Notiz / Note

Relationship between Dominant Conformation and Diastereoselectivity of *O*-Acetal Formation of Saturated 2*H*-3,1-Benzothiazine-2-thiones

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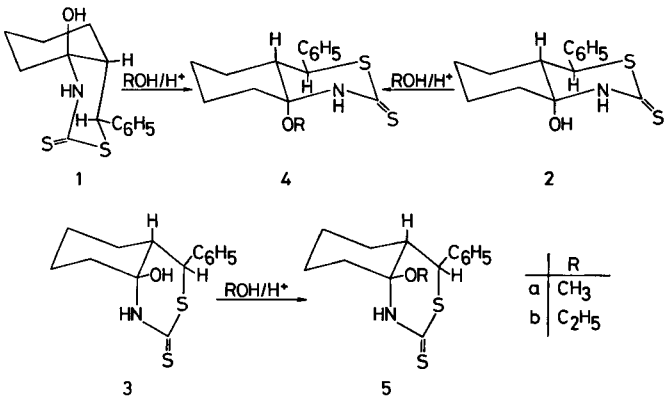
Stereospecific formation of *O*-acetals **4**, **5** of the isomeric octahydro-8a-hydroxy-4-phenyl-2*H*-3,1-benzothiazine-2-thiones **1**–**3** is reported. The stereoselectivity of the reaction is determined by the dominant conformations. During all reactions the phenyl substituent retains its equatorial position.

In a preceding paper we have reported that (*E*)-2-benzylidenecyclohexanone reacts with dithiocarbamic acid to yield isomeric octahydro-8a-hydroxy-4-phenyl-2*H*-benzothiazine-2-thiones (**1**–**3**)[1]. Compound **1** has been found to be an unstable isomer which undergoes thermal or acid-catalyzed isomerization to **2**[1]. Treatment of **1**–**3** with *p*-$H_3CC_6H_4SO_3H$, CF_3CO_2H, or $(C_2H_5)_2O \cdot BF_3$ in aprotic solvents affords isomeric dehydration products, depending on the configuration of **1**–**3** and the dehydration method used[2]. In methanol or ethanol solutions of **1**–**3** in the presence of a catalytic amount of hydrochloric acid, however, the formation of the *O*-alkyl derivatives **4** and **5** is observed (Scheme)[3].

Scheme



The formation of the *O*-alkyl derivatives of **2** and **3** has been found to proceed stereospecifically. ^{1}H-NMR analysis[4] of the crude products obtained in the reactions of **2** and **3** shows only the presence of **4** and **5**, respectively. Treatment of a mixture of **1** and **2**, however, results in the exclusive formation of **4** under the same conditions.

This latter observation is in accordance with the pronounced tendency of **1** to undergo isomerization to **2**, which can be well interpreted as a result of its *N-outside* conformation, which is the less preferred one with this type of saturated heterocycles containing an unsubstituted N-1 atom[7]. In the case of **1** the N-outside conformation predominates due to the preference of the bulky 4-phenyl group to adopt the energetically more preferred equatorial position[2]. Similarly, the predominance of the N-outside conformation with an equatorial 2-aryl group has been reported for one of the epimeric saturated 2-(4-nitrophenyl)-3,1-benzoxazines[8].

This preference of the 4-phenyl group for the equatorial orientation may be responsible for the stereospecific *O*-acetal formation of **2** and **3** as well. On the one hand, inversion of configuration of the C-8a chiral center of **2** would result in the formation of the *O*-alkyl derivatives of **1**, which are not formed from **1** due to its epimerization mentioned above. On the other hand, inversion of configuration at C-8a of **3** would result in the formation of the *trans*-annulated isomer with an energetically non-preferred axial 4-phenyl substituent. The formation of an adduct with such a configuration has not been observed even in the reaction of 2-benzylidenecyclohexanone with dithiocarbamic acid[1,2], most probably for the same reason.

The *O*-acetal structure of **4** and **5** is evidenced by their IR and NMR spectra (see Experimental and Table 1). The characteristic ^{1}H- and ^{13}C-NMR spectroscopic data of **4** and **5** are very similar to those of **2** and **3**, respectively, suggesting the same configuration and conformation of the corresponding compounds (see Scheme). This has further been supported by ^{1}H-^{1}H NOE experiments with **4** and **5**, the results of which are presented in Table 2.

Experimental

Melting points are uncorrected: Boetius apparatus. – IR: Specord 75 IR. – ^{1}H and ^{13}C NMR: TMS as internal standard, Perkin-Elmer R-12 (60 MHz) and Bruker WP-200 SY (200.13 and 50.3 MHz, respectively). COSY-60 ^{1}H-^{1}H correlation spectra, long-range ^{1}H-^{13}C connectivities, and steady-state ^{1}H-^{1}H NOE measurements were performed as described earlier[9]. – Elemental analyses: Department of Organic Chemistry, Eötvös József University, Budapest.

General Procedure for the Formation of **4** *and* **5**: 1.0 mmol of **1**–**3** (**2**, **3**, or approximately a 1:1 mixture of **1** and **2**) is dissolved in 100 ml of anhydrous methanol or ethanol, and the mixture is gently

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Table 1. ^{13}C-NMR (50.3 MHz) spectra of compounds **1**–**5**

Compounds	C-2	C-1'	C-2'	C-3'	C-4'	C-8a	C-4	C-4a	C-8	C-7	C-6	C-5	Others
1[a,b]	189.96	137.19	128.89[c]	128.27[c]	128.00	85.34	48.27	42.90	34.11	18.93	21.85	23.59	
2[a]	191.97	137.25	128.65		127.81	80.92	49.06	43.55	36.87	20.99	24.57	25.44	
3[a]	194.02	136.79	128.57[c]	128.28[c]	127.74	82.26	46.66	43.99	37.73	21.48	22.45	23.78	
4a[a]	193.76	137.22	128.74		127.99	84.11	49.03	43.50	30.57	20.72	24.40	25.66	48.04[e]
4b[a]	193.56	137.28	128.74		127.96	83.94	49.10	43.58	31.44	20.83	24.46	25.66	55.62[f], 15.37[g]
5a[d]	195.98	136.30	128.08[c]	128.15[c]	127.42	85.53	46.46	42.89	32.03	21.92	23.71	21.25	48.14[e]
5b[d]	195.80	136.38	128.17[c]	128.10[c]	127.43	85.39	46.49	42.96	32.92	21.99	23.71	21.16	55.71[f], 15.38[g]

[a] [D_6]DMSO. – [b] Determined from the mixture of **1** and **2**. – [c] Interchangeable assignments. – [d] Polysol. – [e] OCH_3. – [f] CH_2(OEt). – [g] CH_3(OEt).

Table 2. Results of ^{1}H-^{1}H 1D-NOE experiments of compounds **4** and **5**

Compound	Irradiated proton (d)	Observed proton NOE (%)
4a	4a-H (2.20)	NH (1.6), ArH (18.4), 4-H (2.0);
	8-H_{eq} (2.48)	NH (6.0), OCH_3 (7.5), 8-H_{ax} (25.0);
	OCH_3 (3.23)	NH (3.8), 8-H_{eq} (5.0);
	4-H (4.42)	ArH (20.0);
	ArH	4-H (16.4), 4a-H (7.9);
	NH (10.89)	8-H_{eq} (4.3)
4b	4a-H (2.17)	NH (1.2), ArH (16.0), 4-H (2.4)
	8-Heq (2.47)	NH(6.0), CH_2 (OEt) (ca.5), 8-H_{ax} (ca.12)
	CH_2 (OEt) (3.60)	NH(4.5), 8-H_{eq} (3.3), CH_3 (OEt) (12.3);
	4-H (4.42)	ArH (17.0);
	ArH	4-H (14.2), 4a-H (7.6);
	NH (10.87)	8-H_{eq} (4.1)
5a	4a-H (1.99)	ArH (4.3), 4-H (15.2), [8-H_{ax} + 6-H_{ax}] (4.5);
	8-H_{eq} (2.57)	NH (8.0), 8-H_{ax} (31);
	OCH_3 (3.31)	NH (4.2), 4-H (2.1), 8-H_{eq} (3.2);
	4-H (5.22)	ArH (19.1), 4a-H (8.4);
	ArH	4-H (19.1), 4a-H (2.0);
	NH (10.61)	8-H_{eq} (6.1)
5b	4a-H (1.98)	ArH (5.0), 4-H (13.9), 8-H_{ax} (3.4);
	8-H_{eq} (2.56)	NH (5.9), CH_2 (OEt) (7.4), 8-H_{ax} (21.7);
	CH_2 (OEt) (3.60)	NH (4.0), 4-H (1.2), 8-H_{eq} (4.1), CH_3 (OEt) (12.5);
	4-H (5.27)	ArH (18.4), 4a-H (8.9), CH_3 (OEt) (1.1);
	ArH	4-H (17.3), 4a-H (2.4);
	NH (10.77)	CH_2 (OEt) (6.1), 8-H_{eq} (4.5)

heated. The clear solution is then cooled to room temp., and 0.1 ml of a saturated methanolic or ethanolic HCl solution is added. The reaction mixture is kept at room temp. for 2 d, and the solvent is removed under reduced pressure to yield colorless crystals of **4** and **5**.

(4α,4aα,8aβ)-1,4,4a,5,6,7,8,8a-Octahydro-8a-methoxy-4-phenyl-2H-3,1-benzothiazine-2-thione (**4a**): Yield: 0.27 g (92%), m.p. 185–188°C (methanol). – IR (KBr): $\tilde{\nu}$ = 3140 cm^{-1} (NH), 2925 (CH), 1500 (C=C_{Ar}), 1335 (dithiourethane). – ^{1}H NMR: δ = 10.89 (s, 1H, NH), 7.44–7.25 (m, 5H, aromatic H), 4.42 (d, $^3J_{4,4a}$ = 11.3 Hz; 1H, 4-H), 3.23 (s, 3H, OCH_3), 2.48 (m, 1H, 8-H_{eq}), 2.20 (ddd, $^3J_{4a,5ax}$ = 11.5, $^3J_{4a,5eq}$ = 4.3 Hz; 1H, 4a-H), 1.54 (m, 2H, 7-H_{eq}, 5-H_{eq}), 1.50–0.95 (m, 5H, 5-H_{ax}, 6-H_{eq}, 6-H_{ax}, 7-H_{ax}, 8-H_{ax}). – $C_{15}H_{19}NOS_2$ (293.5): calcd. C 61.40, H 6.53, N 4.77; found C 61.23, H 6.44, N 4.68.

(4α,4aα,8aβ)-8a-Ethoxy-1,4,4a,5,6,7,8,8a-octahydro-4-phenyl-2H-3,1-benzothiazine-2-thione (**4b**): Yield: 0.29 g (94%), m.p. 184–187°C (ethanol). – IR (KBr): $\tilde{\nu}$ = 3130 cm^{-1} (NH), 2930 (CH), 1505 (C=C_{Ar}), 1340 (dithiourethane). – ^{1}H NMR: δ = 10.87 (s, 1H, NH), 7.51–7.22 (m, 5H, aromatic H), 4.42 (d, $^3J_{4,4a}$ = 11.6 Hz; 1H, 4-H), 3.60 [m, 2H, CH_2 (OEt)], 2.47 (m, 1H, 8-H_{eq}), 2.17 (ddd, $^3J_{4a,5ax}$ = 11.3, $^3J_{4a,5eq}$ = 4.5 Hz; 1H, 4a-H), 1.53 (m, 2H, 7-H_{eq}, 5-H_{eq}), 1.50–1.05 (m, 5H, 5-H_{ax}, 6-H_{eq}, 6-H_{ax}, 7-H_{ax}, 8-H_{ax}), 1.17 [s, 3H, CH_3 (OEt)]. – $C_{16}H_{21}NOS_2$ (307.5): calcd. C 62.50, H 6.88, N 4.56; found C 62.37, H 6.73, N 4.51.

(4α,4aβ,8aβ)-1,4,4a,5,6,7,8,8a-Octahydro-8a-methoxy-4-phenyl-2H-3,1-benzothiazine-2-thione (**5a**): Yield: 0.27 g (92%), m.p. 194–197°C (methanol). – IR (KBr): $\tilde{\nu}$ = 3100 cm^{-1} (NH), 2930 (CH), 1500 (C=C_{Ar}), 1365 (dithiourethane). – ^{1}H NMR: δ = 10.61 (s, 1H, NH), 7.30–7.50 (m, 5H, aromatic H), 5.22 (d, $^3J_{4,4a}$ = 3.65 Hz; 1H, 4-H), 3.31 (s, 3H, OCH_3), 2.57 (m, 1H, 8-H_{eq}), 1.99 (ddd, $^3J_{4a,5ax}$ = 11.0, $^3J_{4a,5eq}$ = 3.6 Hz; 1H, 4a-H), 1.67 (m, 2H, 7-H_{eq}, 5-H_{eq}), 1.45–0.99 (m, 5H, 5-H_{ax}, 6-H_{eq}, 6-H_{ax}, 7-H_{ax}, 8-H_{ax}). – $C_{15}H_{19}NOS_2$ (293.5): calcd. C 61.40, H 6.53, N 4.77; found C 61.21, H 6.55, N 4.53.

(4α,4aβ,8aβ)-8a-Ethoxy-1,4,4a,5,6,7,8,8a-octahydro-4-phenyl-2H-3,1-benzothiazine-2-thione (**5b**): Yield: 0.28 g (91%), m.p. 192–194°C (ethanol). – IR (KBr): $\tilde{\nu}$ = 3115 cm^{-1} (NH), 2920 (CH), 1500 (C=C_{Ar}), 1370 (dithiourethane). – ^{1}H NMR: δ = 10.77 (s, 1H, NH), 7.43–7.25 (m, 5H, aromatic H), 5.27 (d, $^3J_{4,4a}$ = 3.65 Hz; 1H, 4-H), 3.60 [m, 2H, CH_2 (OEt)], 2.56 (m, 1H, 8-H_{eq}), 1.98 (ddd, $^3J_{4a,5ax}$ = 11.5, $^3J_{4a,5eq}$ = 3.5 Hz; 1H, 4a-H), 1.66 (m, 2H, 7-H_{eq}, 5-H_{eq}), 1.50–1.10 (m, 5H, 5-H_{ax}, 6-H_{eq}, 6-H_{ax}, 7-H_{ax}, 8-H_{ax}), 1.19 [s, 3H, CH_3 (OEt)]. – $C_{16}H_{21}NOS_2$ (307.5): calcd. C 62.50, H 6.88, N 4.56; found C 62.67, H 6.49, N 4.38.

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[3] The compounds are racemates. Only one enantiomer is shown.
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