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Spectroscopic Study of the Conformation of 2-Anilino-2-ethoxy-3-oxothiobutyric Acid Anilides

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Summary. An NMR study of the equilibrium mixture of two conformers of 2-anilino-2-ethoxy-3-oxothiobutyric acid anilides **3** allows to estimate their population ratio in solvents of increasing polarity. X-Ray analysis as well as IR spectroscopy confirmed that the conformer present in the solid state is stabilized by two hydrogen bonds. The structural basis of the second conformer observed in solution is the 1,4-type S···O interaction between the sulfur of the thioanilide moiety and the oxygen of the ethoxy group with a distance of 2.878 Å.

Keywords. 3-Oxothiobutyric acid; Conformational analysis.

Introduction

In continuation of the study on the synthesis and properties of *Schiff* bases containing 1,3-heterodiene systems such as O=C–C=N– [1, 2] we have prepared the hitherto unknown 2-anilino-3-oxothiobutyric acid anilides **2** (Scheme 1). It is known that this 1,3-heterodiene system is prone to react with heterocumulenes yielding five-membered heterocycles as a result of 1,3-dipolar cycloaddition [3–5]. This particular reactivity results from the specific *pseudo-gauche* conformation of the 1,3-heterodiene system, in which unshared electrons of the azomethine nitrogen play an important role.

In our present investigation attention was directed towards the addition reaction of the azomethine C=N bond of compounds **2** with nucleophiles. Treatment of anils **2** with ethanol gave adducts **3** (Scheme 1). The reaction of the C=N bond with nucleophiles is attributed to the enhanced electrophility of the azomethine carbon atom of compounds **2**.

The NMR spectra of the new compounds **3a–d** displayed significant differences when compared with that of the known 2-anilino-2-ethoxy-3-oxobutyric acid anilide

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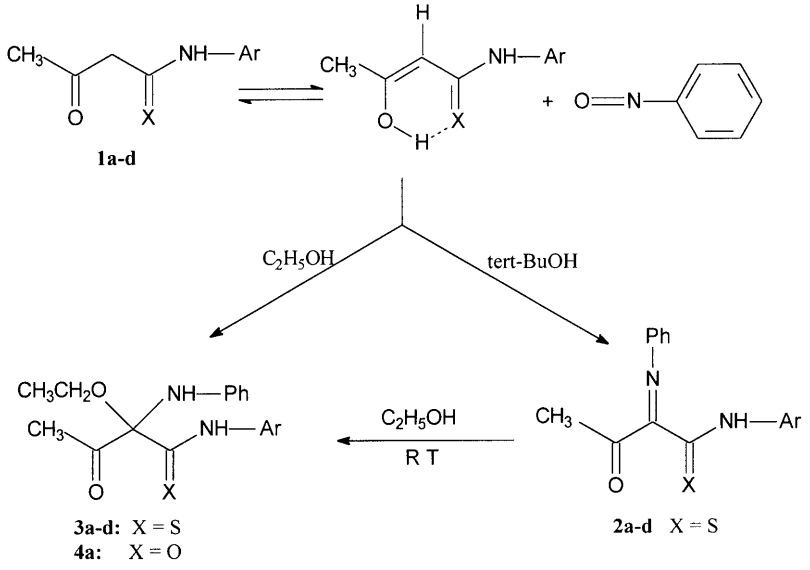


a: Ar = C_6H_5; **b**: Ar = 4-CH_3-C_6H_4; **c**: Ar = 4-CH_3O-C_6H_4; **d**: Ar = 4-Cl-C_6H_4

Scheme 1

4a [1]. For compounds **3a–d**, unexpected signals were observed on the NMR timescale, indicating that **3** exist in solution in an equilibrium mixture of two stabilized conformers. To cast light on their spatial geometry, the solid-state structure of **3d** was established by X-ray single crystal analysis. Starting from the geometry of this structure, a number of possible conformers was generated and analysed.

Results and Discussion

X-Ray measurement

The molecular structure of compound **3d** ((*R*)-configuration) determined in a single crystal X-ray analysis is shown in Fig. 1. The molecule has an asymmetric C(2) atom, and since the compound crystallizes in the centrosymmetric space group $P2_1/n$, both configurations (*R*) and (*S*) are present in the solid state (racemate).

In the crystal, the sulfur atom is located *trans* to the carbonyl oxygen atom O(1) at a distance of 4.730(1) Å. This conformation is stabilized by two intramolecular hydrogen bonds: a strong one (2.960(1) Å) between amine nitrogen N(2) and S (N(2)-H(2) = 0.87(2) Å, H(2)···S = 2.39(2) Å, N(2)-H(2)···S = 122(1)°) and a weaker one (2.709(2) Å) between amide nitrogen N(1) and O(2) (N(1)-H(1) = 0.81 Å, H(1)···O(2) = 2.32 Å, N(1)-H(1)···O(2) = 110(1)°). The amide nitrogen is also engaged in an intramolecular hydrogen bond with oxygen atom O1 of the molecule related by symmetry $-x+1$, $-y$, $-z$. The parameters of this bond are: N(1)-H(1) = 0.81 Å, H(1)···O(1) = 2.18 Å, N(1)···O(1) = 2.90 Å, and N(1)-

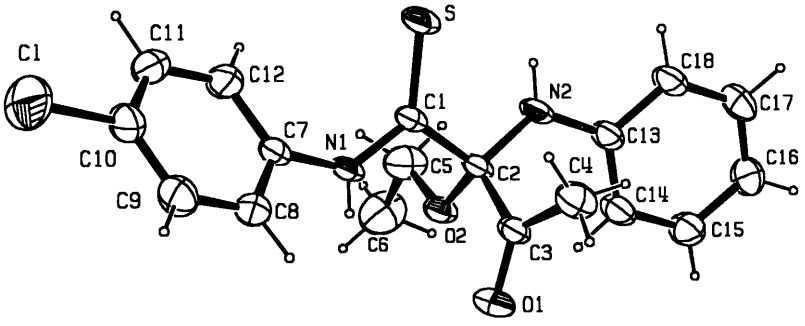


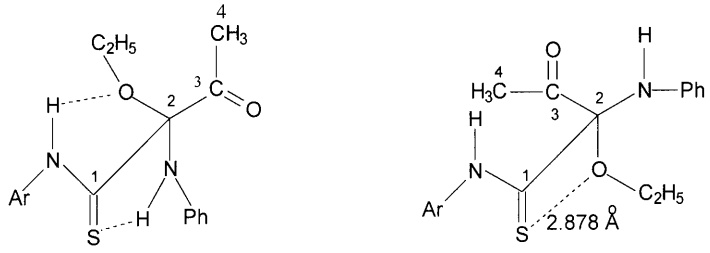
Fig. 1. Structure of **3d** including the atom numbering scheme corresponding to that used in the deposited tables (ORTEP-3 [15]); thermal vibration ellipsoids are scaled to enclose 40% probability; H atoms are represented by circles of arbitrary size

H(1)···O(1) = 148°. The five-membered ring defined by S, C1, C2, N2, H2 is planar, the average deviation of these atoms from the best-fit mean plane is 0.039 Å. The ring defined by C1, N1, H1, O2, C2 is distorted from planarity, the average deviation being 0.206 Å. It should also be noted that the thioamide group has (*Z*) configuration and is rather planar; the average deviation of the atoms S, C1, N1, H1, and C7 from the best-fit mean plane amounting to 0.024 Å. The angle between the plane of the thioamide group and that of the hydrogen bond N2-H2···S is 4.28(2)°.

Calculations

It was postulated that the molecular structure of **3d** found in the solid state (called hereafter conformer **A**) corresponds to the structure of one of the conformers existing in solution. To evaluate the structure of the other conformer, a number of possible conformers was generated starting from the geometry of conformer **A** and changing the torsional angle C3-C2-C1-S. The relative energy of these conformers, their dipole moments, and the intramolecular distances S···O(1) and S···O(2) were calculated with the MOPAC 6.00 program [6]; the results are shown in Table 1. For the conformer in which the C=S group is eclipsed with the oxygen of the ethoxy group (angle S-C1-C2-O: 10.2°), the intramolecular distance S···O(2) is the shortest and equal to 2.878 Å, which is considerably less than sum of the *van der Waals* radii (3.25 Å).

This eclipsed conformation, called hereafter **B**, affords a nearly planar 4-membered *quasi*-ring (S(1)-C(1)-C(2)-O(2)) with an S···O(2) distance of 2.878 Å. This is characteristic for compounds with a close 1,4-contact [8–10]. As a result of the 1,4-S···O interaction, the geometry of the conformer **B** is stabilized by overlap of the lone pair of oxygen O(2) with the antibonding orbital δ^* of the C=S bond. The structures of conformers **A** and **B** are compared in Fig. 2. The difference of the relative energy of these conformers is considerable (Table 1) and can be attributed to a different type of intramolecular interactions of the more stable conformer **A** in the solid state and the higher in energy conformer **B** in solution which may be stabilized by an S···O interaction.



Conformer **A** Conformer **B**

Fig. 2. Conformers of **3a–d** present in solution

Table 1. Relative energy, dipole moments, selected torsion angles, and non-bonded distances optimized for 11 conformers of **3d** and the corresponding geometrical data

Relative energy / kJ · mol^{-1}	μ/D	Torsion angles[a]/°			S···O(2)[b]/Å	S···O(1)/Å
		α	β	γ		
0[c]	1.14[c]	110.7[c]	−10.5[c]	−135.7[c]	3.828[c]	4.730[c]
7.539	1.07	150	26.46	−100.15	3.459	4.764
19.147	2.04	170	45.5	−81.1	3.249	4.719
37.456	3.74	−160	76.35	−51.09	3.023	4.495
39.319	4.82	−130	107.93	−19.99	2.929	4.051
41.504[d]	5.12[d]	−100[d]	136.8[d]	10.2[d]	2.878[d]	3.698[d]
44.145	5.13	−70	167.22	41.38	2.942	3.721
44.706	5.45	−40	−163.06	70.85	3.139	3.455
41.449	5.55	−10	−130.24	100.35	3.444	3.326
29.465	4.96	20	−105.5	130.22	3.711	3.376
19.573	3.77	50	−73.72	161.62	3.903	3.697
4.709	2.00	80	−44.86	−169.22	3.935	4.184

[a] α = C(3)-C(2)-C(1)-S, β = S-C(1)-C(2)-N(2), γ = S-C(1)-C(2)-O(2); [b] sum of the *van der Waals* radii = 3.25 Å [7]; [c] conformer **A** (X-ray data); [d] conformer **B**

NMR Measurements

All ^{1}H NMR spectra (500 MHz) of compounds **3** ($CDCl_3$) show the presence of two conformers, called per analogy **A** and **B**, which differ in their chemical shifts and intensities. Table 2 shows the chemical shifts for compound **3a** and **4a** (Scheme 1).

Two conformations **A** and **B** which do not interconverted rapidly on the ^{1}H NMR time scale are accessible only for the thioamides **3**. Large chemical shift difference ($\Delta\delta = 4$ ppm) between conformers **A** and **B** for NH-Ph confirms that the sulfur atom in conformer **B** encounters a new steric situation. When the sulfur atom was replaced by oxygen to yield compound **4a** the individual conformers could not be detected within the ^{1}H NMR time scale. This suggests that the donor-aceptor 1,4-interaction between sulfur and the oxygen atoms of the ethoxy group plays a crucial role.

Table 2. ^{1}H NMR chemical shifts (ppm) for the two conformers **A** and **B** of compounds **3a** and **4a** ($CDCl_3$, 298 K, 500 MHz)

	CH_3CH_2–O	CH_3CH_2–O	CH_3–CO	NH–CS	NH–Ph
3a (**A**)	1.33, t, 3H	3.44, 3.68, qq, 2H	2.24, s, 3H	10.45, s, 1H	6.21, s, 1H
3a (**B**)	1.24, t, 3H	3.47, 3.71, qq, 2H	2.15, s, 3H	10.77, s, 1H	2.17, s, 1H
4a	1.29, t, 3H	3.44, 3.56, qq, 2H	2.23, s, 3H	8.73, s, 1H	5.88, s, 1H

Table 3. Relative population of the two conformers **A** and **B** in solvents of different polarity (5.6×10^{-2} mol · dm^{-3}, 298 K)

		$CDCl_3$ ($\varepsilon = 4.8$)		CD_3COCD_3 ($\varepsilon = 20.7$)		CD_3OD ($\varepsilon = 33.6$)		*DMSO*-d_6 ($\varepsilon = 47$)	
	Ar	**A**/%	**B**/%	**A**/%	**B**/%	**A**/%	**B**/%	**A**/%	**B**/%
3a	C_6H_5	76	24	59	41	45	55	14	86
3b	4-CH_3-C_6H_4	70	30	54	46	46	54	16	84
3c	4-CH_3O-C_6H_4	70	30	65	35	47	53	14	86
3d	4-Cl-C_6H_4	43	57	39	61	27	73	5	95
4a	C_6H_5	100		100		100		100	

In addition, the relative population of conformers **A** and **B** was determined by measuring the intensities of their signals in solvents of different polarity (Table 3).

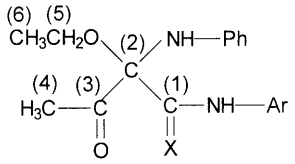
The more polar conformer **B** is strongly preferred in polar solvents such as *DMSO*; the ratio of conformers **A/B** of **3d** changes from 1:1 ($CDCl_3$) to 1:20 (Table 3). Differences in the dipole moments ($\mu = 1.14$ D for **A** and $\mu = 5.12$ D for **B**) of **3d** lead to differences in the solvatation energy of conformers. That is in agreement with the interpretation of the ^{1}H NMR spectra. On the other hand, the less polar low-energy conformer **A** (Table 1) should be present in excess at low temperatures, and the population of **B** should become higher at high temperature. This remarkable fact was confirmed by corresponding ^{1}H NMR measurements for **3a**. In fact, the ratio changes from 3:1 in favour of **A** to 5:1 in favour of **B** over the temperature range of 30 degrees.

The ^{13}C NMR spectra also revealed that compounds **3** exist in solution in an equilibrium of two conformers **A** and **B**. The ^{13}C NMR chemical shifts (Table 4) reflect the significant change of electron density of the thiocarbonyl carbon atom and the carbonyl carbon of the acetyl group. ^{13}C NMR chemical shift differences ($\Delta\delta = 20$ ppm) between conformers **A** and **B** observed for C1 suggest a strong conformational preference for a possible 1,4-close contact O· · ·S [8] stabilizing the structure of conformer **B** in the same way as the intramolecular interaction of oxygen (C3) in the solid state.

IR Measurements

Infrared data for compounds **3** are given in Table 5. It can be seen that in the solid state one characteristic frequency of the acetyl carbonyl absorption at 1734 cm^{-1} is

Table 4. ^{13}C NMR chemical shifts (ppm) for conformers **A** and **B** of compounds **3a–d** and **4a** (5.6×10^{-2} mol · dm^{-3}, $CDCl_3$, 298 K, 125 MHz)



	3a		**3b**		**3c**		**3d**		**4a**
	A	**B**	**A**	**B**	**A**	**B**	**A**	**B**	
C1	182.9	161.4	181.9	161.5	181.9	161.5	183.2	161.2	165
C2	95.1	95.1	95	95	95.1	95.1	95.3	95.2	92.16
C3	194	201.6	193.6	201.7	193	201.7	194.3	201.5	201
C4	23.5	31.5	23.6	31.5	23.6	31.5	23.5	31.4	42.17
C5	59.6	58.4	59.5	58.4	59.5	58.4	59.7	58.4	59.16
C6	15.2	18.4	15.3	18.4	15.3	18.4	15.2	18.4	15.23

Table 5. Infrared carbonyl absorption frequencies

	Ar	ν/cm^{-1} CCl_4^* ($3 \cdot 10^{-2}$ mol/dm^3)	ν/cm^{-1} solid state (KBr)
3a	C_6H_5	1734, 1722	1730
3b	4-CH_3-C_6H_4	1734, 1723	1734
3c	4-CH_3O-C_6H_4	1733, 1720	1731
3d	4-Cl-C_6H_4	1734, 1719	1735
3e	C_6H_5	1734	1731

present. This frequency can be assigned to conformer **A**, whose structure in the solid state was determined by X-ray analysis. In CCl_4, all spectra of **3** are characterized by two carbonyl bands assigned to conformers **A** (higher frequency) and **B**. This is also in good agreement with the NMR spectra.

Conclusions

Contrary to our earlier expectations, the structure with a 1,4-S···O donor acceptor interaction is not present in the solid state of compounds **3** [8] but only in solution. As determined by X-ray analysis, the conformation of **A** is stabilized by two intramolecular hydrogen bonds which successfully compete with the plausible S···O donor-acceptor interaction which is present in conformer **B** and has been reported for similar compounds [7]. Moreover, this stereoelectronic situation probably affects the intramolecular hydrogen bond of the C=O acetyl group. It should also be stressed that in compound **4a**, where the bulky sulfur atom is replaced by an oxygen atom, the individual conformers are not detected. It is pertinent to note that the presence of conformer **B** in solution is confirmed by NMR

and IR spectra as well as by calculations. Our current studies of heterocyclization processes in which compounds **3** are involved seem to indicate that the intramolecular interactions observed in these compounds influence the stereoselectivity of the studied reactions to a high degree.

Experimental

Melting points were determined on an electrothermal IA9000 digital melting point apparatus and are uncorrected. The IR spectra were obtained on a Bruker IFS 48 spectrometer at room temperature. ^{1}H and ^{13}C spectra were recorded with a Bruker AMX 500 NMR spectrometer using *TMS* as internal standard. Chemical shifts are reported in ppm downfield from *TMS*. Semiempirical AM1 calculations were performed using the MOPAC 6.00 program [6]. Conformers were generated by changing the torsional angle α (C3-C2-C1-S) by 30°. The geometry of each conformer was optimized, and the relative energies, dipole moments, and geometric parameters were computed.

General procedure for the preparation of **2a–d**

To 25 cm^3 of a *tert*-butanolic solution of the corresponding 3-oxothiobutyric acid anilide (**1a–d**, 25.9 mmol) and 2.6 g (25.9 mmol) freshly synthesized nitrosobenzene, 0.085 cm^3 of a 33% aqueous solution of NaOH was added with stirring. The mixture was stirred for 0.5 h at room temperature. The precipitate was filtered and purified by crystallization from *tert*-butanol.

3-Oxo-N-phenyl-2-phenylimino-thiobutyramide (**2a**; $C_{16}H_{14}N_2OS$)

Yield: 65%; m.p.: 120°C (orange needles); IR (KBr): $\nu = 3237$ (NH amide), 1711 (C=O), 1632 (C=N), 1122 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.15 (s, 3H, CH_3CO), 7.01–7.99 (m, 10H, CH aromat.), 10.77 (s, 1H, NH amide) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 31.46 (CH_3CO), 120.5, 121.9, 126.7, 126.9, 129, 129.3, 137.7, 145.8 (C aromat), 161.4 (C=N), 182.9 (C=S), 201.6 (C=O) ppm.

3-Oxo-N-(4-methylphenyl)-2-phenylimino-thiobutyramide (**2b**; $C_{17}H_{16}N_2OS$)

Yield: 45%; m.p.: 110°C (orange needles); IR (KBr): $\nu = 3235$ (NH amide), 1709 (C=O), 1632 (C=N), 1120 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.15 (s, 3H, CH_3CO), 2.35 (s, 3H, CH_3), 7.01–7.92 (m, 9H, CH aromat.) 10.67 (s, 1H, NH amide) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 21.1 (CH_3), 31.5 (CH_3CO), 120.6, 124.6, 126.8, 127.5, 129.3, 130.5, 139.1, 145.4 (C aromat.), 161.1 (C=N), 181.9 (C=S), 201.7 (C=O) ppm.

3-Oxo-N-(4-methoxyphenyl)-2-phenylimino-thiobutyramide (**2c**; $C_{17}H_{16}N_2O_2S$)

Yield: 50%; m.p.: 112°C (orange needles); IR (KBr): $\nu = 3237$ (NH amide), 1710 (C=O), 1630 (C=N), 1122 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz); 2.15 (s, 3H, CH_3CO), 3.82 (s, 3H, CH_3O), 7.01–7.91 (m, 9H, CH aromat.), 10.65 (s, 1H, NH amide) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 31.4 (CH_3CO), 55.5 (CH_3O), 114.18, 120.49, 123.66, 124.58, 129.24, 130.87, 145.88, 158.4 (C aromat.), 161.5 (C=N), 181.9 (C=S), 201.7 (C=O) ppm.

3-Oxo-N-(4-chlorophenyl)-2-phenylimino-thiobutyramide (**2d**; $C_{16}H_{13}N_2OSCl$)

Yield: 60%; m.p.: 122°C (orange needles); IR (KBr): $\nu = 3230$ (NH amide), 1710 (C=O), 1632 (C=N), 1123 (C=S) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 2.14 (s, 3H, CH_3CO), 7.01–7.96 (m, 9H,

CH aromat.), 10.77 (s, 1H, NH amide) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 31.5 (CH_3CO), 120.5, 123.1, 124.19, 126.87, 129.23, 129.33, 136.32, 145.67 (C aromat), 161.4 (C=N), 183.9 (C=S), 201.5 (C=O) ppm.

General procedure for the preparation of **3a–d**

To 25 cm^3 of an ethanolic solution of the corresponding 3-oxothiobutyric acid anilide (**1a–d**, 25.9 mmol) and 2.6 g (25.9 mmol) freshly synthesized nitrosobenzene, 0.085 cm^3 of a 33% aqueous solution of NaOH was added with stirring. The mixture was stirred for 0.5 h at room temperature. The precipitate was filtered and purified by crystallization from ethanol.

2-(Ethoxy-phenyl-amino)-3-oxo-N-phenyl-thiobutyramide (**3a**; $C_{18}H_{20}O_2N_2S$)

Yield: 75% m.p.: 95°C (yellow needles); IR (KBr): $\nu = 3299$ (NH amide), 3218 (NH amine), 1730 (C=O), 1120 (C=S) cm^{-1}; conformer **A**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.33 (t, $J = 7.1$ Hz, 3H, CH_3CH_2), 2.24 (s, 1H, CH_3CO), 3.44, 3.68 (qq, 2H, CH_3CH_2), 6.81–7.99 (m, 10H, CH aromat.), 10.45 (s, 1H, NH amide), 6.21 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 15.26 (CH_3CH_2), 23.5 (CH_3CO), 59.6 (CH_3CH_2), 95.1 (C2), 115.34–145.77 (C aromat.), 182.9 (C=S), 194 (C=O) ppm; Conformer **B**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.24 (t, $J = 7.1$ Hz, 3H, CH_3CH_2), 2.15 (s, 1H, CH_3CO), 3.47, 3.71 (qq, 2H, CH_3CH_2), 6.81–7.99 (m, 10H, CH aromat.), 10.77 (s, 1H, NH amide), 2.17 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 18.4 (CH_3CH_2), 31.47 (CH_3CO), 58.43 (CH_3CH_2), 95.1 (C2), 115.34–145.77 (C aromat.), 161.4 (C=S), 201.6 (C=O) ppm.

2-(Ethoxy-phenyl-amino)-3-oxo-N-(4-methylphenyl)-thiobutyramide (**3b**; $C_{19}H_{22}O_2N_2S$)

Yield: 45%; m.p.: 86°C (yellow needles); IR (KBr): $\nu = 3318$ (NH amide), 3230 (NH amine), 1734 (C=O), 1120 (C=S) cm^{-1}; Conformer **A**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.31 (t, $J = 7.06$, 3H, CH_3CH_3), 2.24 (s, 1H, CH_3CO), 2.35 (s, 3H, CH_3), 3.44, 3.67 (qq, 2H, CH_3CH_2), 6.81–7.92 (m, 9H, CH aromat), 10.35 (s, 1H, NH amide), 6.21 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 15.26 (CH_3CH_2), 21.1 (CH_3), 23.59 (CH_3CO), 59.51 (CH_3CH_2), 95 (C2), 115.4–145.2 (C aromat.), 181.9 (C=S), 193.65 (C=O) ppm; Conformer **B**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.24 (t, $J = 7.06$, 3H, CH_3CH_2), 2.15 (s, 3H, CH_3CO), 2.37 (s, 3H, CH_3) 3.45, 3.72 (qq, 2H, CH_3CH_2), 6.81–7.92 (m, 9H, CH aromat.), 10.69 (s, 1H, NH amide), 2.51 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 18.4 (CH_3CH_2), 21.1 (CH_3), 31.5 (CH_3CO), 58.44 (CH_3CH_2), 95 (C2), 115.4–145.2 (C aromat.), 161.51 (C=S), 201.72 (C=O) ppm.

2-(Ethoxy-phenyl-amino)-3-oxo-N-(4-methoxyphenyl)-thiobutyramide (**3c**; $C_{19}H_{22}O_3N_2S$)

Yield: 50%; m.p.: 85°C (yellow needles); IR (KBr): $\nu = 3314$ (NH amide), 3230 (NH amine), 1731 (C=O), 1126 (C=S) cm^{-1}; Conformer **A**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.31 (t, $J = 7.07$ Hz, 3H, CH_3CH_2), 2.24 (s, 3H, CH_3CO), 3.81 (s, 3H, CH_3O), 3.45, 3.67 (qq, 2H, CH_3CH_2), 6.81–7.91 (m, 9H, CH aromat.), 10.36 (s, 1H, NH amide), 6.21 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 15.26 (CH_3CH_2), 23.59 (CH_3CO), 55.49 (CH_3O), 59.51 (CH_3CH_2). 95.1 (C2), 114.18–158.42 (C aromat.) 181.89 (C=S), 193.56 (C=O) ppm; Conformer **B**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.24 (t, $J = 7.07$ Hz, 3H, CH_3CH_2), 2.15 (s, 3H, CH_3CO), 3.84 (s, 3H, CH_3O), 3.47, 3.72 (qq, 2H, CH_3CH_2), 6.81–7.91 (m, 9H, CH aromat), 10.69 (s, 1H, NH amide), 2.51 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 18.4 (CH_3CH_2), 31.47 (CH_3CO), 55.49 (CH_3O), 58.44 (CH_3CH_2), 95.15 (C2), 114.18–158.42 (C aromat.), 161.5 (C=S), 201.71 (C=O) ppm.

2-(Ethoxy-phenyl-amino)-3-oxo-N-(4-chlorophenyl)-thiobutyramide (**3d**; $C_{18}H_{19}O_2N_2SCl$)

Yield: 55%; m.p.: 99°C (yellow needles); IR (KBr): $\nu = 3299$ (NH amide), 3249 (NH amine), 1735 (C=O), 1120 (C=S) cm^{-1}; Conformer **A**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz); 1.32 (t, $J = 7.05$ Hz, 3H, CH_3CH_2), 2.23 (s, 3H, CH_3CO), 3.44, 3.69 (qq, 2H, CH_3CH_2), 6.81–796 (m, 9H, CH aromat.), 10.45 (s, 1H, NH amide), 6.14 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 15.25 (CH_3CH_2), 23.48 (CH_3CO), 59.68 (CH_3CH_2), 95.3 (C2), 115.56–145.67 (C, aromat.), 183.21 (C=S), 194.36 (C=O) ppm; Conformer **B**: ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.24 (t, $J = 7.05$ Hz, 3H, CH_3CH_2), 2.14 (s, 3H, CH_3CO), 3.47, 3.71 (qq, 2H, CH_3CH_2) 6.81–7.96 (m, 9H, CH aromat.), 10.77 (s, 1H, NH amide), 2.51 (s, 1H, NH amine) ppm; ^{13}C NMR ($CDCl_3$, δ, 125 MHz): 18.4 (CH_3CH_2), 31.41 (CH_3CO), 58.43 (CH_3CH_2), 95.2 (C2), 115.56–145.67 (C aromat.), 161.18 (C=S), 201.54 (C=O) ppm.

X-Ray analysis

Crystal data: $C_{18}H_{19}ClN_2O_2S$, $MW = 362.86$, monoclinic, $P2_1/n$, $a = 10.603(2)$, $b = 13.822(3)$, $c = 12.477(2)$ Å, $\alpha = 90.0$, $\beta = 92.486(11)$, $\gamma = 90.0°$, $V = 1826.8(6)$ Å^3, $Z = 4$, $D = 1.319\,Mg \cdot m^{-1}$, $\lambda(MoK_\alpha) = 0.71073$ Å, $\mu = 0.336\,mm^{-1}$, $F(000) = 760$, $T = 227$ K.

Crystals of **3d** suitable for X-ray analysis were grown from an ethanolic solution as gold yellow rhombohedra. A crystal of dimensions of $0.50 \times 0.30 \times 0.28$ mm was used for the X-ray measurements. X-Ray intensities were collected at 227 K on a Siemens SMART CCD diffractometer equipped with a nitrogen gas stream LT device (Bruker LT3) using graphite-monochromated MoK_α radiation. Intensity measurements were carried out in the range $1.4 \leq \theta \leq 31.4°$ with the program SAINT [11] giving 5528 symmetry-independent reflections used for structure solution and refinement. They were corrected for absorption effects using the program SADABS [12]. The structure was solved by direct methods using the program SIR-92 [13] and refined against F^2 by full-matrix least squares using SHELXL-97 [14]. The H-atoms were initially introduced in calculated positions and then refined with isotropic thermal parameters, whereas all non-hydrogen atoms were refined anisotropically. The refinement of 294 parameters by least-square method converged at $R = 0.0415$ and $wR = 0.0846$ for 2684 reflections with $I > 2\sigma(I)$ and $R = 0.0920$ and $wR = 0.0933$ for all data. $w = (\sigma^2 \cdot (F_o^2) + (0.0375p)^2)^{-1}$, where $p = (F_o^2 + 2F_C^2)/3$; extinction coefficient = 0.0000 (4); max. and min. peak on final difference *Fourier* map: 0.58 and $-0.34\,eÅ^{-3}$, respectively. Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Center (CCDC No. 150154).

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