. C); 128.73, 128.68, 128.6, 127.6, 127.3, 126.6 (6*d*, 5 arom. CH); 97.5, 97.1 (2*d*, CH of THP); 75.5, 72.5 (2*d*, PhCH); 63.0, 62.1 (2*t*, CH$_2$ of THP); 30.3, 30.1, 25.2, 25.1, 19.3, 18.7 (6*t*, 3 CH$_2$ of THP).

The crude protected mandelic acid was dissolved in abs. THF (5 ml), the soln. was cooled to *ca.* −10°, and *N*-methylmorpholine (NMM; 405 mg, 4 mmol) and isobutyl chloroformate (ClCO$_2$^{i}Bu; 273 mg, 2 mmol) were added. After 5 min, freshly prepared H_2S (from $Na_2S \cdot H_2O$ and 50% aq. H_2SO_4) was bubbled through the mixture, which was stirred for 1 h at −10°. Then, Et$_2$O was added, the mixture was washed with 0.1M aq. H_3PO_4, the org. phase was dried (Na_2SO_4), the solvents were evaporated, and the residue was dried under high vacuum. The crude THP-protected mandelic thioacid **21** was dissolved in CH_2Cl_2, the soln. was cooled to 0°, **2b** (348 mg, 2 mmol) was slowly added, and the mixture was stirred at r.t. for 15 h. Then, the mixture was extracted with 5% aq. $NaHSO_4$ (3×), the aq. phases were washed with CH_2Cl_2, and the combined org. phases were dried (Na_2SO_4). The solvent was evaporated and chromatographic workup (CC, SiO_2; CH_2Cl_2/Et$_2$O 20:1) gave two fractions, which were crystallized.

Data of **22**. Yield: 443 mg (52%). M.p. 109–110° (Et$_2$O/pentane). Colorless crystals. IR: 3414*w*, 3248*s*, 2940*s*, 2871*w*, 1666v*s*, 1491v*s*, 1463v*s*, 1367v*s*, 1259*m*, 1238*m*, 1204*s*, 1184*m*, 1119v*s*, 1101v*s*, 1077*s*, 1037*s*, 967*s*, 909*m*, 777*m*, 708v*s*. ^{1}H-NMR (2 diastereoisomers): 8.74, 8.67 (2 br. *s*, NH); 7.48–7.10 (*m*, 10 arom. H); 5.02, 4.98 (2*s*, PhC*H*); 4.85, 4.54 (2*t*, *J* = 3, CH of THP); 4.00–3.80, 3.60–3.40 (2*m*, CH$_2$ of THP); 3.70 (*s*, MeN); 2.09–1.26 (*m*, 3 CH$_2$ of THP); 1.62, 1.57, 1.54, 1.43 (4*s*, Me$_2$C). ^{13}C-NMR (2 diastereoisomers): 209.3 (*s*, C=S); 169.4, 168.8 (2*s*, C=O); 147.1, 138.5, 137.4 (3*s*, 2 arom. C); 129.5, 128.2, 127.84, 127.78, 127.0, 126.8 (6*d*, 10 arom. CH); 98.2, 95.3 (2*d*, CH of THP); 78.9, 77.5 (2*d*, PhCH); 62.82, 62.80 (2*s*, Me$_2$*C*); 62.1, 62.0 (2*t*, 1 CH$_2$ of THP); 51.4 (*q*, MeN); 30.5, 30.3 (2*t*, 1 CH$_2$ of THP); 28.1, 28.0, 27.9, 27.8 (4*q*, *Me*$_2$C); 25.4, 25.3 (2*t*, 1 CH$_2$ of THP); 18.9, 18.8 (2*t*, 1 CH$_2$ of THP). ESI-MS (CH_2Cl_2 + NaI): 449 (12, $[M+Na]^+$), 427 (40, $[M+H]^+$), 343 (53, $[M-Ph(Me)N+Na]^+$), 175 (100).

*(2-{[1-Methyl-1-(*N-*methyl*-N-*phenylthiocarbamoyl)ethyl]amino}-2-oxo-1-phenylethyl)(2-methylpropyl)carbonate* (**23**). Yield: 167 mg (20%). Colorless crystals. ^{1}H-NMR: 7.66 (br. *s*, NH); 7.44–7.20 (*m*, 10 arom. H); 5.68 (*s*, PhC*H*); 4.00–3.85 (*m*, CH$_2$); 3.71 (*s*, MeN); 2.53–1.85 (*m*, Me$_2$C*H*); 1.65, 1.60 (2*s*, Me$_2$C); 0.96, 0.95 (2*d*, *J* = 6.7, *Me*$_2$CH). ^{13}C-NMR: 208.3 (*s*, C=S); 165.9, 153.5 (2*s*, 2 C=O); 147.5, 135.5 (2*s*, 2 arom. C); 129.6, 129.0, 128.7, 128.4, 127.5, 126.3 (6*d*, 10 arom. CH); 78.7 (*d*, PhCH); 74.7 (*t*, CH$_2$); 63.0 (*s*, Me$_2$*C*); 51.4 (*q*, MeN); 29.1 (*q*, *Me*$_2$C); 27.8 (*d*, Me$_2$*C*H); 19.0, 18.9 (2*q*, *Me*$_2$CH). CI-MS: 444 (22), 443 (100, $[M+H]^+$), 269 (16), 192 (27). Anal. calc. for $C_{24}H_{30}N_2O_4S$ (442.58): C 65.13, H 6.83, N 6.33, S 7.24; found: C 65.00, H 6.71, N 6.25, S 7.42.

Suitable crystals for the X-ray crystal-structure determination were obtained from hexane by slow evaporation of the solvent.

6.2. *Synthesis of 2-Hydroxy-*N-*[1-methyl-1-(*N-*methyl*-N-*phenylthiocarbamoyl)ethyl]-2-phenylacetamide* (**24**). A mixture of **22** (427 mg, 1 mmol) and pyridinium *para*-toluenesulfonate (PPTS, 30 mg) in EtOH (20 ml) was heated under reflux for 15 h. Then, the solvent was evaporated, the residue was purified by CC (SiO_2; CH_2Cl_2/Et$_2$O 20:1), and recrystallization from AcOEt/hexane 1:1 yielded 348 mg (quant.) of **24**. M.p. 145–146°. Colorless solid. IR: 3324*s*, 3060*m*, 3004*m*, 2983*m*, 2982*m*, 1692*s*, 1673v*s*, 1652v*s*, 1592*m*, 1515v*s*, 1490v*s*, 1465v*s*, 1451v*s*, 1431*s*, 1370v*s*, 1359v*s*, 1256*m*, 1215*s*, 1182*m*, 1163*m*, 1101v*s*, 1068*s*, 1027*m*, 1017*m*, 1003*m*, 992*m*, 777*s*, 729*m*, 707*s*. ^{1}H-NMR: 7.46–7.18 (*m*, 10 arom. H); 4.68 (*s*,

PhC*H*); 3.96 (*s*, MeN); 1.60, 1.52 (2*s*, Me_2C). ^{13}C-NMR: 208.2 (*s*, C=S); 170.3 (*s*, C=O); 147.6, 139.3 (2*s*, 2 arom. C); 129.6, 128.7, 128.5, 128.4, 126.7, 126.3 (6*d*, 10 arom. CH); 74.2 (*d*, PhCH); 62.9 (*s*, Me_2C); 51.3 (*q*, MeN); 29.3, 29.2 (2*q*, Me_2C).

6.3. *Attempted Cyclization of* **24**. Through a soln. of **24** (342 mg, 1 mmol) in abs. toluene (130 ml) at 100–110°, dry HCl gas was bubbled for 20 min. Then, the solvent was evaporated, the residue was dissolved in THF/Et_2O, and the mixture was stirred for 30 min. The precipitate (Me(Ph)NH·HCl) was filtered off, and the solvent was evaporated. Chromatographic workup of the residue gave 33% of the starting material **24** and three fractions of impure isomeric compounds with the mass of the expected *3,3-dimethyl-6-phenyl-2-thioxomorpholin-5-one* (**20**; ESI-MS (CH_2Cl_2 + NaI): 236 ($[M+1]^+$)) in *ca.* 26, 12, and 6% yield, resp.

6.4. *Synthesis of [1-Methyl-1-({2-methyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylthiocarbamoyl)ethyl]-amino}carbonyl)ethyl](2-methylpropyl)carbonate* (**25**). To a soln. of *2-hydroxy-2-methylpropanoic acid* (**1a**; 500 mg, 4.8 mmol) in dry THF (30 ml), NMM (2.43 g, 24 mmol) and $ClCO_2{}^iBu$ (1.6 g, 12 mmol) were added at −10°. Immediately, a white solid precipitated. The mixture was stirred for *ca.* 5 min, then a slow stream of H_2S was bubbled through the soln. for 2.5 h. The mixture was diluted with Et_2O and extracted with 0.1M aq. H_3PO_4 (2×). The combined org. phase was dried ($MgSO_4$), the solvent was evaporated, and the residue was dried under high vacuum. The formed crude thioacid was dissolved in abs. MeCN and cooled to 0°, and **2b** (835 mg, 4.8 mmol) was added slowly. The mixture was allowed to reach r.t. and was stirred, until the starting material was completely consumed (TLC, 24 h). Then, the solvent was evaporated, and the residue was dried under high vacuum. Purification by CC (SiO_2; AcOEt/hexane 1:2) gave 1.68 g (92%) of **25**. ^{1}H-NMR: 8.33 (br. *s*, NH); 7.38–7.16 (*m*, 5 arom. H); 3.82 (*d*, *J* = 6.8, CH_2); 3.66 (*s*, MeN); 3.65–1.87 (*m*, Me_2CH); 1.55, 1.46 (2*s*, 2 Me_2C); 0.90–0.88 (*m*, Me_2CH). ^{13}C-NMR: 209.1 (*s*, C=S); 170.2, 153.0 (2*s*, 2 C=O); 147.2 (*s*, arom. C); 129.5, 128.4, 126.8 (3*d*, 5 arom. CH); 82.7, 62.6 (2*s*, 2 Me_2C); 51.4 (*q*, MeN); 27.7, 24.0 (2*q*, 2 Me_2C); 27.1 (*d*, Me_2CH); 18.9 (*q*, Me_2CH). ESI-MS: 417 (100, $[M+Na]^+$). Anal. calc. for $C_{20}H_{30}NO_4S$: (380.52): C 60.89, H 7.66, N 7.10, S 8.13; found: C 60.73, H 7.50, N 7.28, S 7.99.

6.5. *Synthesis of 2-Hydroxy-2-methyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylthiocarbamoyl)ethyl]propanamide* (**26**). A soln. of **25** (982 mg, 2.58 mmol) in a mixture of dioxane (14.7 ml) and 0.8M NaOH (14.7 ml) was stirred at r.t. for 30 min. After neutralizing by treatment with *Dowex-50* (pyridinium form), the soln. was diluted with H_2O and extracted with CH_2Cl_2 (2×). The org. soln. was dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by CC (SiO_2) and crystallized from hexane/AcOEt 2:1: 646 mg (85%) of **26**. M.p. 112–114°. Colorless crystals. IR: 3314*s*, 3006*w*, 2982*s*, 2930*m*, 1642v*s*, 1593*m*, 1492*s*, 1359*m*, 1262*m*, 1161*m*, 1135*m*, 1099*s*, 1012*w*, 1003*m*, 992*w*, 962*m*, 917*m*, 889*w*, 796*w*, 775*s*, 766*m*, 704v*s*, 671v*s*. ^{1}H-NMR: 7.45 (*s*, NH); 7.45–7.25 (*m*, 5 arom. H); 3.74 (*s*, MeN); 1.59, 1.37 (2*s*, 2 Me_2C). ^{13}C-NMR: 209.0 (*s*, C=S); 174.6 (*s*, C=O); 144.4 (*s*, arom. C); 129.4, 128.3, 126.5 (3*d*, 5 arom. CH); 73.14, 62.52 (2*s*, 2 Me_2C); 52.0 (*q*, MeN); 29.0, 27.2 (2*q*, 2 Me_2C). CI-MS: 297 (6), 296 (18), 295 (100, $[M+1]^+$), 228 (10), 192 (35), 121 (12). Anal. calc. for $C_{15}H_{22}N_2O_2S$ (294.41): C 61.19, H 7.53, N 9.51, S 10.89; found: C 61.01, H 7.42, N 9.33, S 10.81.

Suitable crystals for the X-ray crystal-structure determination were obtained from hexane/AcOEt by slow evaporation of the solvent.

6.6. *Cyclization of* **26**. According to *GP 2*, a soln. of **26** (284 mg, 0.97 mmol) in abs. toluene (50 ml) at 100° under N_2 was treated with dry HCl gas for 25 min. Usual workup and purification by prep. TLC (SiO_2; CH_2Cl_2/Et_2O 2:1) gave 50 mg (20%) of *2-(1-hydroxy-1-methylethyl)-4,4-dimethyl-1,3-thiazol-5(4*H*)-one* (**27**) as a yellow oil and traces of a product, which was proposed to be the expected 3,3,6,6-tetramethyl-2-thioxomorpholin-5-one. Treatment of **27** with toluene led to a colorless solid. IR: 3387*s* (br), 2980*m*, 2934*m*, 2874*w*, 1721v*s*, 1659v*s*, 1514*s*, 1460*m*, 1365*m*, 1227*m*, 1193*m*, 967*m*, 919*w*, 848*w*, 827*m*, 810*m*, 768*w*, 651*m*, 621*m*. ^{1}H-NMR: 3.56 (br. *s*, OH); 1.51, 1.41 (2*s*, 2 Me_2C). ^{13}C-NMR: 211.3 (*s*, C=O); 172.4 (*s*, C=N); 83.1 (*s*, C(4)); 67.3 (*s*, Me_2C); 28.4, 24.3 (2*q*, 2 Me_2C). Anal. calc. for $C_8H_{13}NO_2S$: (187.26): C 15.31, H 7.00, N 7.48, S 17.12; found: C 15.07, H 7.22, N 7.29, S 17.34.

7. *Attempted Synthesis of 3,3,6,6-Tetramethylthiomorpholine-2,5-dione* (**28**). 7.1. *2-Bromo-2-methyl-*N*-[1-methyl-1-(*N*-methyl-*N*-phenylcarbamoyl)ethyl]propanamide* (**31**). According to *GP 1:* 802 mg (4.8 mmol) of 2-bromo-2-methylpropanoic acid (**30**) in MeCN (35 ml), 836 mg (4.8 mmol) of **2b**, 2.5 h at r.t. Purification by CC (SiO_2; CH_2Cl_2/MeOH 10:1) and drying under high vacuum. Yield: 1.6 g

(97%). M.p. 135.4–136.2°. Colorless crystals. IR: 3294*s*, 3039*w*, 3002*m*, 2981*m*, 2928*m*, 1663v*s*, 1643v*s*, 1594*m*, 1532*s*, 1493*s*, 1471*m*, 1394*m*, 1372s, 1360*m*, 1288*m*, 1221*m*, 1203*m*, 1111*m*, 930*m*, 916*m*, 775*m*, 715*s*, 645*m*. ^{1}H-NMR: 7.80 (br. *s*, NH); 7.65–7.45 (*m*, 5 arom. H); 3.51 (*s*, MeN); 2.10, 1.68 (2*s*, 2 Me_2C). ^{13}C-NMR: 179.6, 175.0 (2*s*, 2 C=O); 144.9 (*s*, arom. C); 129.4, 128.5, 128.1 (3*d*, 5 arom. CH); 62.5, 59.5 (2*s*, 2 Me_2*C*); 41.5 (*q*, MeN); 32.0, 25.0 (2*q*, 2 *Me*$_2$C). CI-MS: 341 (100, $[M+H]^+$). Anal. calc. for $C_{15}H_{21}BrN_2O_2$ (341.24): C 52.80, H 6.20, N 8.21, Br 23.42; found: C 52.73, H 6.24, N 8.22, Br 23.30.

7.2. *Attempted Synthesis of 2-Methyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]-2-sulfanylpropanamide* (**29**). According to [25], to a soln. of **31** (1.0 g, 2.9 mmol) in DMF (6.3 ml) was added a soln. of $Na_3PO_3S \cdot 12\ H_2O$ (2.3 g, 5.8 mmol) in H_2O (31.5 ml). The mixture was stirred for 5 h, then the pH was lowered to 4.0 by addition of 3.5% HCl, and stirring was continued overnight. The mixture was extracted with CH_2Cl_2 (3×), washed with brine, and dried ($MgSO_4$). The filtered org. soln. was evaporated, and the residue was dried under high vacuum to yield 210 mg (27.5%) of *2-Methyl*-N-*[1-methyl-1-(*N-*methyl*-N-*phenylcarbamoyl)ethyl]prop-2-enamide* (**32**) as a colorless solid.

Recrystallization from MeOH/hexane gave colorless crystals suitable for an X-ray crystal-structure determination.

7.3. *Synthesis of* **29**. According to *GP 1:* 167.2 mg (1.4 mmol) of *2-methyl-2-sulfanylpropanoic acid* (**33**), which was prepared from **30** according to the protocol described in [25], in MeCN (20 ml), 242 mg (1.4 mmol) of **2b**, 16 h at r.t. Purification by CC (SiO_2; CH_2Cl_2/Et_2O 2:1) and drying under high vacuum. Yield: 389 mg (95%). M.p. 140–141°. Colorless solid. IR: 3421*s*, 2927*s*, 1655v*s*, 1624v*s*, 1615*s*, 1516*s*, 1466v*s*, 1391*s*, 1372*m*, 1281*m*, 1245*m*, 1225*m*, 1152*m*, 942*m*, 815*m*, 775*m*, 758*s*, 691*s*, 604*s*. ^{1}H-NMR: 7.43 (*s*, NH); 7.41–7.23 (*m*, 5 arom. H); 3.27 (*s*, MeN); 1.49, 1.48 (2*s*, 2 Me_2C); 1.44 (br. *s*, SH). ^{13}C-NMR: 173.5, 173.1 (2*s*, 2 C=O); 144.7 (*s*, arom. C); 129.4, 128.5, 127.9 (3*d*, 5 arom. CH); 58.2, 47.5 (2*s*, 2 Me_2*C*); 41.5 (*q*, MeN); 29.8, 25.7 (2*q*, 2 *Me*$_2$C). CI-MS: 295 (100, $[M+H]^+$), 188 (25, $[C_8H_{14}NOS]^+$), 108 (26, $[C_7H_8N]^+$). Anal. calc. for $C_{15}H_{22}NO_2S$ (294.41): C 61.19, H 7.53, N 9.52, S 10.89; found: C 61.30, H 7.27, N 9.54, S 10.71.

7.4. *Attempted Cyclization of* **29**. According to *GP 2*, a stirred suspension of **29** (90 mg, 0.32 mmol) in dry toluene (15 ml) was heated to 100° under N_2. An intense stream of dry HCl gas was bubbled through the soln. for 15 min. Then, the soln. was purged with N_2 for 30 min to remove remaining HCl, toluene was evaporated, and THF/Et_2O 1:1 (20 ml) was added to the residue. After 30 min of stirring at r.t., the suspension was filtered, and the solvent was evaporated leading to a solid crude product, which was purified by prep. TLC (SiO_2; CH_2Cl_2/Et_2O 2:1). Yield: 40 mg (60%) of *2-methyl-2-[(2-methyl-2-sulfanylpropanoyl)amino]propanoic acid* (**34**). Colorless solid. IR: 3330*s*, 3039*w*, 2987*m*, 2968*m*, 2924*s*, 2854*m*, 1744*w*, 1655v*s*, 1624v*s*, 1592*s*, 1530v*s*, 1495*s*, 1469*m*, 1381*s*, 1369*s*, 1356*m*, 1276*m*, 1221*m*, 1040*m*, 1022*m*, 974*m*, 890*m*, 776*s*, 706*s*, 699*s*. ^{1}H-NMR: 7.78 (br. *s*, NH); 2.74, 2.65 (2*s*, 2 Me_2C); 1.24 (*s*, SH). ^{13}C-NMR: 175.4, 173.0 (2*s*, 2 C=O); 58.6, 57.3 (2*s*, 2 Me_2*C*); 36.2, 31.1 (2*q*, 2 *Me*$_2$C). Anal. calc. for $C_8H_{15}NO_3S$ (205.28): C 46.81, H 7.37, N 6.82, S 15.62; found: C 46.73, H 7.25, N 6.90, S 15.75.

8. *X-Ray Crystal-Structure Determination of* **3aa**, **4aa**, **10a**, **11a**, **23**, **26**, **32**, *and* **34** (*Table 2* and *Figs. 1–5*)[7]). All measurements, with the exception of those of **23**, were performed on a *Nonius KappaCCD* diffractometer [28] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. Data reduction was performed with HKL Denzo and Scalepack [29]. In the case of **23**, the measurements were made on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and a 12-kW rotating anode generator. The data collection and refinement parameters are given in *Table 2*, and views of the molecules are shown in *Figs. 1–5*. The intensities were corrected for *Lorentz* and polarization effects, and absorption corrections based on the multi-scan method [30] were applied in the cases of **10a**, **11a**, **26**, and **34**. The structures of **3aa**, **10a**, **11a**, **23**, **26**, **32**, and **34** were solved by direct methods using SIR92 [31] and those of **4aa** and the second polymorph of **10a** by using SHELXS97 [32], which revealed the positions of all non-H-atoms. In the case of the second polymorph of **10a** and **26**, there are two and three symmetry-independent molecules, resp., in the asymmetric unit. The atomic coordinates for these structures were tested carefully

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[7]) CCDC-789182–789190 contain the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 2. *Crystallographic Data for Compounds* **3aa**, **4aa**, **10a**, **11a**, **23**, **26**, **32**, *and* **34**

	3aa	**4aa**	**10a** (polymorph 1)	**10a** (polymorph 2)	**11a**
Crystallized from	MeCN	toluene	toluene	toluene	toluene
Empirical formula	$C_{15}H_{22}N_2O_3$	$C_8H_{13}NO_3$	$C_8H_{13}NO_2S$	$C_8H_{13}NO_2S$	$C_8H_{13}NOS_2$
M_r	278.35	171.19	187.26	187.26	203.32
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism	colorless, prism	yellow, prism
Crystal dimensions [mm]	$0.25 \times 0.30 \times 0.35$	$0.12 \times 0.12 \times 0.20$	$0.10 \times 0.15 \times 0.30$	$0.20 \times 0.20 \times 0.25$	$0.08 \times 0.20 \times 0.28$
Temp. [K]	160(1)	160(1)	160(1)	160(1)	160(1)
Crystal system	monoclinic	monoclinic	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/n$	$P\bar{1}$	$P2_1/c$
Z	4	4	4	4	2
Reflections for cell determination	4594	2117	56335	31739	25594
2θ Range for cell determination [°]	4 – 60	2 – 55	2 – 60	4 – 60	2 – 55
Unit cell parameters:					
a [Å]	5.8729(1)	7.9778(4)	5.6490(1)	8.7363(1)	5.6152(2)
b [Å]	19.2439(4)	5.9714(4)	22.0010(4)	11.3121(2)	14.8426(5)
c [Å]	13.6467(3)	18.626(1)	8.2026(1)	11.3342(1)	6.3708(2)
α [°]	90	90	90	66.6701(6)	90
β [°]	93.8172(8)	94.380(3)	108.7734(8)	70.2665(6)	111.185(1)
γ [°]	90	90	90	71.5837(5)	90
V [Å^3]	1538.89(5)	884.7(1)	965.21(3)	946.37(2)(1)	495.09(3)
D_x [g cm^{-3}]	1.201	1.285	1.289	1.314	1.364
μ(MoK_α) [mm^{-1}]	0.0838	0.0981	0.297	0.303	0.491
Scan type	ϕ and ω	ω	ϕ and ω	ϕ and ω	ϕ and ω
$2\theta_{(max)}$ [°]	60	55	60	60	55
Transmission factors [min; max]	–	–	0.843; 0.955	0.822; 0.943	0.828; 0.967
Total reflections measured	32625	11734	22304	39683	9550
Symmetry-independent reflections	4478	2019	2808	5530	1122
Reflections used [$I > 2\sigma(I)$]	3148	1319	2316	4520	997
Parameters refined	190	113	114	225	63
Final $R(F)$	0.0761	0.0571	0.0583	0.0410	0.0405
$wR(F)$	0.0765	0.0602	0.0739	0.0507	0.0521
Weighting parameter [a][a])	0.01	0.015	0.005	0.008	0.007
Goodness-of-fit	3.247	2.058	4.197	2.874	2.920
Secondary extinction coefficient	$4.9(9) \times 10^{-6}$	–	$6(2) \times 10^{-6}$	–	–
Final $\Delta_{(max)}/\sigma$	0.0002	0.002	0.0002	0.002	0.0002
$\Delta\rho$ (max; min) [e Å^{-3}]	0.39; −0.44	0.29; −0.27	0.35; −0.30	0.50; −0.33	0.28; −0.27

[a]) $w^{-1} = \sigma^2(F_o) + (aF_o)^2$.

for a relationship from a higher-symmetry space group using the program PLATON [33], but none could be found. In the case of **11a**, the molecule sits across a crystallographic center of inversion, so that the O-atom and NH group are necessarily disordered with equal site occupation factors of 0.5. The non-H-

Table 2 (cont.)

	23	**26**	**32**	**34**
Crystallized from	hexane	hexane/AcOEt	MeOH/hexane	toluene
Empirical formula	$C_{24}H_{30}N_2O_4S$	$C_{15}H_{22}N_2O_2S$	$C_{15}H_{20}N_2O_2$	$C_8H_{15}NO_3S$
M_r	442.57	294.41	260.33	205.27
Crystal color, habit	colorless, prism	colorless, prism	colorless, plate	colorless, prism
Crystal dimensions [mm]	$0.20 \times 0.40 \times 0.50$	$0.22 \times 0.27 \times 0.32$	$0.13 \times 0.30 \times 0.30$	$0.20 \times 0.20 \times 0.25$
Temperature [K]	213(1)	160(1)	160(1)	160(1)
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$C2/c$	$P2_1/n$	Cc	$P2_1/n$
Z	8	12	4	4
Reflections for cell determination	25	104075	2126	17370
2θ Range for cell determination [°]	30 – 39	4 – 60	4 – 60	4 – 60
Unit cell parameters:				
a [Å]	24.388(2)	10.0643(1)	8.8101(1)	10.3232(2)
b [Å]	7.002(4)	11.9354(1)	17.8470(3)	9.5082(2)
c [Å]	27.823(2)	40.4795(3)	9.9602(2)	11.1870(2)
α [°]	90	90	90	90
β [°]	97.336(6)	96.5109(3)	114.0449(7)	112.5896(7)
γ [°]	90	90	90	90
V [Å^3]	4712(2)	4831.09(7)	1430.19(4)	1013.82(3)
D_x [g cm^{-3}]	1.248	1.214	1.209	1.345
μ(MoK_α) [mm^{-1}]	0.169	0.204	0.0808	0.296
Scan type	ω	ϕ and ω	ω	ϕ and ω
$2\theta_{(max)}$ [°]	55	60	60	60
Transmission factors [min; max]	–	0.764; 0.961	–	0.904; 0.946
Total reflections measured	5985	70128	19923	28726
Symmetry-independent reflections	5404	13807	4058	2969
Reflections used [$I > 2\sigma(I)$]	3612	7052	3575	2081
Parameters refined	280	553	175	127
Final $R(F)$	0.0520	0.0449	0.0424	0.0333
$wR(F)$	0.0482	0.0494	0.0420	0.0427
Weighting parameter [a][a])	0.005	0.005	0.005	0.005
Goodness-of-fit	1.886	1.256	2.501	1.043
Secondary extinction coefficient	–	–	$4.2(6) \times 10^{-6}$	$4(5) \times 10^{-7}$
Final $\Delta_{(max)}/\sigma$	0.0008	0.0004	0.0006	0.0003
$\Delta\rho$ (max; min) [e Å^{-3}]	0.51; −0.28	0.29; −0.36	0.18; −0.18	0.29; −0.29

[a]) $w^{-1} = \sigma^2 (F_o) + (aF_o)^2$.

atoms in each structure were refined anisotropically, except for the N-atom in **11a**, which was refined isotropically. The hydroxy, amide (except in **23**, **26**, and **32**), and sulfide H-atoms were placed in the positions indicated by a difference electron-density map, and their positions were allowed to refine with

individual isotropic displacement parameters. All other H-atoms were fixed in geometrically calculated positions, and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom. The refinement of each structure was carried out on F using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)^2$. A correction for secondary extinction was applied in the cases of **3aa** and **10a** (polymorph 1), **32**, and **34**. Neutral atom scattering factors for non-H-atoms were taken from [34a], and the scattering factors for H-atoms were taken from [35]. Anomalous dispersion effects were included in F_c [36]; the values for f' and f'' were those of [34b]. The values of the mass attenuation coefficients are those of [34c]. All calculations were performed using the teXsan [37] crystallographic software package.

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