SYNTHESIS OF 8,9-DIHYDRO-3-METHYL-6H-[1,4]THIAZINO[4,3-c][1,3] THIAZINE-1,4(3H,9aH)-DIONE, A NOVEL HETEROCYCLIC RING SYSTEM

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Abstract- The synthesis of the novel 8,9-dihydro-3-methyl-6H-[1,4]thiazino [4,3-c][1,3]thiazine-1,4(3H,9aH)-dione is described.

In our search for biologically active compounds we became interested in the synthesis of 1,4 thiazinothiazines. Although 1,4 thiazines are well known in the literature[2] we could not find any reference to 1,4-thiazinothiazines. Therefore, we wish to report the synthesis of 8,9-dihydro-3-methyl-6H-[1,4]thiazino[4,3-c][1,3]thiazine-1,4(3H,9aH)-dione(4), the first entry into the 1,4-thiazinothiazine ring system.[3]

Results and Discussion

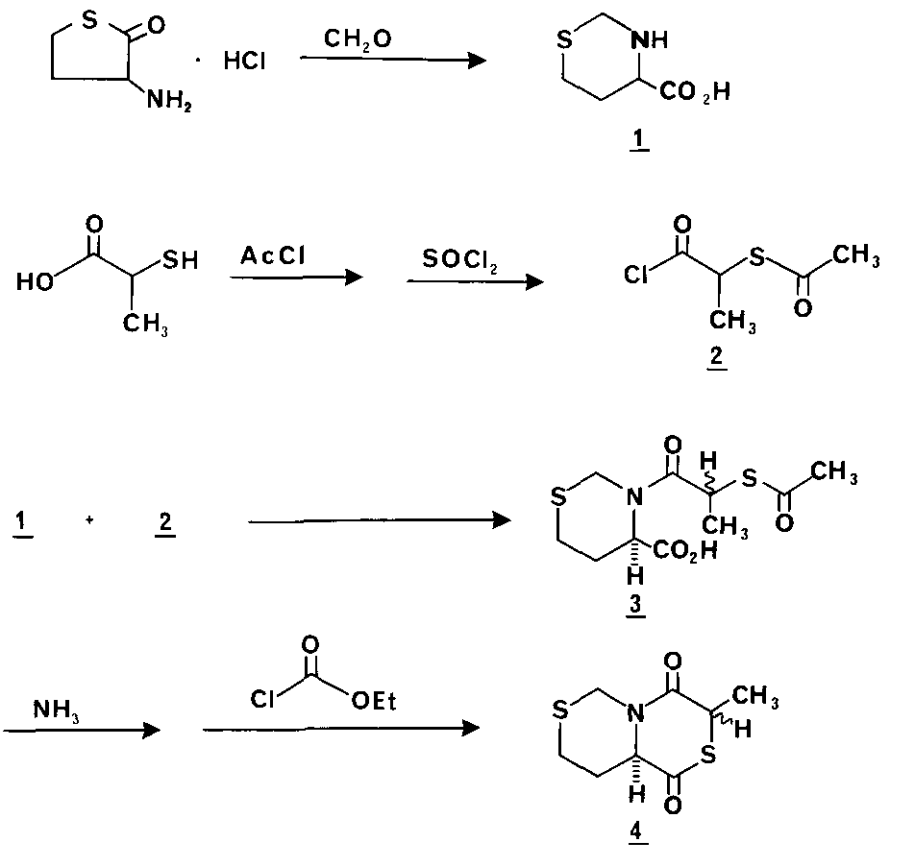
8,9-Dihydro-3-methyl-6H-[1,4]thiazino[4,3-c][1,3]thiazine-1,4(3H,9aH)-dione(4) was synthesized by the route shown in the Scheme. Treatment of racemic homocysteine thiolactone hydrochloride with formaldehyde and one equivalent of sodium hydroxide gave 1,3 thiazin-4-carboxylic acid (1).[4] Although the one equivalent of sodium chloride generated in the reaction could be removed by ion exchange chromatography, we found it expedient to lyophilize the reaction mixture and carry the resulting solid to the next step.

Reaction of the intermediate 1 with 2-(acetylthio)propanoyl chloride prepared from racemic thiolactic acid by treatment with acetyl choride and thionyl chloride, respectively, gave 3-[2-(acetylthio)propanoyl]-1,3-thiazine-4-carboxylic acid (3) as a mixture of diastereomers. Separation of the two diastereomers at this point was not practical. We reasoned that epimers of a rigid bicyclic ring system would be more easily separated, therefore, we turned our attention to the final cyclization step.

Cyclization of intermediate 3 was effected by a two step, "one pot" sequence. The thiol protecting group was removed by introducing ammonia beneath the surface of a methanolic solution of 3. Oxygen dissolved in the methanol solvent must be removed to prevent disulfide formation. This was accomplished by bubbling nitrogen gas through the methanol prior to reaction. Taking advantage of

the reactivity of anhydrides, we treated the resulting carboxylic acid with ethyl chloroformate. We observed a slow evolution of gas. Apparently, a mixed anhydride is formed first, then upon intramolecular attack of thiol with subsequent liberation of carbon dioxide and ethanol, 8,9-dihydro-3-methyl-6H-[1,4]thiazino[4,3-c][1,3]thiazine-1,4(3H,9aH)-dione (4) is obtained as a mixture of diastereomers. The epimeric mixture was then cleanly separated by HPLC[5] on silica gel using hexane/methylene chloride/ethanol as an eluent. The assignment of the relative stereochemistry to the respective fractions is based on NMR analysis.

Scheme

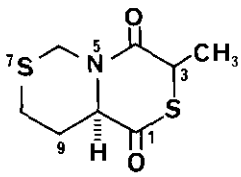


Our assignment of the proton resonances in the 90 MHz NMR spectra of fractions 4a and 4b are indicated in the Table. The most interesting result was the relative chemical shifts of the C-6 methylene protons. For fraction 4a there was a pair of doublets ($J_{6,6}$ = 14 Hz) at 3.85 and 5.22

ppm. The chemical shifts can be ascribed to the deshielding effect by the lactam group and the neighboring sulfur on the C-6 geminal protons. The difference in chemical shifts between the two methylene C-6 protons of 1.17 ppm can be explained by the differential deshielding of the equatorial and axial protons caused by the electron attracting lactam group. Simliar differences in chemical shifts between axial and equatorial protons are seen in the analogous quinolizin-4-ones[6], substituted 2,3-diphenyl-1,6,7,8,9,9a-hexahydro-4H-quinolizin-4-ones[7] and 6,7,8,9-tetrahydropyrido-[2,1b]quinazolin-11-ones.[8] In each of these systems the lower field signal was assigned to the equatoral proton and the higher field signal to the axial one.

In contrast, the C-6 methylene protons of 4b are assigned to a pair of doublets ($J_{6,6}$ = 15 Hz) at 4.60 and 4.80 ppm. The difference in chemical shifts between the equatorial/axial C-6 protons (Δ C-6 eq/ax) of 0.20 ppm was significantly less than Δ C-6 eq/ax of 4a. We considered that this difference in Δ C-6 eq/ax for 4a and 4b may serve as a basis for assigning relative stereochemistry.

Table Proton NMR Data for Compounds 4a and 4b



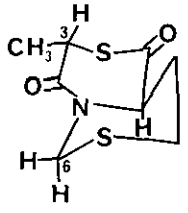
	-CH_3	C-9	C-8	C-3	C-9a	C-6	
	chemical shift (ppm)						
	#, coupling, J (Hz)						
4a	1.59	2.20	3.00	3.97	4.22	3.85(ax)	5.22(eq)
	3H,d,6.6	2H,m	2H,m	1H,q,6.6	1H;dd;12.0,3.0	1H,d,14.0	1H,d,14.0
4b	1.60	2.45	2.97	4.03	4.33	4.60	4.80
	3H,d,6.6	2H,m	2H,m	1H,q,6.6	1H;dd;9.0,4.5	1H,d,15.0	1H,d,15.0

Spectra were run at 90 MHz in deuterochloroform solution and chemical shifts are related to tetramethylsilane.

An examination of Dreiding models of structure 4 where the C-3 methyl group is in the alpha relative configuration (same side as the 9a angular proton) and where the lactam describes a plane reveals that the C-6 equatorial proton is in the lactam plane (Figure 1). Since the C-6 equatorial proton is in the deshielding cone of the lactam, one would predict a large Δ C-6 ax/eq chemical shift. As a first approximation, this allows us to assign a configuration of alpha to the C-3 methyl of compound 4a.

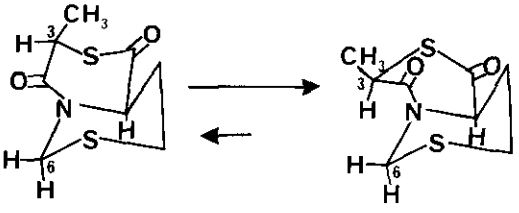
In contrast, the C-3 beta methyl (opposite of the angular 9a proton) in the above conformation would occupy a pseudo-axial position. Since this is unstable due to bow strain, the ring system would adopt a conformation with the C-3 methyl in a pseudo-equatorial position (Figure 2). In this conformation both C-6 protons lie below the lactam. As a result it would be reasonable to predict a small Δ C-6 ax/eq chemical shift. Therefore, the configuration of C-3 beta methyl is consistant with the data obtained for compound 4b.

Figure 1



4a

Figure 2



4b **4b**

Additional support for the above assignment of relative configuration is seen in the IR. The 4a lactam carbonyl absorbs at 1635 cm^{-1}, whereas, the same carbonyl in 4b absorbs at 1675 cm^{-1}. The Dreiding model with the C-3 beta methyl in the pseudo-equatorial position indicates that the lactam carbonyl is twisted out of plane, thus providing an explaination for the 40 cm^{-1} increase in carbonyl absorption for 4b relative to 4a.

EXPERIMENTAL

1,3-Thiazine-4-carboxylic acid (1)[4]

To a solution of racemic homocysteine thiolactone hydrochloride (15.4 g) in 1 N aqueous sodium hydroxide (100 ml) was added a solution of 37 % aqueous formaldehyde (8.2 ml) in water (75 ml). The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was filtered and lyophilized giving 17.3 g (84 % yield) of solid, mp 210°C-dec. NMR (D_2O): 4.3, s, 2H; 3.7, dd, 1H; 2.6, m, 2H; 2.1, m, 2H. IR (KBr): 3100-2000, 1610 cm^{-1}. MS: m/e 147 (M^+).

2-(Acetylthio)propanoyl chloride (2)

To a solution of thiolactic acid (106 g) in dioxane (500 ml) at 0°C was slowly added triethylamine (305 ml). Acetyl chloride (86.4 g) was then added dropwise over a 30 min period and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was filtered and concentrated to an oil. Aqueous 5% hydrochloric acid was added. The resulting mixture was stirred for 1 h and extracted with methylene chloride (2X). The extract was dried ($MgSO_4$) and concentrated to an oil. The 2-(acetylthio)propanoic acid thus obtained (151.8 g) was dissolved in toluene (500 ml), treated with thionyl chloride (90 ml) and DMF (10 ml) and heated at 80°C for 4 h. The solvent was removed in vacuo and the product was distilled (45°C, 0.75 mm Hg) to give 54.5 g (23 % yield) of a clear oil. NMR ($CDCl_3$): 4.5, q, 1H; 2.4, s, 3H; 1.6, d, 3H. IR (neat) 1790, 1700 cm^{-1}.

3-[2-(Acetylthio)propanoyl]-1,3-thiazine-4-carboxylic acid (3)

To a solution of 1,3-thiazine-4-carboxylic acid/sodium chloride (1) (44.1 g) in water (300 ml), THF (300 ml) and triethylamine (40 ml) was added 2-(acetylthio)propanoyl chloride (2) (22.3 g). The reaction was stirred for four days at room temperature. The THF was removed in vacuo. The aqueous mixture was acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine; dried ($MgSO_4$) and concentrated to an oil. The oil was purified by HPLC[5] using a mixture of hexane, ethyl acetate and acetic acid in a 66:33:1 ratio as an eluent giving 13.1 g (35 % yield) of product. NMR ($CDCl_3$): 5.5, m, 1H; 4.6, s, 2H; 4.5, m, 1H; 2.7, m, 2H; 2.3, s, 3H; 2.2, m, 2H; 1.5, dd, 3H. IR (neat): 3300-2500, 1740, 1700 cm^{-1}. MS: CI m/e 278 (M^+), 146 ($-COCHCH_3SCOCH_3$).

8,9-Dihydro-3-methyl-6H-[1,4]thiazino[4,3-c][1,3]thiazine-1,4(3H,9aH)-dione (4)

Ammonia was slowly injected beneath the surface of a solution of 3-[2-(acetylthio)propanoyl]-1,3-thiazin-4-carboxylic acid(3) (7.3 g) in methanol (N_2 gas was bubbled through the methanol prior to reaction). The solvent was removed in vacuo giving an oil. The

3-[2-(thiol)propanoyl]-1,3-thiazine-4-carboxylic acid thus obtained was dissolved in THF (100 ml) and treated with ethyl chloroformate (2.7 ml). Triethylamine (4.0 ml) was then added and the reaction was stirred overnight at room temperature. The THF was removed in vacuo. Methylene chloride was added and the mixture was washed with water (2x), brine; dried (Na_2SO_4) and concentrated to an oil. The oil was purified by HPLC[5] using a mixture of hexane, methylene chloride, and ethanol in a 6:3:1 ratio as an eluent. Compound 4a was first to be eluted (0.7 g, 12 % yield), mp 78-81°C. NMR (see Table). IR: 1655, 1635 cm^{-1}. MS: m/e 217 (M^+); 189 (M^+-CO); 161 (M^+-$COCHCH_3$); 156 (M^+-$HSCH_2CH_2$). Anal. calcd. for $C_8H_{11}NO_2S_2$: C, 44.22; H, 5.10; N, 6.45. Found: C, 44.12; H, 5.10; N, 6.31.

Compound 4b was eluted second (2.0 g, 35 % yield), mp 50-54°C. NMR (see Table). IR 1675, 1660 cm^{-1}. Anal. found: C, 44.41; H, 4.98; N ,6.30.

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Received, 4th December, 1984