# Synthesis and Stereochemistry of Saturated and Partially Saturated 4-Aryl-4*H*-3,1-benzothiazine-2(1*H*)-thiones

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The reaction of 2-arylidenecyclohexanones **1** with dithiocarbamic acid gave three of the four possible diastereomers of 4-aryl-4a,5,6,7,8,8a-hexahydro-8a-hydroxy-4*H*-3,1-benzothiazine-2(1*H*)-thiones **2**–**4**. The isomeric composition of the reaction products was found to depend on the quantity of hydrochloric acid used as catalyst. $^1$H-NMR studies showed that the preferred conformation of the *cis* isomers **2** and **4** is controlled by the bulky 4-aryl group, which always occupies the energetically more favourable quasiequatorial position. Dehydration of **2**–**4** afforded the corresponding 4-aryl-tetrahydro-4*H*-3,1-benzothiazine-2(1*H*)-thiones **5** and **6**. The orientation of the dehydration reactions depends on the configuration of the starting compounds **2**–**4** and the reaction conditions used.

**Synthese und Stereochemie gesättigter und partiell gesättigter 4-Aryl-4*H*-3,1-benzothiazin-(1*H*)-thione**

Die Reaktion von 2-Arylidenecyclohexanonen **1** mit Dithiocarbaminsäure ergab drei von den vier möglich Diastereomeren von 4-Aryl-4a,5,6,7,8,8a-hexahydro-8a-hydroxy-4*H*-3,1-benzothiazin-2(1*H*)-thionen **2**–**4**. Die Isomeren-Zusammensetzung der Reaktionsprodukte ist von der Menge der als Katalysator verwendeten Salzsäure abhängig. $^1$H-NMR-Spektroskopie zeigt, daß die begünstigte Konformation der *cis*-anellierten Isomeren **2** und **4** von der sterisch anspruchsvollen 4-Aryl-Gruppe bestimmt wird, die immer die energetisch günstigere quasiäquatoriale Position besetzt. Dehydratisierung von **2**–**4** führte zu den entsprechenden 4-Aryl-tetrahydro-4*H*-3,1-benzothiazin-2(1*H*)-thionen **5** und **6**. Die Richtung der Dehydratisierungsreaktionen war abhängig von der Konfiguration der Ausgangsverbindungen **2**–**4** und den Reaktionsbedingungen.

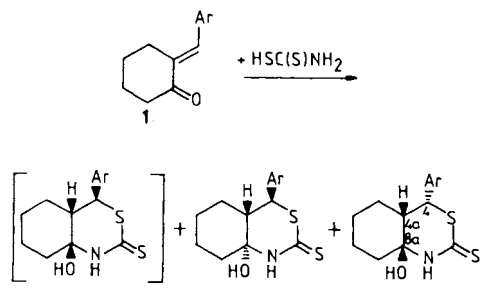
The acid-catalyzed reaction of thiocarbonic acid derivatives (e.g. thioamides, dithiocarbamates, thioureas) with α,β-unsaturated carbonyl compounds is a method frequently used for synthesis of 1,3-thiazines[1]. Earlier, we have shown that reaction of dithiocarbamic acid with α,β-unsaturated ketones is a suitable model to study the mechanism[2] and the stereochemistry[3] of this type of addition reactions. As a continuation of our earlier work in this field, we report here the results obtained by treating dithiocarbamic acid with 2-arylidenecyclohexanones **1a**–**d**[4]. This reaction gave further information on the stereochemistry of the addition process and offered a versatile route for the synthesis of the so far unknown saturated derivatives of 4-aryl-4*H*-3,1-benzothiazine-2(1*H*)-thiones, which have both pharmacological[5] and chemical[6] interest.

## Results and Discussion

The reaction of dithiocarbamic acid with compounds **1a**–**d** was carried out in acidic aqueous methanol/acetone solution at −5°C to yield three of the four possible diastereomers of the expected 4-aryl-4a,5,6,7,8,8a-hexahydro-8a-hydroxy-4*H*-3,1-benzothiazine-2(1*H*)-thiones **2**–**4** (Scheme 1)[7].

In order to investigate the stereochemical outcome of the reactions, the crude products were analyzed by $^1$H-NMR

Scheme 1




**a** Ar = $C_6H_5$ **b** Ar = $C_6H_4$–$OCH_3$(p)

**c** Ar = $C_6H_4$–$CH_3$(p) **d** Ar = $C_6H_4$–Cl(p)

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spectroscopy in each case (see Experimental). The results obtained showed that under conditions described in our earlier paper[2] (using nearly equimolar amounts of hydrochloric acid and ammonium dithiocarbamate; Method A) **1a–d** afforded a ca. 1:1 mixture of **2a–d** and **3a–d**. Upon increasing the reaction time for 24 hours, only the presence of **3a–d** could be detected. This experimental result can be well interpreted by the epimerization of the kinetic products **2a–d** into the thermodynamically more stable ones **3a–d**. This was also supported by the fact that compounds **2a–d** underwent epimerization to the respective **3a–d** during crystallization; thus, only compounds **3a–d** could be isolated as homogeneous products. If more hydrochloric acid was used (3:2 molar excess of hydrochloric acid over ammonium dithiocarbamate; Method B) the formation of compounds **3a–d** could be detected as sole products.

If we used only a quarter of an equivalent of hydrochloric acid compared to ammonium dithiocarbamate (Method C), only **4a–d** were formed. These diastereomers were configurationally stable even under the conditions indicated in Method B. Changing the quantity of hydrochloric acid employed between the values indicated in Method B and C, the formation of all three diastereomers could be observed in different quantities depending on the volume of hydrochloric acid used. It was found that neither the solvent (methanol/aceton) nor the aromatic substitution of **1a–d** changed significantly the isomeric composition of the respective mixtures.

The structures of the compounds obtained were elucidated by IR, MS, and $^1$H-NMR studies. In the IR spectra the ν(C=O) band of the starting ketones was absent and a broad band due to the overlapping ν(OH) and ν(NH) vibrations appeared in the range 3640–3210 cm$^{-1}$. The mass spectra of **3a** and **4a** exhibited molecular ions at $m/z$ = 279 with the expected elemental composition of $C_{14}H_{17}NOS_2$ as determined by exact mass measurements and revealed from isotope distribution. In the spectra a number of abundant fragment ions appeared at common $m/z$ values, indicating easy loss of $H_2O$, $CS_2H$, and $NH_2CS_2$ as neutral entities as well as formation of $C_6H_5CH{=}SH^+$ and $C_7H_7^+$ ions from both molecules.

The stereochemical characterization of the diastereomeric structures was established by applying the $^1$H-NMR method described in detail in connection with the conformational analysis of related saturated heterocycles[8]. The deciding spectral parameters concerning the stereochemistry of compounds **2–4** [δ(8a-OH), δ(4-H), δ(4a-H), and $^3J$(4,4a)] are given in Table 1.

Investigation of the closely related bicyclic (fused skeleton) saturated 1,3-oxazines (thiazines)[9–11] showed that the *trans*-fused isomers have only one, while the *cis*-annulated isomers have two (*N*-inside and *N*-outside) possible chair-chair conformations. The possible chair-chair conformations of the *cis*-annulated isomers **2** and **4** are shown in Figure 1.

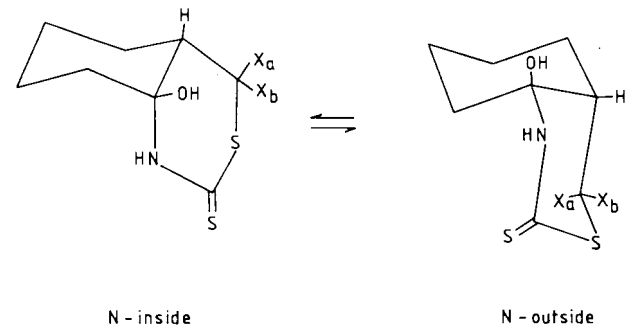



Figure 1. *N*-inside and *N*-outside conformations of compounds **2** and **4** (**2**: $X_a$ = H, $X_b$ = Ar; **4**: $X_a$ = Ar, $X_b$ = H)

The $^1$H-NMR and $^1$H-$^1$H 1D-NOE difference measurement[12] data as documented in Tables 1 and 2 prove the constitution and configuration of compounds **2–4**. The data suggest conformationally homogenous systems and show that the preferred conformation of the *cis*-fused compounds **2** and **4** (*N*-outside and *N*-inside, respectively) is controlled by the bulkyl 4-aryl group, which always occupies the energetically more favourable quasiequatorial position. This is in good agreement with the earlier results showing that the preferred conformation of the nearly analogous *cis*-annulated bicyclic 1,3-oxazine (thiazine) derivatives[9–11] primarily depends on the steric requirement of the groups attached to the annulated carbon atoms.

Table 1. $^1$H-NMR data (60 MHz, [D$_6$]DMSO, δ in ppm, $J$ in Hz) of compounds **2–4**

| | NH s (1H) | ArH s (4H) | 8a-OH s (1H) | 4-H d (1H) | $^3J$(4,4a) | 4a-H[a] m (1H) | $CH_2$ (5,6,7,8) m (8H) | Other signals |
|---|---|---|---|---|---|---|---|---|
| **2a**[b] | 10.40 | 7.26[c] | 6.21 | 4.83 | 11.6 | 2.39 | [d] | |
| **2b**[b] | 10.35 | 6.8–7.4[e] | 6.18 | 4.69 | 12.7 | 2.37 | [d] | 3.74[f] |
| **2c**[b] | 10.49 | 7.13 | 6.21 | 4.89 | 12.1 | 2.44 | [d] | 2.30[g] |
| **2d**[b] | 10.36 | 7.38 | 6.24 | 4.86 | 11.1 | 2.38 | [d] | |
| **3a** | 10.59 | 7.30[h] | 6.21 | 4.38 | 11.2 | 1.96 | 0.8–2.4 | |
| **3b** | 10.60 | 6.8–7.4[e] | 6.18 | 4.33 | 11.0 | 1.93 | 0.7–2.4 | 3.74[f] |
| **3c** | 10.59 | 7.18 | 6.21 | 4.37 | 10.9 | 1.94 | 0.7–2.4 | 2.30[g] |
| **3d** | 10.59 | 7.41 | 6.24 | 4.41 | 11.3 | 2.01 | 0.7–2.4 | |
| **4a** | 10.55 | 7.34[h] | 6.44 | 5.23 | 3.7 | 1.88 | 0.7–2.4 | |
| **4b** | 10.55 | 6.9–7.5[e] | 6.46 | 5.24 | 3.2 | 1.84 | 0.7–2.4 | 3.78[f] |
| **4c** | 10.51 | 7.20 | 6.42 | 5.24 | 3.6 | 1.89 | 0.7–2.4 | 2.31[g] |
| **4d** | 10.52 | 7.47 | 6.44 | 5.25 | 3.8 | 1.90 | 0.7–2.4 | |

[a] Determined by double resonance experiment. – [b] Data determined from the corresponding mixtures of **2** and **3**. – [c] m (5H). – [d] Cannot be determined. – [e] m (4H). – [f] $CH_3O$, s (3H). – [g] $CH_3$, s (3H). – [h] s (5H).

Table 2. Selected $^1$H-NMR data (200 MHz, [D$_6$]DMSO, δ in ppm, *J* in Hz) and results of $^1$H-$^1$H 1D-NOE difference experiments[a] of compounds **2a**, **3a**, and **4a**

| Compound | Irradiated proton | Observed proton NOE (%) |
|---|---|---|
| **2a**[b] | 4-H 4.83 [d, $^3J$(4,4a) = 11.3] | 5-H$_{eq}$ (6) |
| | 8a-OH 6.20 [d, $^4J$(8a-OH, 8-H$_{ax}$) = 1.5] | NH (5), 4a-H (14) |
| | NH 10.40 (s) | 8a-OH (8), 5-H$_{eq}$ (4) |
| **3a** | 4-H 4.38 [d, $^3J$(4,4a) = 11.7] | 8a-OH (6) |
| | 8a-OH 6.29 [d, $^4J$(8a-OH, 4a-H) = 1.2] | 4-H (6) |
| | NH 10.68 (s) | 8a-OH (5), 8-H$_{eq}$ (5) |
| **4a** | 4-H 5.24 [d, $^3J$(4,4a) = 3.5] | 8a-OH (8), 4a-H (6) |
| | 8a-OH 6.50 (s) | 4-H (6) |
| | NH 10.93 (s) | 8-H$_{eq}$ (3) |

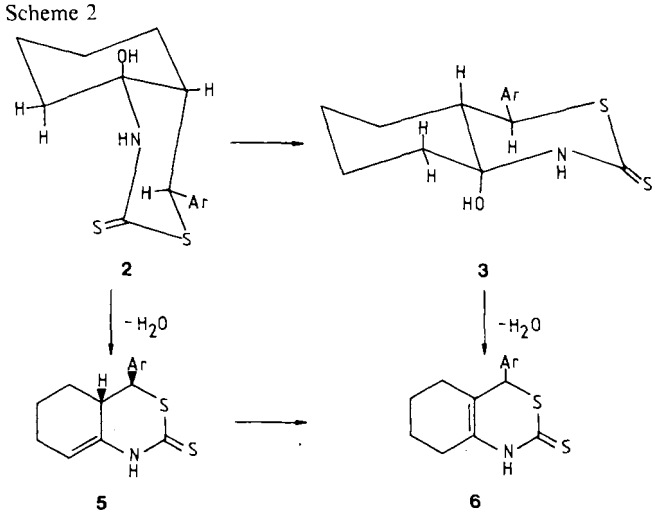
[a] Performed as described in Experimental. – [b] Data were determined from the mixtures of **2a** and **3a**.

Another subject of the present work was a study on the dehydration of the obtained compounds **2**–**4**. We chose three acid-catalyzed reactions to investigate [Method A: *p*-TSA/PhH; Method B: TFA/PhH; Method C: $(C_2H_5)_2O-BF_3/CHCl_3$]; partly to study the scope and limitation of the earlier results[13] obtained in dehydration of some monocyclic 4-hydroxy-1,3-thiazine-2-thiones (Methods A and B), and partly to investigate the action of $(C_2H_5)_2O-BF_3$ (Method C), which proved to be an effective catalyst in the reaction of **1a** with cyclic thioureas to give tricyclic 1,3-thiazine derivatives[14].

$^1$H-NMR analysis of the crude products (see Experimental) showed that dehydration of **3a**–**d** and **4a**–**d** furnished only the thermodynamically more stable **6a**–**d** under all of the three conditions investigated. Dehydration of the isomeric mixtures of **2a**–**d** and **3a**–**d** using Method A or Method C led to the formation of the respective **6a**–**d**, too. Using Method B in the latter case, however, the mixtures of **2a**–**d** and **3a**–**d** underwent dehydration the corresponding mixtures of **5a**–**d** and **6a**–**d**. It was found that the isomeric ratio of compounds **2** and **3** in the starting mixtures corresponded well with that of **5** and **6** in the dehydrated products, respectively. Taking into consideration that the separated **5a**–**d** underwent isomerization into the respective **6a**–**d** on longer treatment under all the dehydration methods investigated, the above results strongly suggest that dehydration of **2a**–**d** using Method B led to the formation of the corresponding **5a**–**d**. Such a difference between the observed orientations of dehydration of diastereomers **2** and **3** can be well interpreted by the stereoelectronically most preferred *trans*-diaxial orientation of the leaving groups[15] (Scheme 2)[7].

As for dehydration of compounds **4a**–**d**, the above results allow us to propose that formation of the corresponding **6a**–**d** can be considered as a result of a specific elimination

Scheme 2




process. The orientation pattern can be explained as a consequence of the steric effect of the bulky 4-aryl substituent, which should occupy an unfavoured quasiaxial position in the respective Hofmann rule products.

The structures of the compounds obtained were determined by IR, $^1$H-NMR, and MS. Comparing the IR spectra of derivatives **5** and **6** with those of the respective **3** and **4**, the most marked change is the disappearance of the ν(OH) bands, and the presence of the bands in the range 1690 to 1655 cm$^{-1}$ due to the newly formed carbon–carbon double bond. The isomeric structures **5** and **6** can be easily distinguished on the basis of the $^1$H-NMR spectra, in which the 4-H resonance is a singlet for **6a**–**d** but shows a doublet for **5a**–**d**. In the latter case the appearance of the olefinic signal (δ = 5.6–5.7) is unambiguous evidence of the progress of the elimination reaction. The magnitude of $^3J$(4,4a) (ca. 11 Hz) for **5a**–**d** is in agreement with the antiperiplanar position[16] of the 4-H and 4a-H protons, i.e. the *trans* configuration of the compounds. The mass spectra of **5a** and **6a** showed significant differences in the abundance of several fragment ions, which are also in accord with the structural isomerism. For example, the C-4a–C-8a double bond (**6a**) promotes the $CS_2H$ elimination by a retro Diels-Alder reaction, while it hinders the $C_6H_5CH{=}SH^+$ ion formation in contrast to the case of **5a**, where the latter process dominates.

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## Experimental

Melting points, uncorrected: Boetius apparatus. – IR spectra: Specord 75 IR. – $^1$H-NMR spectra, TMS as internal standard: Perkin-Elmer R12 (60 MHz) and Bruker WP-200 SY (200 MHz). – $^1$H-$^1$H 1D-NOE measurements: Samples were not degassed. Typically 35 dB (attenuated below 0.2 W) preirradiation power was applied for saturation of $^1$H transitions. The lines of a multiplett were consecutively irradiated[12b] resulting in a total duration of ca. 10 sec.

For NOE difference calculations, spectrum differences were calculated by an Aspect 2000 computer. – Mass spectra: AEI MS-

902 (70 eV, 100 μA, 8 kV, direct inlet, 160°C source temperature). – Microanalyses: Performed in-house and at the Central Research Laboratory, University Medical School, Pécs.

2-Arylidenecyclohexanones used as starting materials were synthesized according to literature methods[17]. Their (*E*) configuration was based on $^1$H-NMR investigations[18].

The isomeric composition of the reaction products was determined by $^1$H-NMR spectroscopy (60 MHz), based on the integrated peak areas of the well separated 4-H signals.

*General Procedures for the Addition of* **1a–d** *to Dithiocarbamic Acid:* To a solution of 0.175 mol (19.30 g) of freshly prepared ammonium dithiocarbamate[19] dissolved in 150.0 ml of 50% methanol (cooled to −5°C), 25.0 ml (Method A), 40 ml (Method B), or 6.5 ml (Method C) of 6.5 N hydrochloric acid (cooled to −5°C) was added dropwise, with stirring. Cooling and stirring was continued, and 0.030 mol of unsaturated ketone in 300 ml of methanol or 200 ml of acetone (for **1a–c**) or in 200 ml of acetone (for **1d**) (cooled to −5°C) was added dropwise to the reaction mixture. After stirring at this temperature for 4 h, the mixture was diluted with water, the precipitate formed was filtered off, washed free of acid with water, and crystallized to give colourless crystals.

*(4α,4aα,8aβ)-4a,5,6,7,8,8a-Hexahydro-8a-hydroxy-4-phenyl-4H-3,1-benzothiazine-2(1H)-thione* (**3a**): Yield 7.0 g (84%; Method B), m.p. 224–227°C (ethanol). – IR (KBr): ν = 3600–3260 cm$^{-1}$ (OH + NH), 2935 (CH), 1505 (C=C), 1340 (dithiourethane). – MS: *m/z* (%) = 281 (7), 280 (11), 279.0754 (65) [$M^+$, $C_{14}H_{17}NOS_2$, calcd. 279.429], 261 (46) [$M^+ - H_2O$], 228 (3), [$M^+ - H_2O$ – SH], 220 (16) [$M^+$ – HCNS], 202 (13) [$M^+ - CS_2H$], 187 (63) [$M^+ - H_2NCS_2$], 186 (41), 185 (34) [$M^+ - H_2O - CS_2$], 184 (13), 169 (51), 143 (27), 129 (17), 128 (16), 123 (61) [$C_6H_5CH{=}SH^+$], 117 (34), 115 (28), 98 (35), 97 (22), 91 (100) [$C_7H_7^+$].

$C_{14}H_{17}NOS_2$ (279.4) Calcd. C 60.18 H 6.13 S 22.95
Found C 60.43 H 6.02 S 22.68

*(4α,4aα,8aβ)-4a,5,6,7,8,8a-Hexahydro-8a-hydroxy-4-(4-methoxyphenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**3b**): Yield 7.5 g (81%; Method B), m.p. 219–222°C (ethanol). – IR (KBr): ν = 3600–3250 cm$^{-1}$ (OH + NH), 2930 (CH), 1605/1500 (C=C), 1340 (dithiourethane).

$C_{15}H_{19}NO_2S_2$ (309.5) Calcd. C 58.22 H 6.19 S 20.72
Found C 57.99 H 6.32 S 20.65

*(4α,4aα,8aβ)-4a,5,6,7,8,8a-Hexahydro-8a-hydroxy-4-(4-methylphenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**3c**): Yield 7.5 g (85%; Method B), m.p. 222–225°C (ethanol). – IR (KBr): ν = 3590–3230 cm$^{-1}$ (OH + NH), 2930 (CH), 1505 (C=C), 1340 (dithiourethane).

$C_{15}H_{19}NOS_2$ (293.5) Calcd. C 61.40 H 6.53 S 21.85
Found C 61.25 H 6.49 S 21.66

*(4α,4aα,8aβ)-4-(4-Chlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-hydroxy-4H-3,1-benzothiazine-2(1H)-thione* (**3d**): Yield 8.4 g (89%; Method B), m.p. 221–224°C (ethanol). – IR (KBr): ν = 3620–3270 cm$^{-1}$ (OH + NH), 2940 (CH), 1515/1490 (C=C), 1345 (dithiourethane).

$C_{14}H_{16}ClNOS_2$ (313.9) Calcd. C 53.57 H 5.14 S 20.43
Found C 53.79 H 5.38 S 20.75

*(4α,4aβ,8aβ)-4a,5,6,7,8,8a-Hexahydro-8a-hydroxy-4-phenyl-4H-3,1-benzothiazine-2(1H)-thione* (**4a**): Yield 6.5 g (78%; Method C), m.p. 186–189°C (benzene/petroleum ether). – IR (KBr): ν = 3560–3230 cm$^{-1}$ (OH + NH), 2940 (CH), 1500 (C=C), 1335 (dithiourethane). – MS: *m/z* (%) = 281 (4), 280 (7), 279.0756 (36) [$M^+$, $C_{14}H_{17}NOS_2$, calcd. 279.429], 261 (100) [$M^+ - H_2O$], 228 (11) [$M^+ - H_2O$ – SH], 220 (13) [$M^+$ – HCNS], 202 (15) [$M^+ - CS_2H$], 187 (38) [$M^+ - H_2NCS_2$], 186 (25), 185 (32) [$M^+ - H_2O - CS_2$], 184 (51), 169 (52), 143 (23), 129 (13), 128 (13), 123 (57) [$C_6H_5CH{=}SH^+$], 117 (26), 115 (26), 98 (28), 97 (19), 91 (79) [$C_7H_7^+$].

$C_{14}H_{17}NOS_2$ (279.4) Calcd. C 60.18 H 6.13 S 22.95
Found C 60.39 H 6.32 S 23.10

*(4α,4aβ,8aβ)-4a,5,6,7,8,8a-Hexahydro-8a-hydroxy-4-(4-methoxyphenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**4b**): Yield 7.0 g (75%; Method C), m.p. 151–154°C (benzene/petroleum ether). – IR (KBr): ν = 3600–3230 cm$^{-1}$ (OH + NH), 2930 (CH), 1590/1480 (C=C), 1340 (dithiourethane).

$C_{15}H_{19}NO_2S_2$ (309.5) Calcd. C 58.22 H 6.19 S 20.72
Found C 58.41 H 6.38 S 20.51

*(4α,4aβ,8aβ)-4a,5,6,7,8,8a-Hexahydro-8a-hydroxy-4-(4-methylphenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**4c**): Yield 6.8 g (77%; Method C), m.p. 168–171°C (benzene/petroleum ether). – IR (KBr): ν = 3600–3245 cm$^{-1}$ (OH + NH), 2930 (CH), 1500 (C=C), 1335 (dithiourethane).

$C_{15}H_{19}NOS_2$ (293.5) Calcd. C 61.40 H 6.53 S 21.85
Found C 61.34 H 6.37 S 22.16

*(4α,4aβ,8aβ)-4-(4-Chlorophenyl)-4a,5,6,7,8,8a-hexahydro-8a-hydroxy-4H-3,1-benzothiazine-2(1H)-thione* (**4d**): Yield 7.6 g (81%; Method C), m.p. 164–167°C (benzene/petroleum ether). – IR

Table 3. $^1$H-NMR data (60 MHz, [$D_6$]DMSO, δ in ppm, *J* in Hz) of compounds **5** and **6**

| | NH s (1H) | ArH s (4H) | 4-H d (1H) | $^3J$(4,4a) | 4a-H[a] m (1H) | $CH_2$ (5,6,7,8) m (8H) | Other signals |
|---|---|---|---|---|---|---|---|
| **5a** | 11.89 | 7.36[b] | 4.31 | 11.3 | 2.95 | 0.8–2.3[c] | 5.64[d] |
| **5b** | 11.86 | 6.8–7.4[e] | 4.23 | 10.8 | 2.90 | 0.7–2.3[c] | 5.64[f], 3.72[g] |
| **5c** | 11.90 | 7.19 | 4.22 | 11.1 | 2.89 | 0.7–2.4[c] | 5.64[h], 2.26[i] |
| **5d** | 11.93 | 7.43 | 4.36 | 10.9 | 2.89 | 0.7–2.3[c] | 5.70[j] |
| **6a** | 11.51 | 7.26[b] | 4.55[k] | – | – | 1.3–2.5 | – |
| **6b** | 11.46 | 6.8–7.3[e] | 4.48[k] | – | – | 1.2–2.5 | 3.72[g] |
| **6c** | 11.48 | 7.09 | 4.50[k] | – | – | 1.2–2.5 | 2.26[i] |
| **6d** | 11.50 | 7.1–7.4[e] | 4.59[k] | – | – | 1.2–2.5 | – |

[a] Determined by double resonance experiment. – [b] s (5H). – [c] m (6H). – [d] 8-H, dt (1H), $^3J$(7,8) = 4.1 Hz, $^3J$(8,4a) = 1.7 Hz. – [e] m (4H). – [f] 8-H, dt (1H), $^3J$(7,8) = 4.3 Hz, $^3J$(8,4a) = 1.6 Hz. – [g] $CH_3O$, s (3H). – [h] 8-H, dt (1H), $^3J$(7,8) = 4.1 Hz, $^3J$(8,4a) = 1.6 Hz. – [i] $CH_3$, s (3H). – [j] 8-H, dt (1H), $^3J$(7,8) = 4.1 Hz, $^3J$(8,4a) = 1.5 Hz. – [k] s (1H).

(KBr): ν = 3640–3210 $cm^{-1}$ (OH + NH), 2940 (CH), 1495 (C=C), 1340 (dithiourethane).

$C_{14}H_{16}ClNOS_2$ (313.9) Calcd. C 53.57 H 5.14 S 20.43
Found C 53.65 H 5.33 S 20.67

*General Procedures for the Dehydration of Compounds* **2**–**4**: To the hot suspension of **2**–**4** (5 mmol) in 50 ml of dry benzene a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) (Method A) or trifluoroacetic acid (TFA) (Method B) was added, and the reaction mixture was refluxed for 10 min. The benzene solution, after cooling to room temp., was washed with 3 × 50 ml of water, dried ($Na_2SO_4$), and evaporated to yield pale yellow crystals. – Method C: To the suspension of **2**–**4** (5 mmol) in 50 ml of dry $CHCl_3$ 5 mmol of $(C_2H_5)_2O-BF_3$ was added dropwise at −5°C. The reaction mixture was stirred with cooling for 2 h, then the stirring was continued at room temp. for 1 d. Then the mixture was cooled and made alkaline with 25% $NH_3$ solution. The organic layer was separated, washed with water (3 × 50 ml), dried ($Na_2SO_4$), and evaporated to give pale yellow crystals.

*Separation of Tetrahydro-3,1-benzothiazines* **5** *and* **6**: The mixture of **5** and **6** (2 mmol), obtained in dehydration of the isomeric mixture of **2** and **3** by Method B, was subjected to column chromatography over neutral $Al_2O_3$ (Reanal, Brockman IV activity; *L* = 40 cm, ∅ = 2.5 cm; benzene) to give two fractions. TLC analysis [Aluminum oxide 60 $F_{254}$ neutral, Type E, Merck; benzene/ethyl acetate (40:1)] showed that isomers **6** were obtained as first fractions ($R_f \approx 0.3-0.4$). Evaporation of the second fractions ($R_f \approx 0.1-0.2$) afforded the isomeric compounds **5** as colourless crystals.

*trans-4a,5,6,7-Tetrahydro-4-phenyl-4H-3,1-benzothiazine-2(1H)-thione* (**5a**): Yield 0.70 g (54%; Method B), m.p. 243–246°C (ethanol). – IR (KBr): ν = 1655 $cm^{-1}$ (C=C), 1505 (C=C), 1335 (dithiourethane). – MS: *m/z* (%) = 263 (10), 262 (17), 261.0651 (100) [$M^+$, $C_{14}H_{15}NS_2$, calcd. 261.414], 232 (2), 228 (5) [$M^+$ – SH], 202 (2) [$M^+$ – HCNS], 184 (17) [$M^+$ – $CS_2H$], 169 (4) [$M^+$ – $H_2NCS_2$], 168 (3), 129 (3), 128 (4), 123 (42), [$C_6H_5CH{=}SH^+$], 91 (17), 79 (12), 77 (8).

$C_{14}H_{15}NS_2$ (261.4) Calcd. C 64.33 H 5.78 S 24.53
Found C 63.99 H 5.64 S 24.66

*trans-4a,5,6,7-Tetrahydro-4-(4-methoxyphenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**5b**): Yield 0.75 g (51%; Method B), m.p. 229–232°C (ethanol). – IR (KBr): ν = 1655 $cm^{-1}$ (C=C), 1605/1505 (C=C), 1330 (dithiourethane).

$C_{15}H_{17}NOS_2$ (291.4) Calcd. C 61.82 H 5.88 S 22.01
Found C 62.06 H 5.81 S 22.31

*trans-4a,5,6,7-Tetrahydro-4-(4-methylphenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**5c**): Yield 0.70 g (51%; Method B), m.p. 236–239°C (ethanol). – IR (KBr): ν = 1655 $cm^{-1}$ (C=C), 1510 (C=C), 1335 (dithiourethane).

$C_{15}H_{17}NS_2$ (275.4) Calcd. C 65.41 H 6.22 S 23.28
Found C 65.69 H 6.16 S 23.41

*trans-4-(4-Chlorophenyl)-4a,5,6,7-tetrahydro-4H-3,1-benzothiazine-2(1H)-thione* (**5d**): Yield 0.70 g (47%; Method B), m.p. 246–249°C (ethanol). – IR (KBr): ν = 1655 $cm^{-1}$ (C=C), 1510/1490 (C=C), 1330 (dithiourethane).

$C_{14}H_{14}ClNS_2$ (295.9) Calcd. C 56.84 H 4.77 S 21.68
Found C 57.09 H 4.80 S 21.83

*5,6,7,8-Tetrahydro-4-phenyl-4H-3,1-benzothiazine-2(1H)-thione* (**6a**): Yield 1.15 g (88%; Method A) and 1.20 g (92%; Method C), m.p. 187–189°C (ethanol). – IR (KBr): ν = 1690 $cm^{-1}$ (C=C), 1505 (C=C), 1335 (dithiourethane). – MS: *m/z* (%) = 263 (10), 262 (17), 261.0648 (100) [$M^+$, $C_{14}H_{15}NS_2$, calcd. 261.414], 232 (4), 228 (15), [$M^+$ – SH], 202 (5) [$M^+$ – HCNS], 184 (81) [$M^+$ – $CS_2H$], 169 (19) [$M^+$ – $H_2NCS_2$], 168 (13), 129 (6), 128 (8), 123 (2), 91 (17), 79 (3), 77 (7).

$C_{14}H_{15}NS_2$ (261.4) Calcd. C 64.33 H 5.78 S 24.53
Found C 64.30 H 5.44 S 24.69

*5,6,7,8-Tetrahydro-4-(4-methoxyhenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**6b**): Yield 1.15 g (79%; Method A) and 1.20 g (82%; Method C), m.p. 171–173°C (ethanol). – IR (KBr): ν = 1685 $cm^{-1}$ (C=C), 1605/1510 (C=C), 1330 (dithiourethane).

$C_{15}H_{17}NOS_2$ (291.4) Calcd. C 61.82 H 5.88 S 22.01
Found C 61.68 H 5.59 S 21.96

*5,6,7,8-Tetrahydro-4-(4-methylphenyl)-4H-3,1-benzothiazine-2(1H)-thione* (**6c**): Yield 1.10 g (80%; Method A) and 1.15 g (84%; Method C), m.p. 163–165°C (ethanol). – IR (KBr): ν = 1680 $cm^{-1}$ (C=C), 1500 (C=C), 1330 (dithiourethane).

$C_{15}H_{17}NS_2$ (275.4) Calcd. C 65.41 H 6.22 S 23.28
Found C 65.73 H 5.95 S 23.05

*4-(4-Chlorophenyl)-5,6,7,8-tetrahydro-4H-3,1-benzothiazine-2(1H)-thione* (**6d**): Yield 1.25 g (85%; Method A and Method C), m.p. 175–178°C (ethanol). – IR (KBr): ν = 1675 $cm^{-1}$ (C=C), 1490 (C=C), 1335 (dithiourethane).

$C_{14}H_{14}ClNS_2$ (295.9) Calcd. C 56.84 H 4.77 S 21.68
Found C 56.71 H 5.05 S 21.95

CAS Registry Numbers

**1a**: 5682-83-7 / **1b**: 5765-29-7 / **1c**: 42858-51-5 / **1d**: 24765-16-0 / **2a**: 110660-29-2 / **2b**: 118332-73-3 / **2c**: 118332-74-4 / **2d**: 118332-75-5 / **3a**: 110660-30-5 / **3b**: 118227-91-1 / **3c**: 118227-92-2 / **3d**: 118227-93-3 / **4a**: 110606-39-8 / **4b**: 118332-70-0 / **4c**: 118332-71-1 / **4d**: 118332-72-2 / **5a**: 118227-94-4 / **5b**: 118227-95-5 / **5c**: 118227-96-6 / **5d**: 118227-97-7 / **6a**: 118227-98-8 / **6b**: 118227-99-9 / **6c**: 118228-00-5 / **6d**: 118228-01-6 / $HSC(S)NH_2 \cdot NH_3$: 513-74-6

[1] E. N. Cain, N. R. Warrener, *Aust. J. Chem.* **23** (1970) 51.
[2] P. Perjési, D. Szabó, A. Földesi, *Acta Chim. Hung.* **122** (1986) 119.
[3] [3a] Gy. Argay, A. Kálmán, P. Perjési, D. Szabó, *Acta Cristallogr., Sect. C*, **43** (1987) 324. – [3b] A. Kálmán, Gy. Argay, P. Perjési, D. Szabó, *Acta Cristallogr., Sect. C*, **44** (1988) 1955.
[4] Preliminary communication: P. Perjési, D. Szabó, Gy. Batta, A. Földesi, *Tetrahedron Lett.* **28** (1987) 571.
[5] Fujisawa Phermaceutical Co., Ltd. (S. Umio, K. Kariyone, T. Kishimota, Inv.), Jap. Pat. 69 27,033 (November 11, 1969) [*Chem. Abstr.* **72** (1970) P 31 823].
[6] D. Lednicer, D. E. Emmert, *J. Heterocycl. Chem.* **8** (1971) 903.
[7] The compounds are racemates. Only one enantiomer is shown in the Scheme.
[8] [8a] P. Sohár, L. Gera, G. Bernáth, *Org. Magn. Reson.* **14** (1980) 204. – [8b] P. Sohár, G. Bernáth, *Org. Magn. Reson.* **5** (1973) 159. – [8c] P. Sohár, G. Stájer, G. Bernáth, *Org. Magn. Reson.* **21** (1983) 512.
[9] P. Sohár, F. Fülöp, G. Bernáth, *Org. Magn. Reson.* **22** (1984) 527.
[10] [10a] G. Bernáth, Gy. Göndös, K. Kovács, P. Sohár, *Tetrahedron* **29** (1973) 981. – [10b] G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth, P. Sohár, *Heterocycles* **19** (1982) 1191.
[11] G. Bernáth, F. Fülöp, Gy. Csirinyi, S. Szalma, *Monatsh. Chem.* **118** (1987) 503.
[12] [12a] J. H. Noggle, R. E. Schirmer, *The Nuclear Overhauser Effect*, Academic Press, New York 1971. – [12b] K. E. Kövér, *J. Magn. Reson.* **59** (1984) 485.
[13] S. Hoff, A. P. Block, *Recl. Trav. Chim. Pays-Bas* **92** (1973) 631.
[14] P. Perjési, A. Földesi, D. Szabó, A. Zschunke, M. Mák, *Chem. Ber.* **120** (1987) 1449.

[15] [15a] S. Patai, *The Chemistry of Alkenes*, Chapter 2, Interscience Publishers, London 1964. – [15b] W. H. Saunders, Jr., A. F. Cockerill, *Mechanisms of Elimination Reactions*, Sections III and V, Wiley and Sons, New York 1973. – [15c] P. Deslongschamps, *Stereoelectronic Effects in Organic Chemistry*, Chapter 6, Pergamon Press, Oxford 1983.

[16] M. Karplus, *J. Chem. Phys.* **30** (1959) 11.
[17] R. Adams, *Org. React.*, Vol. 16, Wiley and Sons, New York 1986.
[18] A. Hassner, T. C. Mead, *Tetrahedron* **20** (1964) 2201.
[19] *Org. Synth.* Coll. Vol. 3, p. 763, Wiley and Sons, New York 1955.

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