Stereoselective Synthesis of 4*H*-5,6-Dihydro-1,3-thiazines by the Reaction of 3-*N*-Acylamino Alcohols with Lawesson's Reagent

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The 4*H*-5,6-Dihydro-1,3-thiazine derivatives **13**–**15** were obtained exclusively and stereoselectively in fair yields by treating the 3-*N*-acylamino alcohols **5**–**8** with an equimolar amount of Lawesson's reagent (LR), while the corresponding thiols **9**–**12** were afforded stereoselectively when only 0.5 equiv. of LR was used in this reaction.

Introduction

2,4-Bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide, commonly known as Lawesson's reagent (LR), is an excellent reagent for converting carbonyl compounds into thiocarbonyl compounds.[1] LR is also used in the synthesis of five- and six-membered phosphorus[2] or sulfur-containing heterocycles.[3−8] Recently, we reported the use of LR for the direct conversion of alcohols into thiols,[4] and also for the novel synthesis of sulfur-containing heterocyclic compounds such as tetrahydrothiophene-2-imines,[5] tetrahydrothiophene-2-thione,[5] thiazolines,[6−7] benzothiazines,[6] thiazolones,[7] 2-aminothiophenes[8] and 4*H*-1,3-thiazines.[9] The above syntheses were accomplished by reacting LR with substrates containing two functional groups, for example ω-hydroxy amides,[5] 2-*N*-acylamino alcohols,[6] *N*-acylthreonine derivatives,[7] ω-keto amides[8] and 3-*N*-acylamino ketones.[9] The results mentioned above suggest that in bifunctional systems such as 3-*N*-acylamino alcohols, which have both hydroxy and amide groups, the opportunity exists for a ring-closure reaction to give the six-membered sulfur-containing heterocycles, 4*H*-5,6-dihydro-1,3-thiazines. The 4*H*-5,6-dihydro-1,3-thiazine derivatives are known to have interesting biological activities, and several methods for the syntheses of these compounds have been reported.[10] Many of them, however, suffer from problems: for example, with some methods the usage is restricted to synthesizing the thiazines with particular functional group such as amino, cyano, OR, SR, or halogen, or the starting material is difficult to obtain. Therefore, we investigated the reactions between the 3-*N*-acylamino alcohols **5**−**8**, which were easily obtained by the reduction of 3-*N*-acylamino ketones with sodium borohydride, with LR and here report the facile and stereoselective synthesis of the 4*H*-5,6-dihydro-1,3-thiazines **13**−**15**.

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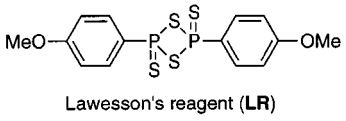
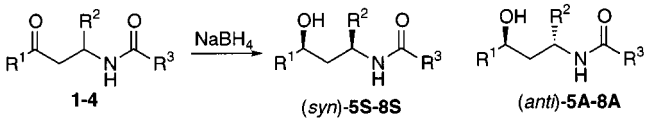
Results and Discussion

The 3-*N*-acylamino alcohols **5**−**8** were obtained as two diastereomers (*syn*- and *anti*-form), which were easily separated by a column chromatography, upon treatment of the 3-*N*-acylamino ketones **1**−**4** with sodium borohydride (Scheme 1). The structures of compounds **5**−**8** were elucidated on the basis of spectroscopic data and microanalyses. The stereochemistry of 1,3-diphenyl-3-*N*-(*p*-toluoyl)amino-propan-1-ol (**5S**) was confirmed by X-ray structural analysis as the *syn*-configuration.[11]



Lawesson's reagent (**LR**)



1-4 (*syn*)-**5S-8S** (*anti*)-**5A-8A**

1; R^1=R^2=Ph R^3=*p*-Tol
2; R^1=R^2=Ph R^3=*p*-Cl-C_6H_4
3; R^1=R^2=R^3=*p*-Tol
4; R^1=Ph R^2=Me R^3=*p*-Tol

syn **5S** (53 %)
syn-**6S** (45 %)
syn-**7S** (48 %)
syn-**8S** (40 %)

anti-**5A** (45 %)
anti-**6A** (41 %)
anti-**7A** (50 %)
anti-**8A** (60 %)

Scheme 1. Synthesis of the 3-*N*-acylamino alcohols **5**−**8** from the 3-*N*-acylamino ketones **1**−**4**

The *syn*-3-*N*-acylamino alcohols (**5S**−**8S**) were treated with 0.5 equiv. of LR in toluene at reflux temperature to yield the corresponding *syn*-3-*N*-acylamino thiols **9S**−**12S** exclusively in fair yields (Scheme 2; Table 1). The treatment of the *anti*-3-*N*-acylamino alcohols **5A**−**8A** with 0.5 equiv. of LR under the same conditions also gave exclusively the *anti*-3-*N*-acylamino thiols **9A**−**12A**. The stereochemistry of the *syn*- (**5S**−**8S**) and *anti*-3-*N*-acylamino thiols (**5A**−**8A**) is predictable from mechanistic considerations. We have previously reported that the direct conversion of alcohols

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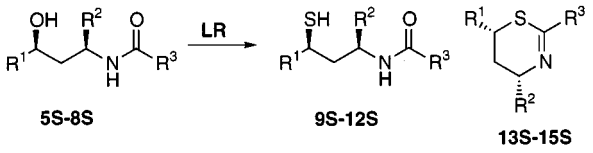
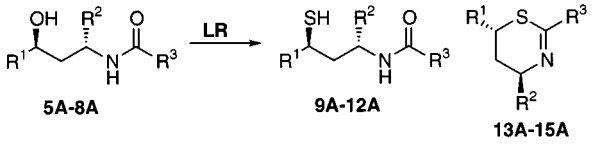
into thiols by thionation of alcohols with LR proceeds with retention of configuration.[4] In the same manner, the treatment of the *syn*- and *anti*-3-*N*-acylamino alcohols **5−8** with an equimolar amount of LR yielded the *syn*- and *anti*-4*H*-5,6-dihydro-1,3-thiazine derivatives **13−15**, respectively, in fair yields (Table 1). Treatment of 1-phenyl-3-(*p*-toluoyl)aminobutan-1-ol (**8**), in which R^2 is an alkyl group, with an equimolar amount of LR gave an inseparable mixture and the corresponding 5,6-dihydro-1,3-thiazine could not be obtained in a pure form. The structures of **13−15** were elucidated on the basis of spectroscopic data and microanalyses, and the stereochemistry of 5,6-dihydro-4,6-diphenyl-2-(*p*-tolyl)1,3-thiazine (**13A**), which was obtained from the reaction of *anti*-3-*N*-acylamino alcohol (**5A**) with LR, was proved to have an *anti* configuration from its X-ray structural analysis,[11] suggesting that the *syn*-thiazine (**13S**) is formed from the *syn*-alcohol (**5S**); therefore this reaction is stereoselective. The 4*H*-5,6-Dihydro-1,3-thiazines **13S** and **13A** were also obtained by the reaction of 3-*N*-acylamino thiols **5S** and **5A** with 0.5 equiv. of LR under the same conditions.





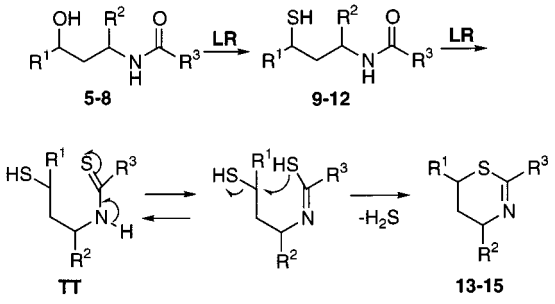
Scheme 2. Synthesis of the 3-*N*-acylamino thiols **9−12** and the 4*H*-5,6-dihydro-1,3-thiazines **13−15**

Table 1. Yields of the thiols **9−12** and thiazines **13−15**

	R^1	R^2	R^3	Molar ratio LR/**5−8**	Yield (%)[a] Thiol	Thiazine
5S	Ph	Ph	*p*-Tol	1	–	(**13S**) 59
5S				0.5	(**9S**) 49	–
5A				1	–	(**13A**) 66
5A				0.5	(**9A**) 32	–
6S	Ph	Ph	*p*-ClC_6H_4	1	–	(**14S**) 46
6S				0.5	(**10S**) 20	–
6A				1	–	(**14A**) 88
6A				0.5	(**10A**) 29	–
7S	*p*-Tol	*p*-Tol	*p*-Tol	1	–	(**15S**) 56
7S				0.5	(**11S**) 52	–
7A				1	–	(**15A**) 40
7A				0.5	(**11A**) 73	–
8S	Ph	Me	*p*-Tol	1	intractable mixture	
8S				0.5	(**12S**) 48	–
8A				1	intractable mixture	
8A				0.5	(**12A**) 49	–

[a] Isolated yield.

The proposed stereochemistry of the 3-*N*-acylamino thiols **9−12** and the 4*H*-5,6-dihydro-1,3-thiazines **13−15** can be reasonably explained by the following mechanistic considerations (Scheme 3). The 3-*N*-acylamino alcohols **5−8** are initially converted into the corresponding thiols **9−12** since the hydroxy group tends to have a greater reactivity toward LR than the amide group,[5,6,9] while their configuration remains unchanged as mentioned above.[4] Subsequently, a further thionation on the amide group of the 3-*N*-acylamino thiols **9−12** takes place and gives the 3-*N*-acylthioamino thiols (**TT**). The iminothiol form of **TT** then undergoes cyclization through an S_N2 attack at the iminothiol followed by the elimination of hydrogen sulfide to yield the 4*H*-5,6-dihydro-1,3-thiazines **13−15**. The method described here can be utilized for a stereoselective synthesis of aryl-substituted 4*H*-5,6-dihydro-1,3-thiazine derivatives.



Scheme 3. A plausible reaction mechanism for the formation of the 4*H*-5,6-dihydro-1,3-thiazines **13−15**.

Experimental Section

General: Melting and boiling points were measured with a Yanako micro melting point apparatus (MP-3J) and a Shibata glass tube oven distillation apparatus (GTO-350RD), respectively, and are uncorrected. IR Spectra were recorded on a JASCO FT/IR-300 spectrophotometer; absorption are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were run on JEOL-JNM-EX270 (270 MHz) or Varian GEMINI 200 (200 MHz) spectrometers with $CDCl_3$ as solvent and tetramethylsilane as internal standard. δ and *J* values are given in ppm and Hz, respectively. Flash column chromatography was carried out with silica gel Wakogel C-300.

Preparation of the Amino-Alcohols 5−8: A solution of $NaBH_4$ (2 mmol) in ethanol (4 mL) was added under argon at 0 °C (ice bath) to a solution of the 3-*N*-acylamino ketone (**1−4**)[12] (2 mmol) in ethanol (40 mL), and the mixture was then stirred for 30 min. at room temperature. The ethanol solution was condensed under reduced pressure, then poured into dil. HCl solution and extracted with ethyl acetate. The extract was washed with sat. sodium hydrogen carbonate solution, then water, and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on a silica gel column with toluene/ethyl acetate (19:1−2:1) to give the *syn*- and *anti*-3-*N*-acylamino alcohols **5−8**.

***syn*-1,3-Diphenyl-3-(*p*-toluoyl)aminopropan-1-ol (5S):** Yield 53%, m.p. 163−165 °C. − IR (KBr): $\tilde{\nu}$ = 3297, 1643, 1613, 1534, 1500, 1451, 1359, 1316, 1280, 1063, 761, 748, 700 cm^{-1}. − ^1H NMR: δ = 2.09−2.35 (m, 2 H), 2.39 (s, 3 H), 4.10 (br. s, 1 H, exchangeable with D_2O), 4.69−4.75 (m, 1 H), 5.46−5.55 (m, 1 H), 7.18−7.38 (m, 12 H), 7.71 (d, *J* = 8.3, 2 H). − ^{13}C NMR: δ = 21.4, 45.4,

51.5, 70.7, 125.7, 126.5, 127.1, 127.4, 127.5, 128.4, 128.8, 129.3, 131.0, 141.2, 142.2, 143.9, 167.6. − MS: *m*/*z* = 345 [M$^+$], 327, 236, 225. − $C_{23}H_{23}NO_2$ (345.42): calcd. C 79.97, H 6.71, N 4.06; found C 79.73, H 6.80, N 4.00.

***anti*-1,3-Diphenyl-3-(*p*-toluoyl)aminopropan-1-ol (5A):** Yield 45%, m.p. 160−161 °C. − IR (KBr): $\tilde{\nu}$ = 3440, 3330, 1626, 1542, 1506, 1303, 753, 699 cm^{-1}. − ^{1}H NMR: δ = 2.10−2.20 (m, 1 H), 2.30−2.43 (m, 1 H), 2.35 (s, 3 H), 3.20 (br. s, 1 H, exchangeable with D_2O), 4.68−4.74 (m, 1 H), 5.19−5.27 (m, 1 H), 7.11−7.63 (m, 12 H), 7.61 (d, J = 8.3, 2 H). − ^{13}C NMR: δ = 21.4, 45.6, 53.4, 72.7, 125.7, 126.3, 127.0, 127.3, 127.6, 128.5, 128.7, 129.1, 131.4, 141.8, 142.4, 144.5, 166.9. − MS: *m*/*z* = 345 [M$^+$], 327, 236, 225. − $C_{23}H_{23}NO_2$ (345.42): calcd. C 79.97, H 6.71, N 4.06; found C 79.68, H 6.82, N 3.95.

***syn*-3-(*p*-Chlorobenzoyl)amino-1,3-diphenylpropan-1-ol (6S):** Yield 45%, m.p. 136−137 °C. − IR (KBr): $\tilde{\nu}$ = 3314, 1645, 1595, 1528, 1483, 1276, 1090, 1063, 762, 700 cm^{-1}. − ^{1}H NMR: δ = 2.09−2.32 (m, 2 H), 3.76 (br. s, 1 H), 4.69 (dd, *J* = 2.6, 10.2, 1 H), 5.44 (dt, *J* = 3.6, 7.9, 1 H), 7.20−7.39 (m, 12 H), 7.72 (d, *J* = 8.6, 2 H). − ^{13}C NMR: δ = 44.7, 51.9, 71.1, 125.6, 126.4, 127.5, 127.6, 128.5, 128.8, 132.3, 137.9, 141.0, 143.8, 166.3. − MS: *m*/*z* = 365 [M$^+$]. − $C_{22}H_{20}ClNO_2$ (365.86): calcd. C 72.22, H 5.47, N 3.83; found C 72.38, H 5.75, N 3.90.

***anti*-3-(*p*-Chlorobenzoyl)amino-1,3-diphenylpropan-1-ol (6A):** Yield 41%, m.p. 161−163 °C. − IR (KBr): $\tilde{\nu}$ = 3314, 1625, 1596, 1543, 1487, 1319, 1091, 1014, 848, 758, 699 cm^{-1}. − ^{1}H NMR: δ = 2.11−2.20 (m, 1 H), 2.30−2.43 (m, 1 H), 2.91 (br. s, 1 H), 4.74 (dd, *J* = 3.3, 8.9, 1 H), 5.23 (td, *J* = 5.9, 8.9, 1 H), 7.22−7.31 (m, 12 H), 7.63 (d, *J* = 8.6, 2 H). − ^{13}C NMR: δ = 45.4, 53.7, 72.9, 125.6, 126.3, 127.4, 127.8, 128.4, 128.6, 128.7, 132.6, 137.6, 142.2, 144.3, 165.9. − $C_{22}H_{20}ClNO_2$ (365.86): calcd. C 72.22, H 5.47, N 3.83; found C 72.28, H 5.57, N 4.09.

***syn*-1,3-Di(*p*-tolyl)-3-(*p*-toluoyl)aminopropan-1-ol (7S):** 48%, m.p. 166−167 °C. − IR (KBr): $\tilde{\nu}$ = 3564, 3333, 1632, 1532, 1421, 1304, 1286, 1033, 816, 744, 725 cm^{-1}. − ^{1}H NMR: δ = 2.07−2.29 (m, 2 H), 2.31 (s, 3 H), 2.33 (s, 3 H), 2.39 (s, 3 H), 4.00 (br. s, 1 H), 4.70 (dd, *J* = 2.6, 10.2, 1 H), 5.46 (dt, *J* = 3.3, 8.3, 1 H), 7.09−7.26 (m, 10 H), 7.70 (d, *J* = 7.9, 2 H). − ^{13}C NMR: δ = 21.0, 21.4, 45.5, 52.9, 72.5, 125.7, 126.3, 127.0, 129.0, 129.2, 129.3, 131.5, 136.9, 137.3, 139.4, 141.5, 141.7, 166.8. − $C_{25}H_{27}NO_2$ (373.49): calcd. C 80.39, H 7.29, N 3.75; found C 80.46, H 7.39, N 3.69.

***anti*-1,3-Di(*p*-tolyl)-3-(*p*-toluoyl)aminopropan-1-ol (7A):** Yield 50%, m.p. 161−162 °C. − IR (KBr): $\tilde{\nu}$ = 3360, 3284, 1643, 1612, 1538, 1504, 1331, 1299, 1085, 805, 759 cm^{-1}. − ^{1}H NMR: δ = 2.10−2.20 (m, 1 H), 2.30 (s, 6 H), 2.35 (s, 3 H), 2.30−2.44 (m, 1 H), 4.69 (dd, *J* = 4.0, 8.6, 1 H), 5.21 (dd, *J* = 6.3, 14.9, 1 H), 7.04 (d, *J* = 6.6, 1 H), 7.09−7.24 (m, 10 H), 7.59 (d, *J* = 8.3, 2 H). − ^{13}C NMR: δ = 21.0, 21.4, 45.4, 51.2, 70.6, 125.6, 126.5, 127.1, 129.1, 129.2, 129.5, 131.1, 137.0, 137.2, 138.3, 141.0, 142.1, 167.5. − $C_{25}H_{27}NO_2$ (373.49): calcd. C 80.39, H 7.29, N 3.75; found C 80.15, H 7.40, N 3.72.

***syn*-1-Phenyl-3-(*p*-toluoyl)aminobutan-1-ol (8S):** Yield 40%, m.p. 130−131 °C. − IR (KBr): $\tilde{\nu}$ = 3392, 3247, 1610, 1542, 1505, 1432, 1338, 1302, 1047, 835, 757, 699 cm^{-1}. − ^{1}H NMR: δ = 1.24 (d, *J* = 6.6, 3 H), 1.78−1.88 (m, 2 H), 1.98−2.11 (m, 1 H), 2.35 (s, 3 H), 4.18−4.27 (m, 1 H), 4.73−4.79 (m, 1 H), 6.78 (br. s, 1 H, exchangeable with D_2O), 7.11−7.34 (m, 7 H), 7.59 (d, *J* = 8.3, 2 H). − ^{13}C NMR: δ = 20.9, 21.4, 43.3, 47.1, 70.3, 125.6, 127.0, 127.1, 128.3, 129.2, 131.1, 142.1, 144.1, 168.2. − $C_{18}H_{21}NO_2$ (283.39): calcd. C 76.29, H 7.47, N 4.94; found C 76.20, H 7.48, N 4.90.

***anti*-1-Phenyl-3-(*p*-toluoyl)aminobutan-1-ol (8A):** Yield 60%, m.p. 59−60 °C. − IR (KBr): $\tilde{\nu}$ = 3483, 3259, 1613, 1550, 1509, 1452, 1356, 1302, 1035, 754, 699 cm^{-1}. − ^{1}H NMR: δ = 1.32 (d, *J* = 6.3, 3 H), 1.64−1.74 (m, 1 H), 1.88−2.01 (m, 1 H), 2.39 (s, 3 H), 4.50 (br. s, 1 H), 4.73 (br. d, *J* = 10.6, 2 H), 6.78 (br. s, 1 H, exchangeable with D_2O), 7.19−7.34 (m, 7 H), 7.69 (d, *J* = 7.9, 2 H). − ^{13}C NMR: δ = 21.2, 21.4, 44.9, 45.9, 72.6, 125.6, 126.9, 127.4, 128.4, 129.1, 131.7, 141.7, 144.8, 167.3. − $C_{18}H_{21}NO_2$ (283.39): calcd. C 76.29, H 7.47, N 4.94; found C 75.96, H 7.43, N 4.87.

Reaction of the 3-*N*-Acylamino Alcohols 5−8 with Lawesson's Reagent (LR): A solution of 3-*N*-acylamino alcohols (**5−8**) (1 mmol) and LR (0.5 or 1 mmol) in toluene (50 mL) was heated to reflux under argon for 15 min. After removal of the solvent, the residue was chromatographed on a silica gel column with toluene/hexane (4:1−50:1) or toluene/ethyl acetate (19:1−4:1) to give the corresponding thiols (**9−12**) or thiazine derivatives (**13−15**).

***syn*-1,3-Diphenyl-3-(*p*-toluoyl)aminopropan-1-thiol (9S):** Yield 49%, m.p. 114−115 °C. − IR (KBr): $\tilde{\nu}$ = 3368, 2580, 1635, 1526, 1498, 1451, 1277, 831, 751, 699 cm^{-1}. − ^{1}H NMR: δ = 2.02 (d, *J* = 5.9, 1 H), 2.37 (s, 3 H), 2.46−2.65 (m, 2 H), 3.85−3.93 (m, 1 H), 5.25−5.34 (m, 1 H), 6.41 (br. d, *J* = 8.3, 1 H), 7.15−7.37 (m, 12 H), 7.55 (d, *J* = 8.2, 2 H). − ^{13}C NMR: δ = 21.4, 40.8, 45.5, 52.6, 126.7, 126.9, 127.5, 127.8, 128.9, 129.1, 131.3, 141.1, 142.0, 143.6, 166.9. − $C_{23}H_{23}NOS$ (361.50): calcd. C 76.43, H 6.41, N 3.88; found C 76.70, H 6.46, N 3.69.

***anti*-1,3-Diphenyl-3-(*p*-toluoyl)aminopropan-1-thiol (9A):** Yield 32%, m.p. 160−161 °C. − IR (KBr): $\tilde{\nu}$ = 3290, 2580, 1631, 1541, 1508, 759, 696 cm^{-1}. − ^{1}H NMR: δ = 2.28 (d, *J* = 5.9, 1 H), 2.37 (s, 3 H), 2.38−2.52 (m, 1 H), 2.66−2.78 (m, 1 H), 3.87−3.95 (m, 1 H), 5.19−5.28 (m, 1 H), 6.51 (br. d, *J* = 7.7, 1 H), 7.16−7.39 (m, 12 H), 7.56 (d, *J* = 8.3, 1 H). − ^{13}C NMR: δ = 21.4, 40.8, 45.9, 52.6, 126.5, 126.9, 127.5, 127.6, 128.9, 129.1, 131.4, 141.1, 141.9, 144.3, 166.4. − $C_{23}H_{23}NOS$ (361.50): calcd. C 76.43, H 6.41, N 3.88; found C 76.45, H 6.51, N 3.87.

***syn*-3-(*p*-Chlorobenzoyl)amino-1,3-diphenylpropan-1-thiol (10S):** Yield 20%, m.p. 126−128 °C. − IR (KBr): $\tilde{\nu}$ = 3276, 2559, 1635, 1594, 1541, 1484, 1451, 1091, 1013, 844, 755, 698 cm^{-1}. − ^{1}H NMR: δ = 2.01 (d, *J* = 5.9, 1 H), 2.48−2.62 (m, 2 H), 3.87 (dd, *J* = 6.9, 13.2, 1 H), 5.28 (dd, *J* = 7.2, 14.4, 1 H), 6.49 (br. d, *J* = 7.3, 1 H), 7.22−7.37 (m, 12 H), 7.54 (d, *J* = 8.6, 2 H). − ^{13}C NMR: δ = 40.8, 45.3, 52.9, 126.7, 126.8, 127.5, 127.9, 128.3, 128.7, 128.9, 132.4, 137.7, 140.8, 143.5, 165.6. − $C_{22}H_{20}ClNOS$ (381.92): calcd. C 69.19, H 5.28, N 3.67; found C 69.51, H 5.32, N 3.47.

***anti*-3-(*p*-Chlorobenzoyl)amino-1,3-diphenylpropan-1-thiol (10A):** Yield 29%, m.p. 43−44 °C. − IR (KBr): $\tilde{\nu}$ = 3289, 2550, 1635, 1595, 1541, 1485, 1316, 1092, 1013, 844, 759, 698 cm^{-1}. − ^{1}H NMR: δ = 2.22 (d, *J* = 5.9, 1 H), 2.40−2.57 (m, 1 H), 2.64−2.76 (m, 1 H), 3.89 (dd, *J* = 7.3, 13.5, 1 H), 5.19 (dd, *J* = 7.9, 14.9, 1 H), 6.53 (d, *J* = 7.9, 1 H), 7.20−7.39 (m, 12 H), 7.55 (d, *J* = 8.6, 2 H). − ^{13}C NMR: δ = 40.7, 45.6, 52.8, 126.5, 126.9, 127.5, 127.8, 128.3, 128.7, 128.9, 129.0, 132.5, 137.8, 140.8, 144.2, 165.5. − $C_{22}H_{20}ClNOS$ (381.92): calcd. C 69.19, H 5.28, N 3.67; found C 68.92, H 5.57, N 3.80.

***syn*-1,3-Di(*p*-tolyl)-3-(*p*-toluoyl)aminopropan-1-thiol (11S):** Yield 52%, m.p. 93−94 °C. − IR (KBr): $\tilde{\nu}$ = 3258, 2570, 1631, 1540, 1506, 1441, 1325, 839, 818, 758 cm^{-1}. − ^{1}H NMR: δ = 1.98 (d,

J = 6.0, 1 H), 2.32 (s, 6 H), 2.37 (s, 3 H), 2.43−2.60 (m, 2 H), 3.86 (dd, J = 7.2, 13.5, 1 H), 5.25 (dd, J = 7.3, 14.5, 1 H), 6.36 (d, J = 7.9, 1 H), 7.10−7.25 (m, 12 H), 7.52 (d, J = 7.9, 2 H). − ^{13}C NMR: δ = 21.4, 21.7, 40.9, 45.9, 52.8, 127.0, 127.1, 127.2, 129.4, 129.9, 131.7, 137.5, 138.5, 140.9, 142.2, 166.9. − $C_{25}H_{27}NOS$ (389.55): calcd. C 77.09, H 6.99, N 3.60; found C 76.95, H 7.18, N 3.37.

***anti*-1,3-Di(*p*-tolyl)-3-(*p*-toluoyl)aminopropan-1-thiol (11A):** Yield 73%, m.p. 170−171 °C. − IR (KBr): $\tilde{\nu}$ = 3307, 2548, 1630, 1539, 1506, 1318, 1186, 813, 759 cm^{-1}. − ^{1}H NMR: δ = 2.22 (d, J = 5.6, 1 H), 2.30 (s, 3 H), 2.33 (s, 3 H), 2.36 (s, 3 H), 2.39−2.48 (m, 1 H), 2.63−2.75 (m, 1 H), 3.87 (dd, J = 6.9, 14.0, 1 H), 5.14 (dd, J = 7.6, 14.8, 1 H), 6.36 (d, J = 7.9, 1 H), 7.09−7.19 (m, 10 H), 7.54 (d, J = 8.2, 2 H). − ^{13}C NMR: δ = 21.1, 21.4, 40.4, 45.9, 52.4, 126.4, 126.8, 126.9, 129.1, 129.5, 129.6, 131.5, 137.2, 138.1, 141.4, 141.9, 166.3. − $C_{25}H_{27}NOS$ (389.55): calcd. C 77.09, H 6.99, N 3.60; found C 77.00, H 7.09, N 3.59.

***syn*-1-Phenyl-3-(*p*-toluoyl)aminobutan-1-thiol (12S):** Yield 48%, m.p. 117−118 °C. − IR (KBR) 3305, 2540, 1633, 1566, 1537, 1504, 1307, 835, 754, 697 cm^{-1}. − ^{1}H NMR: δ = 1.28 (d, J = 6.6, 3 H), 1.70 (br. s, 1 H), 2.08−2.32 (m, 2 H), 2.38 (s, 3 H), 4.05−4.14 (m, 1 H), 4.34−4.46 (m, 1 H), 5.90 (br. d, J = 8.6, 1 H), 7.17−7.42 (m, 7 H), 7.54 (d, J = 8.2, 2 H). − ^{13}C NMR: δ = 21.2, 21.4, 41.1, 44.4, 46.7, 126.8, 127.3, 128.5, 128.9, 129.1, 131.6, 141.8, 144.0, 166.8. − $C_{18}H_{21}NOS$ (299.43): calcd. C 72.21, H 7.07, N 4.68; found C 71.98, H 6.97, N 4.32.

***anti*-1-Phenyl-3-(*p*-toluoyl)aminobutan-1-thiol (12A):** Yield 49%, b.p. 250 °C/2 Torr (dec.). − IR (film) 3236, 2560, 1627, 1543, 1508, 1451, 1343, 1307, 1191, 1154, 837, 754, 696 cm^{-1}. − ^{1}H NMR: δ = 1.17 (d, J = 6.3, 3 H), 2.01 (d, J = 5.3, 1 H), 2.15−2.21 (m, 1 H), 2.36 (s, 3 H), 3.69−3.82 (m, 1 H), 4.05−4.15 (m, 2 H), 6.22 (br. s, 1 H, exchangeable with D_2O), 7.05−7.32 (m, 7 H), 7.56 (d, J = 7.8, 2 H). − ^{13}C NMR: δ = 20.8, 21.3, 40.8, 44.4, 46.6, 126.8, 126.9, 127.3, 128.1, 128.7, 128.9, 129.0, 141.6, 144.2, 166.1. − MS: m/z = 299 [M$^+$], 265, 174, 163, 119. The result of elemental analysis of **12A** was not in agreement with the calculated values since **12A** decomposed on distillation

***syn*-5,6-Dihydro-4,6-diphenyl-2-(*p*-tolyl)-1,3-thiazine (13S):** Yield 59%, m.p. 80−81 °C. − IR (KBr): $\tilde{\nu}$ = 1605, 1492, 1450, 1282, 1231, 1178, 1060, 933, 817, 767, 749, 697 cm^{-1}. − ^{1}H NMR: δ = 1.90 (dd, J = 12.2, 25.4, 1 H), 2.37 (s, 3 H), 2.51 (td, J = 3.3, 13.2, 1 H), 4.76 (dd, J = 3.3, 12.2, 1 H), 4.88 (dd, J = 3.3, 11.2, 1 H), 7.17−7.47 (m, 12 H), 7.84 (d, J = 8.2, 2 H). − ^{13}C NMR: δ = 21.4, 37.4, 45.8, 63.1, 126.5, 126.8, 126.9, 127.6, 128.1, 128.5, 128.9, 129.0, 136.2, 140.7, 140.8, 144.8, 159.3. − $C_{23}H_{21}NS$ (343.49): calcd. C 80.44, H 6.16, N 4.08; found C 80.14, H 5.88, N 3.95.

***anti*-5,6-Dihydro-4,6-diphenyl-2-(*p*-tolyl)-1,3-thiazine (13A):** Yield 66%, m.p. 97−98 °C. − IR (KBr): $\tilde{\nu}$ = 1600, 1489, 1449, 1256, 1176, 1019, 766, 701 cm^{-1}. − ^{1}H NMR: δ = 2.24−2.29 (m, 2 H), 2.35 (s, 3 H), 4.22 (dd, J = 5.3, 7.9, 1 H), 5.30−5.33 (m, 1 H), 7.18−7.36 (m, 12 H), 7.87 (d, J = 7.9, 2 H). − ^{13}C NMR: δ = 21.3, 34.5, 40.7, 59.3, 126.4, 126.8, 126.9, 127.7, 128.4, 128.7, 129.0, 136.3, 140.7, 141.0, 142.6, 159.3. − $C_{23}H_{21}NS$ (343.49): calcd. C 80.44, H 6.16, N 4.08; found C 80.71, H 6.22, N 4.38.

***syn*-2-(*p*-Chlorophenyl)-5,6-dihydro-4,6-diphenyl-1,3-thiazine (14S):** Yield 46%, b.p. 230 °C/2 Torr. − IR (film) 1605, 1485, 1453, 1090, 1012, 938, 833, 755, 698 cm^{-1}. − ^{1}H NMR: δ = 1.89 (dd, J = 13.5, 23.7, 1 H), 2.51 (td, J = 3.3, 13.5, 1 H), 4.77 (dd, J = 3.3, 12.2, 1 H), 4.86 (dd, J = 3.3, 11.2, 1 H), 7.14−7.40 (m, 12 H), 7.88 (d, J = 8.6, 2 H). − ^{13}C NMR: δ = 37.1, 45.9, 63.2, 126.7, 127.0, 127.5, 127.9, 128.2, 128.5, 128.6, 128.9, 136.6, 137.2, 140.3, 144.5, 158.3. − MS: m/z = 363 [M$^+$]. − $C_{22}H_{18}ClNS$ (363.90): calcd. C 72.60, H 4.99, N 3.85; found C 72.95, H 5.18, N 3.70.

***anti*-2-(*p*-Chlorophenyl)-5,6-dihydro-4,6-diphenyl-1,3-thiazine (14A):** Yield 88%, b.p. 245 °C/2 Torr. − IR (film) 1604, 1486, 1452, 1090, 1013, 936, 833, 760, 699 cm^{-1}. − ^{1}H NMR: δ = 2.27−2.33 (m, 2 H), 4.26 (dd, J = 5.6, 7.9, 1 H), 5.33 (t, J = 4.3, 1 H), 7.14−7.40 (m, 12 H), 7.91 (d, J = 8.6, 2 H). − ^{13}C NMR: δ = 34.4, 40.9, 59.5, 126.8, 127.1, 127.8, 127.9, 128.0, 128.6, 128.9, 129.0, 136.7, 140.7, 142.4, 158.9. − MS: m/z = 363 [M$^+$]. − $C_{22}H_{18}ClNS$ (363.90): calcd. C 72.60, H 4.99, N 3.85; found C 72.62, H 5.18, N 3.58.

***syn*-5,6-Dihydro-2,4,6-tri-(*p*-tolyl)-1,3-thiazine (15S):** Yield 56%, b.p. 250 °C/2 Torr. − IR (film) 1613, 1513, 1454, 1301, 1177, 1069, 934, 816, 754 cm^{-1}. − ^{1}H NMR: δ = 1.87 (dd, J = 12.2, 25.1, 1 H), 2.33 (s, 3 H), 2.35 (s, 3 H), 2.36 (s, 3 H), 2.33−2.51 (m, 1 H), 4.72 (dd, J = 3.3, 12.2, 1 H), 4.84 (dd, J = 3.3, 11.5, 1 H), 7.12−7.35 (m, 10 H), 7.82 (d, J = 7.9, 2 H). − ^{13}C NMR: δ = 21.1, 21.4, 37.3, 45.5, 62.9, 126.5, 126.7, 127.4, 128.9, 129.1, 129.5, 136.2, 136.4, 137.7, 138.0, 140.7, 141.9, 159.2. − $C_{25}H_{25}NS$ (371.54): calcd. C 80.83, H 6.78, N 3.77; found C 80.44, H 6.49, N 3.58.

***anti*-5,6-Dihydro-2,4,6-tri-(*p*-tolyl)-1,3-thiazine (15A):** Yield 40%, m.p. 92−93 °C. − IR (KBr): $\tilde{\nu}$ = 1600, 1509, 1261, 1176, 1026, 935, 869, 819 cm^{-1}. − ^{1}H NMR; 2.22−2.28 (m, 2 H), 2.31 (s, 3 H), 2.33 (s, 3 H), 2.37 (s, 3 H), 4.19 (dd, J = 5.9, 8.2, 1 H), 5.33 (t, J = 4.3, 1 H), 7.05−7.22 (m, 10 H), 7.85 (d, J = 8.2, 2 H). − ^{13}C NMR: δ = 21.0, 21.3, 29.7, 34.5, 40.4, 59.3, 126.4, 126.7, 127.7, 129.0, 129.1, 129.4, 129.5, 136.4, 137.5, 138.0, 139.6, 140.7, 159.6. − $C_{25}H_{25}NS$ (371.54): calcd. C 80.83, H 6.78, N 3.77; found C 80.64, H 6.80, N 3.70.

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[1] M. P. Cava, M. I. Levinson, *Tetrahedron* **1985**, *41*, 5061−5087; D. Brillon, *Sulfur Rep.* **1992**, *12*, 297−338.

[2] [2a] B. S. Pedersen, S.-O. Lawesson, *Tetrahedron* **1979**, *35*, 2433−2437. − [2b] A. A. El- Barbary, K. Clausen, S.-O. Lawesson, *Tetrahedron* **1980**, *36*, 3309−3315. − [2c] A. A. El-Barbary, S.-O. Lawesson, *Tetrahedron* **1981**, *37*, 2641−2646. − [2d] S. Sheibye, S.-O. Lawesson, C. Romming, *Acta Chem. Scand., Ser. B* **1981**, *35*, 239−246. − [2e] S. Sheibye, R. Shabana, S.-O. Lawesson, *Tetrahedron* **1982**, *38*, 993−1001. − [2f] R. Shabana, F. H. Osman, S. S. Atrees, *Tetrahedron* **1994**, *50*, 6975−6988. − [2g] N. Dubeu-Assibat, A. Baceiredo, G. Bertrand, *J. Org. Chem.* **1995**, *60*, 3904−3906. − [2h] R. N. Butler, E. C. MaKenna, D. Grogen, *Chem. Commun.* **1997**, 2149−2150. − [2i] Y. A. Ibrahim, A. Z. Kadry, M. R. Ibrahim, J. N. Lisgarten, B. S. Potter, R. A. Palmer, *Tetrahedron Lett.* **1999**, *55*, 13457−13462.

[3] [3a] K. Clausen, S.-O. Lawesson, *Bull. Soc. Chim. Belg.* **1979**, *88*, 305−311. − [3b] K. Clausen, S.-O. Lawesson, *Nouv. J. Chim.* **1980**, *4*, 43−46. − [3c]A. Ishii, J. Nakayama, M.-X. Ding, N. Kataoka, M. Hoshino, *J. Org. Chem.* **1990**, *55*, 2421−2427. − [3d]P. N. Nugara, N.-Z. Huang, M. V. Lakshmikantham, M. P. Cava, *Heterocycles* **1991**, *32*, 1559−1561. − [3e] K-T. Kang, J. S. U, *Synth. Commun.* **1995**, *25*, 2647−2653. − [3f] T. Ozturk, *Tetrahedron Lett.* **1996**, *37*, 2821−2824. − [3g] C. W. Ong, M.

Chen, L. F. Wang, P. C. Shieh, *Tetrahedron Lett.* **1998**, *39*, 9191−9192. − [3h] E. Ertas, T. Ozturk, *Chem. Commun.* **2000**, 2309−2310
[4] T. Nishio, *J. Chem. Soc., Chem. Commun.* **1989**, 205−206; *J. Chem. Soc., Perkin Trans. 1* **1993**, 1113−1117.
[5] [5a] T. Nishio, *Tetrahedron Lett.* **1995**, *36*, 6113−6116. − [5b] T. Nishio, H. Sekiguchi, *Tetrahedron* **1999**, *55*, 5017−5026.
[6] T. Nishio, *J. Org. Chem.* **1997**, *62*, 1106−1111.
[7] M. Ori, T. Nishio, *Heterocycles (Special issue)* **2001**, *54*, 2011−108.
[8] T. Nishio, *Helv. Chim. Acta* **1998**, *81*, 1207−1214.
[9] M. Ori, T. Nishio, *Heterocycles (Special issue)* **2000**, *52*, 111−116.
[10] [10a] H. Quiniou, O. Guilloton, in *Advances in Heterocyclic Chemistry* (Ed.: A. R. Katritzky), Academic Press Inc.: San Diego, California, **1990**, Vol. 50; p 85−156. − [10b] M. Sainbury, in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford, **1984**; vol. 3; p. 995−1038; **1996**; vol. 6; p. 383−413 and references cited therein. − [10c] N. Yasuda, M. Karikomi, T. Toda, *Chem. Lett.* **1995**, 1141−1142. − [10d] A. J. Liepa, S. Saubern, *Aust. J. Chem.* **1997**, *50*, 755−758. − [10e] P. Wipf, G. B. Hayes, *Tetrahedron* **1998**, *54*, 6987−6998.
[11] Tables of crystal data are available as supplementary data. Atomic coordinates, bond lengths and angles and thermal parameters of X-ray crystal structures of **5S** (CCDC-167043) and **13A** (CCDC-167044) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].
[12] D. L. Boger, R. J. Wysocki, Jr, *J. Org. Chem.* **1989**, *54*, 714−718; C. Kashima, Y. Yamamoto, Y. Omote, *J. Org. Chem.* **1975**, *40*, 526−527.

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