STUDY OF TAUTOMERIC AND ISOMERIC BEHAVIOUR OF NEW 2-ARYLHYDRAZONO-1,4-BENZOTHIAZINES

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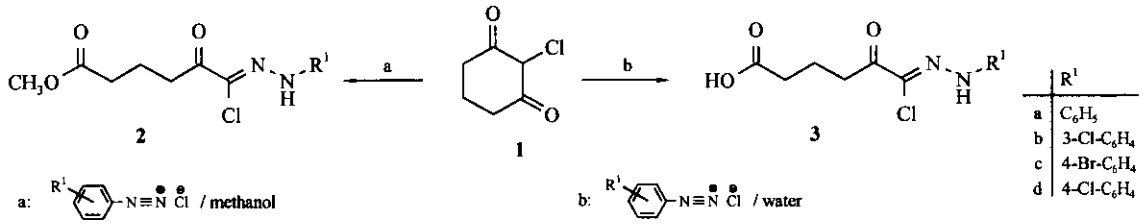
Abstract - Cyclization reactions of α-ketohydrazonyl chlorides such as methyl 6-arylhydrazono-6-chloro-5-oxohexanoates (**2**) and the 6-arylhydrazono-6-chloro-5-oxohexanoic acids (**3**) with *o*-aminothiophenol lead to 1,4-benzothiazine derivatives. The tautomeric and isomeric equilibria are discussed using ^{1}H and ^{15}N NMR as well as X-Ray diffraction analysis.

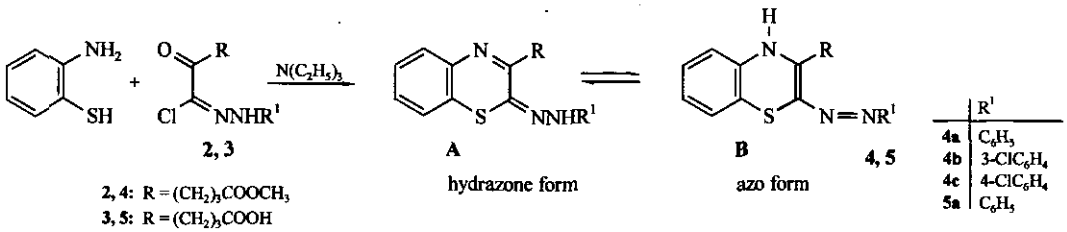
In a previous paper[1] we described the synthesis of methyl 6-arylhydrazono-6-chloro-5-oxohexanoates (**2**) obtained by the Japp-Klingemann-cleavage of 2-chlorocyclohexane-1,3-dione (**1**). The reaction was carried out with methanol as the solvent. The 6-arylhydrazono-6-chloro-5-oxohexanoic acids (**3a-3d**) were formed under aqueous conditions (see Scheme 1).



Scheme 1

Due to their reactivity and their ease of preparation α-ketohydrazonyl chlorides are used as starting compounds for the formation of various heterocyclic systems. Recently, we reported the synthesis of

1,4-benzothiazine derivatives (**4**) through the reaction of **2** with *o*-aminothiophenol.[2] According to our findings the 1,4-benzothiazinyl derivative of butanoic acid (**5a**) was obtained from **3a** and *o*-aminothiophenol (see Scheme 2).



Scheme 2

Compounds (**4**) and (**5**) can exist in the tautomeric hydrazone form **A** or azo form **B**, but according to literature the hydrazone form should be preferred.[3] The measured UV-absorption spectrum of **4a** shows a maximum near 400 nm. Analogous azo compounds have an UV-maximum near 500 nm.[4] The UV-absorption curves of **4a** measured in DMSO or acetone exhibit an additional maximum near 510 nm (see Table 1).

Table 1: *UV absorption maxima λ_{max} in nm (lg ε) and chemical shift δ in ppm of the ^{1}H NMR signal for the NH proton of compound (**4a**) dependent on the solvent and pH value*

solvent	λ_{max} in nm (lg ε, sh = shoulder)	solvent	*δ in ppm*
heptane	404 (sh), 386 (4.22), 297 (sh), 272 (4.27)		
toluene	390 (4.21), 305 (sh), -	benzene-d_6	6.71
chloroform	392 (4.28), 304, 295 (sh), 278 (4.33)	$CDCl_3$	7.20
methanol	402 (4.22), 308 (sh), 290 (4.29)	CD_3OD	7.78
acetone	514 (3.08), 398 (4.25), -	acetone-d_6	8.77
DMSO	512 (3.57), 402 (4.30), 294 (4.36), 278 (sh)	DMSO-d_6	9.48
pyridine	530 (2.99), 404 (4.27), 304 (4.30), -	pyridine-d_5	10.04
1.0 M KOH [a]	514 (3.90), 404 (3.98), 305 (sh), 294 (4.15)	-	
1.0 M HCl [a]	498 (4.30), 403 (4.27), 314 (4.23), 290 (sh), 272 (4.19)	TFA	8.89 [b]

[a] methanolic
[b] additional signal at 11.7-11.9 for $[=NH-]^+$

The solution of **4a** in chloroform is yellow, in DMSO it is red. We supposed the equilibrium between the hydrazone form **A** and the azo form **B** to shift towards the azo tautomer if dissolved in dipolar aprotic agents. A tautomeric behaviour of similar compounds in DMSO was described by Kurasawa *et al.*[5] They investigated both solvent and substituent effects on the tautomer ratios between the hydrazone imine and diazenyl enamine form in 3-arylhydrazonomethyl-2-oxo-1.2-dihydroquinoxalines using the ^{1}H NMR signals of the hydrazone or diazenyl C-H.[6] The ^{1}H NMR spectra of the compounds (**4**) and (**5**)

exhibit the signals expected for the methyl ester group, for the methylen protons and for the aryl protons [see experimental part, ^{1}H NMR spectrum of compound (**5**) and literature[2]]. The signal of the NH proton strongly depends on the solvent (see Table 1 and 2). We assume the great difference in the chemical shift of the NH proton to indicate a different tautomer ratio in a solvent dependent manner.

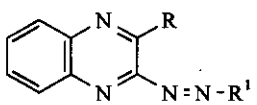
Table 2: *Chemical shift δ in ppm of the ^{1}H signals for the NH proton in dependence on the solvent*

	4a	**4b**	**4c**	**5a**
$CDCl_3$	7.20	7.15	7.16	7.22
DMSO-d_6	9.48	9.66	9.61	9.48

Using NOE-experiments we demonstrated that the tautomeric hydrazone structure (**4A**) does not only exist in the solvent $CDCl_3$ but also in DMSO-d_6 because we observed an NOE-signal of the NH proton to the ortho-protons of the phenyl substituent R^1 in either solvent.

Furthermore, the recorded ^{15}N NMR spectrum of compound (**4a**) in $CDCl_3$ with DMF as internal standard displays two signals for the =N- near -50 ppm and one signal for the -NH- nitrogen at -236 ppm. Similar chemical shifts of ^{15}N-signals appear in the spectrum of **4a** recorded in DMSO-d_6 (see Table 3). Recently, we described the synthesis of compounds such as **6** and **7** containing an -N=N- structure (see Scheme 3). According to literature data[7] the chemical shifts of ^{15}N-signals for an azo group were found in the range of 50-150 ppm (see Table 3). However, no signal near 100 ppm was observed in the ^{15}N NMR spectrum of **4a** (see Table 3).

Scheme 3



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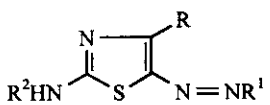

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$R = (CH_2)_3COOCH_3$
$R^1 = C_6H_5$
$R^2 = CH_3(CH_2)_3$

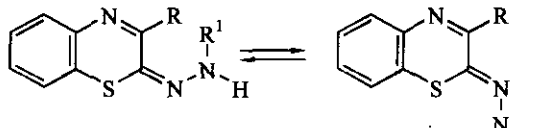
Table 3: *Chemical shift δ in ppm of the ^{15}N signals in dependence of the solvent (DMF was used as internal standard)*

compound	solvent	-NH-	=N-	-N=N-
4a	$CDCl_3$	-235.7	-61.0, -77.8	
	DMSO-d_6	-231.8	-59.1, -78.8	
	DMSO-d_6/10% TFA	-202.2, -196.6	-30.3	
6	$CDCl_3$		-47.7, -84.5	159.5, 128.4
7	DMSO-d_6	-276.9	-126.3	53.0, 76.2

Although small amounts of the other tautomer could have been detected, we did not found an additional ^{1}H NMR signal for another NH proton. As a result of these observations we can exclude a tautomeric equilibrium. The hydrazone form **A** is preferred in polar and non polar solvents. The additional UV

maximum of **4a** in DMSO at 510 nm cannot be interpreted by the changes in tautomer ratio from the hydrazone towards the azo form. Additionally, we measured a ^{15}N NMR spectrum in the mixture of trifluoroacetic acid (TFA) and DMSO-d_6 (see Table 3) to assess whether the UV absorption maximum at 498 nm of compound (**4a**) in 1.0 M methanolic HCl results from changes in tautomer ratio according to the literature.[6] The signal found at -30 ppm was easily assigned to =N- and at -202 and -196 ppm to -NH by analogy with those in DMSO-d_6 alone, respectively. However, no signal appears at 100 ppm for an azo group. The colour of the acidic solution of compound (**4a**) cannot be explained by changes in the tautomeric equilibrium despite an additional UV maximum is observed. This phenomenon is construed by the resonance-stabilized positive charge in the protonated molecule. In conclusion from the NMR data we excluded any tautomeric changes of compound (**4a**).

To investigate the occurrence of the additional absorption maximum of **4a** in DMSO solution we considered the possibility of two geometric isomers.



4 E **4 Z**

Hegarty and Cunningham described the isomerization of amidrazones.[8] They assigned the isomer ratio by ^1H and ^{13}C NMR data and studied the pH-dependent isomerization of the prepared Z amidrazones. Interestingly, they observed a bathochromic shift of the absorption band near 400 nm when solving the substances in 1.0 M KOH. This observation was explained with a change in isomer ratio towards the E isomer. Besides, their observed up-shift for about 20 nm does not correspond to our additionally observed absorption maximum of **4a** near 510 nm. Furthermore, the NOE experiments in $CDCl_3$ and DMSO-d_6 revealed no effect of the NH proton to the methylen group neighbouring to the heterocyclic system. All these data confirm the compounds (**4**) and (**5**) to prefer the tautomer hydrazone form with Z configuration.

AM1-CI calculations show that the first excitable state with the lowest energy of compound (**4c**) is a triplet at about 530 nm and the second a singlet at about 400 nm. We suppose the dipolar aprotic solvents to lead to a polar interaction with the H atom of the hydrazone group and to increase the excitation probability of the triplet state.[9]

Contrarily the recrystallization of compound (**4c**) from heptane/chloroform and from DMSO gave yellow and red crystals, respectively. We carried out an X-Ray diffraction analysis to clarify these differences in colour. Surprisingly the crystal structures of both were identical in all parameters. Compound (**4c**) exists in a Z configuration (Figure 1) that is stabilized by a weak interaction between

the hydrogen atom at N3 and S1 [distance N3...S1 2.869(2) Å, distance H3N...S1 2.50(2) Å, angle N3-H3N...S1 109(2)°].

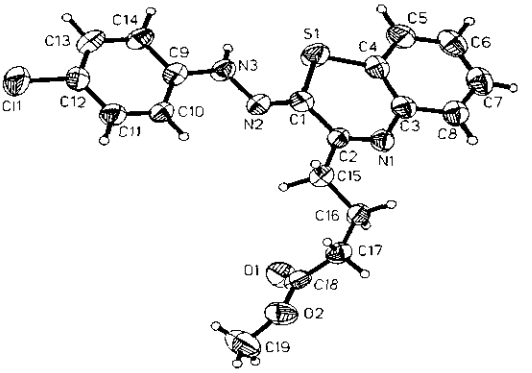


Figure 1

*ORTEP-drawing of the molecular structure in the crystal of compound (**4c**) (displacement ellipsoides with 50% probability)*

The benzothiazine and the phenylhydrazone groups form a planar moiety caused by the conjugative effect of the π–electron system. Adjacent molecules related by an inversion centre of the space group are associated through weak intermolecular hydrogen bonds [distance N3...O1a 3.094(2) Å, distance H3N...O1a 2.33(2) Å, angle N3-H3N...O1a 155(2)°], thus forming molecular pairs within the crystal packing (Figure 2).

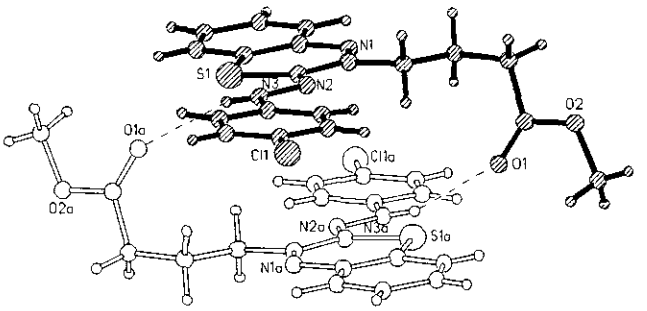


Figure 2

*Structure of a centrosymmetrical molecular pair in the crystal of compound **4c** showing hydrogen bonds (dashed lines)*

ACKNOWLEDGEMENT

The X-Ray crystallographic experiments were supported by the Fond für Chemische Industrie.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus; IR spectra were recorded on a Specord 75 IR (Carl Zeiss Jena); UV spectra were determined with a dioden-array-spectrophotometer HP8452A; mass spectra by means of an AMD 402 of the firm AMD INTEDRA (70 eV); the NMR spectra were recorded on a Varian Unity 500 and Gemeni 200, operating at 499.84 MHz and 199.95 MHz for ^{1}H and 50.67 MHz for ^{15}N NMR spectra. TMS was used as internal standard for ^{1}H NMR and formamide for ^{15}N NMR, deuteriochloroform or DMSO-d_6 as the solvent for all substances. Chemical shifts are given in δ units and refer to the centre of the signal.

6-Arylhydrazono-6-chloro-5-oxohexanoic acids (**3**)

General procedure

The appropriate arylamine (0.1 mol) was dissolved in 50 mL of 18% HCl and diazotized with a solution of sodium nitrite (0.1 mol, 6.9 g) in 25 mL of water at 0-5°C. The freshly prepared solution of the diazotized aniline was dropped to the mixture of sodium acetate trihydrate (0.2 mol, 27.0 g) and 2-chlorocyclohexane-1,3-dione (0.1 mol, 14.5 g) in 500 mL of water at 5-10°C. After stirring for 1 h the solid was collected, washed with water, dried and recrystallized from methanol/water.

6-Chloro-6-phenylhydrazono-5-oxohexanoic acid (**3a**)

Compound was prepared from aniline (0.1 mol, 9.3 g). Yield: 21.5 g (80%), yellow needles, mp 140-149°C.

3a: IR (KBr): ν 3270 (NH), 1700 (C=O acid), ^{1}H NMR (DMSO-d_6): δ 1.81 (m, J = 7.2 Hz, 2H, CH_2), 2.28 (t, J = 7.2 Hz, 2H, CH_2), 2.98 (t, J = 7.2 Hz, 2H, CH_2), 6.98-7.46 (m, 5H, Ar-H), 10.64 (s, 1H, NH), 12.07 (brs, 1H, COOH); MS m/z 268 (50) [M^+], 93 (100), 65 (78); Anal. Calcd for $C_{12}H_{13}N_2O_3Cl$: C, 53.64; H, 4.88; N, 10.43; Cl, 13.19. Found: C, 53.84; H, 5.01; N, 10.83; Cl, 12.87.

6-Chloro-6-(3-chlorophenyl)hydrazono-5-oxohexanoic acid (**3b**)

The above procedure was repeated using 3-chloroaniline (0.1 mol, 12.8 g). Yield: 21.2 g (70%), yellow needles, mp 144-152°C.

3b: IR (KBr): ν 3270 (NH), 1700 (C=O acid), ^{1}H NMR (DMSO-d_6): δ 1.80 (m, J = 7.2 Hz, 2H, CH_2), 2.28 (t, J = 7.3 Hz, 2H, CH_2), 2.99 (t, J = 7.4 Hz, 2H, CH_2), 6.97-7.43 (m, 4H, Ar-H), 10.74 (s, 1H, NH), 12.04 (brs, 1H, COOH); MS m/z 302 (80) [M^+], 127 (100), 99 (60), 87 (75); Anal. Calcd for $C_{12}H_{12}N_2O_3Cl_2$: C, 47.55; H, 3.99; N, 9.24; Cl, 23.39. Found: C, 47.46; H, 4.08; N, 9.22; Cl, 23.12.

6-(4-Bromophenyl)hydrazono-6-chloro-5-oxohexanoic acid (**3c**)

The above procedure was repeated using 4-bromoaniline (0.1 mol, 17.2 g). Yield: 20.2 g (58%), yellow needles, mp 189-191°C.

3c: IR (KBr): ν 3270 (NH), 1700 (C=O acid), ^{1}H NMR (DMSO-d_6): δ 1.80 (m, J = 7.2 Hz, 2H, CH_2), 2.27 (t, J = 7.3 Hz, 2H, CH_2), 2.97 (t, J = 7.3 Hz, 2H, CH_2), 6.97-7.53 (dd, J = 9.0 and 9.2 Hz, 4H, Ar-H), 10.73 (s, 1H, NH), 12.05 (s, br., 1H, COOH); MS m/z 302 (85) [M^+], 127 (100), 99 (50), 87 (75); Anal. Calcd. for $C_{12}H_{12}BrClN_2O_3$: C, 41.47; H, 3.48; N, 8.06. Found: C, 41.47; H, 3.56; N, 7.88.

6-Chloro-6-(4-chlorophenyl)hydrazono-5-oxohexanoic acid (**3d**)

The above procedure was repeated using 4-chloroaniline (0.1 mol, 12.8 g). Yield: 20.6 g (68%) of yellow needles, mp 170-175°C.

3d: IR (KBr): ν 3270 (NH), 1700 (C=O acid), ^{1}H NMR (DMSO-d6): δ 1.80 (m, J = 7.2 Hz, 2H, CH_2), 2.28 (t, J = 7.3 Hz, 2H, CH_2), 2.99 (t, J = 7.4 Hz, 2H, CH_2), 6.97-7.48 (dd, J = 8.8 and 8.8 Hz, 4H, Ar-H), 10.74 (s, 1H, NH), 12.05 (brs, 1H, COOH); MS m/z 348 (75) [M^+], 171 (75), 91 (100), 87

(70),63 (45), 55 (45); Anal. Calcd for $C_{12}H_{12}N_2O_3Cl_2$: C, 47.55; H, 3.99; N, 9.24; Cl, 23.39. Found: C, 47.49; H, 4.11; N, 9.22; Cl, 22.94.

Methyl 4-(2-arylhydrazono-2H-1,4-benzothiazin-3-yl) butanoates (**4**)

General procedure

A solution of triethylamine (10 mmol, 1.40 mL) in 20 mL of ethanol was added dropwise to a solution of methyl 6-arylhydrazono-6-chloro-5-oxohexanoate (**2**) and the equimolar amount of *o*-aminothiophenol (10 mmol, 1.26 g) in 75 mL of ethanol at rt. The mixture was stirred and refluxed for 2 h. After cooling the crystalline product was collected and recrystallized from methanol.

Methyl 4-(2-phenylhydrazono-2H-1,4-benzothiazin-3-yl) butanoate (**4a**)

From methyl 6-chloro-6-phenylhydrazono-5-oxohexanoate (**2a**) (10 mmol, 2.82 g). Yield: 1.42 g (40%) of dark yellow orange needles, mp 110-112°C.

Methyl 4-[2-(3-chlorophenyl)hydrazono-2H-1,4-benzothiazin-3-yl] butanoate (**4b**)

The procedure carried out with methyl 6-chloro-6-(3-chlorophenyl)hydrazono-5-oxohexanoate (**2b**) (10 mmol, 3.16 g). Yield: 2.66 g (69%) of yellow crystals, mp 98-100°C.

Methyl 4-[2-(4-chlorophenyl)hydrazono-2H-1,4-benzothiazin-3-yl] butanoate (**4c**)

From methyl 6-chloro-6-(4-chlorophenyl)hydrazono-5-oxohexanoate (**2c**) (10 mmol, 3.16 g). Yield: 1.53 g (79%) of yellow crystals, mp 165-168°C.

Further analytical data for compounds (**4a-4c**) see literature.[2]

X-Ray crystal structure analysis of **4c**:

The experiments were carried out with a four-circle diffractometer Stoe STADI4.

Cell parameters were derived from a least squares treatment of the setting angles of 72 reflections ($7.5 \leq \theta \leq 17.8°$). Intensities for 7990 reflections ($1.97 \leq \theta \leq 26.97$) were measured. The structure was solved by direct methods and refined by full matrix least squares on F^2 for 3995 unique data. Hydrogen atoms have been located in a difference Fourier map and their positions refined with isotropic displacement parameters.[10] The final R indices are R1 [I>2sigma(I)] = 0.0359 and R2 (all data) = 0.0993, the goodness of fit is S = 1.038.

Crystal data:

empirical formula	$C_{19}H_{18}N_3O_2SCl$	formula weight	387.87
temperature	293(2) K	wavelength	0.71073 Å
volume	1831.1(7) $Å^3$	Z	4
crystal system	monoclinic	space group	$P2_1/n$
unit cell dimensions	a = 9.396(2) Å, α = 90°	density (calculated)	1.400 Mg/m^3
	b = 20.627(5) Å, β = 103.01(2)°	absorption coeff.	0.342 mm^{-1}
	c = 9.696(2) Å, γ = 90°	F(000)	808
crystal size	0.36 x 0.26 x 0.15 mm	crystal colour	yellow

Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-405830, the names of the authors, and the journal citation.

4-(2-Phenylhydrazono-2H-1,4-benzothiazin-3-yl)butanoic acid (**5a**)

Compound was prepared as described above using 6-chloro-6-phenylhydrazono-5-oxohexanoic acid (**3a**). Yield: 1.35 g (40%), dark orange crystals, mp 171-178°C.

5a: IR (KBr): ν 3270 (NH), 1710 (C=O acid), ^{1}H NMR (DMSO-d_6): δ 1.97 (m, J = 7.4 Hz, 2H, CH_2), 2.36 (t, J = 7.2 Hz, 2H, CH_2), 2.92 (t, J = 7.4 Hz, 2H, CH_2), 6.88-7.46 (m, 9H, Ar-H), 9.48 (s, 1H, NH), 11.4-12.6 (brs, 1H, COOH); MS m/z 339 (100) [M^+], 188 (50), 162 (70), 149 (45), 93 (60), 77 (50); Anal. Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38; S, 9.43. Found: C, 63.51; H, 5.11; N, 12.19; S, 9.31.

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