

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

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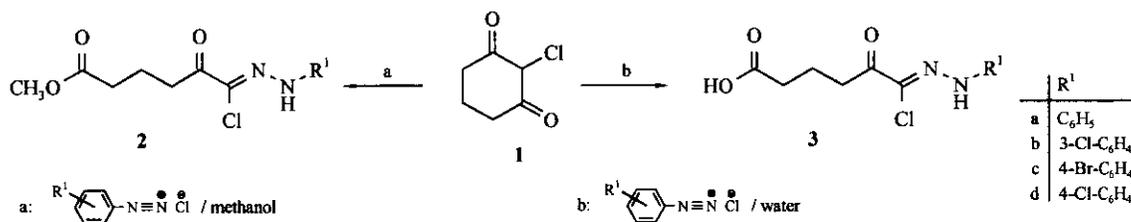
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Abstract - Cyclization reactions of α -keto-hydrazone chlorides such as methyl 6-arylhydrazone-6-chloro-5-oxohexanoates (**2**) and the 6-arylhydrazone-6-chloro-5-oxohexanoic acids (**3**) with *o*-aminothiophenol lead to 1,4-benzothiazine derivatives.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

In a previous paper¹ we described the synthesis of methyl 6-arylhydrazone-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-arylhydrazone-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 -keto-hydrazone chlorides are used as starting compounds for the formation of various heterocyclic systems. Recently, we reported the synthesis of

exhibit the signals expected for the methyl ester group, for the methylen protons and for the aryl protons [see experimental part, ^1H NMR spectrum of compound (5) and literature²]. 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 ^1H 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 data⁷ 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

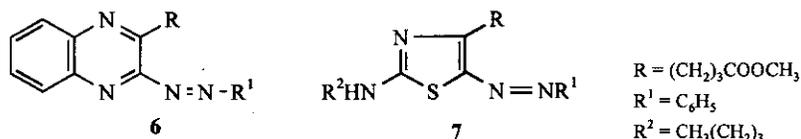


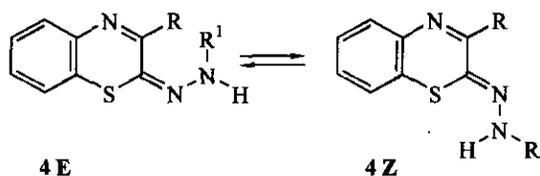
Table 3: Chemical shift δ in ppm of the ^{15}N signals in dependence of the solvent (DMF was used as internal standard)

| compound | solvent | -NH- | =N- | -N=N- |
|----------|----------------------------|----------------|--------------|--------------|
| 4a | CDCl_3 | -235.7 | -61.0, -77.8 | |
| | DMSO-d_6 | -231.8 | -59.1, -78.8 | |
| | $\text{DMSO-d}_6/10\%$ 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 find an additional ^1H 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.



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.

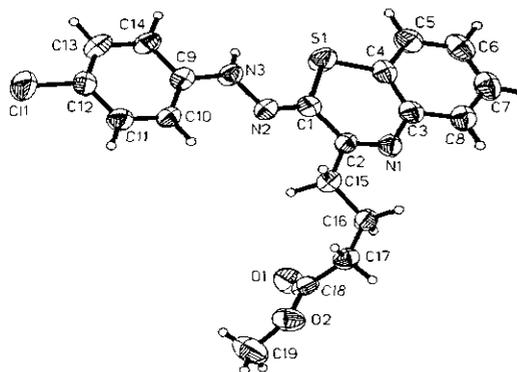
AM1-CI calculations show that the first excitable state with the lowest energy of compound (**4c**) is a triplet at about 530 nm and the second a singlet at about 400 nm. We suppose the dipolar aprotic solvents to lead to a polar interaction with the H atom of the hydrazone group and to increase the 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 ellipsoids with 50% probability)

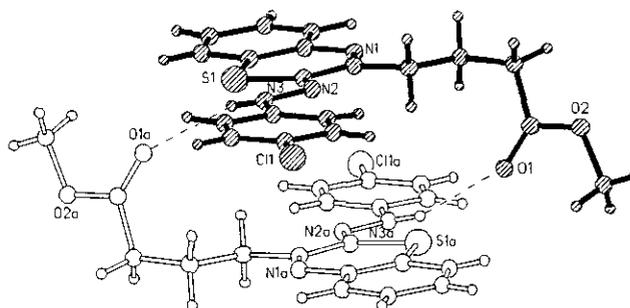


The benzothiazine and the phenylhydrazone groups form a planar moiety caused by the conjugative effect of the π -electron system.

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

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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 Gemini 200, operating at 499.84 MHz and 199.95 MHz for ^1H and 50.67 MHz for ^{15}N NMR spectra. TMS was used as internal standard for ^1H 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-Arylhrazono-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), $^1\text{H NMR}$ (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 $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_3\text{Cl}$: 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), $^1\text{H NMR}$ (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 $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3\text{Cl}_2$: 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), $^1\text{H NMR}$ (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 $\text{C}_{12}\text{H}_{12}\text{BrClN}_2\text{O}_3$: 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), $^1\text{H NMR}$ (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), 6.97-7.48 (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 ($7.5 \leq \theta \leq 17.8^\circ$). Intensities for 7990 reflections ($1.97 \leq \theta \leq 26.97^\circ$) 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 $R1 [I > 2\sigma(I)] = 0.0359$ 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, $\alpha = 90^\circ$ $b = 20.627(5)$ Å, $\beta = 103.01(2)^\circ$ $c = 9.696(2)$ Å, $\gamma = 90^\circ$ | density (calculated) | 1.400 Mg/m ³ |
| | | absorption coeff. | 0.342 mm ⁻¹ |
| | | 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), $^1\text{H NMR}$ (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 $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$: 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.

REFERENCES

1. P. Froberg, C. Kupfer, P. Stenger, U. Baumeister, and P. Nuhn, *Arch. Pharm. (Weinheim)*, 1995, **328**, 505
2. P. Froberg, M. Wiese, and P. Nuhn, *Arch. Pharm. Pharm. Med. Chem.*, 1997, **330**, 47
3. N. E. MacKenzie, R. H. Thomson, and C. W. Greenhalgh, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2923
4. C. Parkanyi, A. O. Abdelhamid, and A. S. Shawali, *J. Heterocycl. Chem.*, 1984, **21**, 521
5. Y. Kurasawa, A. Satoh, S. Ninomiya, H. Arai, K. Arai, Y. Okamoto, and A. Takada, *J. Heterocycl. Chem.*, 1987, **24**, 1229; Y. Kurasawa, K. Yamazaki, S. Tajima, Y. Okamoto, and A. Takada, *J. Heterocycl. Chem.*, 1986, **23**, 957
6. Y. Kurasawa, T. Hosaka, A. Takada, H. S. Kim, and Y. Okamoto, *J. Heterocycl. Chem.*, 1995, **32**, 531; Y. Kurasawa, T. Hosaka, A. Takada, H. S. Kim, and Y. Okamoto, *J. Heterocycl. Chem.*, 1995, **32**, 445
7. E. Breitmaier, *PharmUZ*, 1983, 12, 161
8. I. D. Cunningham and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. II*, 1986, 537
9. O. Lichtenberger and P. Froberg, publication in preparation
10. G. M. Sheldrick, SHELXS-86, Program for the solution of crystal structures, Univ. Göttingen, Germany (1986), G. M. Sheldrick, SHELXL-93, Program for the refinement of crystal structures, Univ. Göttingen, Germany (1993)

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