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Stereoselective Synthesis of 2-Acyl-3,4-dihydro-1,4-Benzothiazines.

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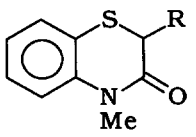
Abstract: 2-Benzylidene-4-methyl-3-oxo-2H-1,4-benzothiazine **2** undergoes 1,2-addition with MeMgI and allylic magnesium halides to give 2-acyl-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazines **3a-d**. Lithiation of **3a** and subsequent reaction with MeI and $PhCH_2Br$ leads to compounds **3e**, **3f**, **3h** and **3i**. In contrast, the reaction of lithiated **3a** with benzaldehyde and 2,6-dichlorobenzaldehyde furnished compounds **3k** and **3l** respectively.

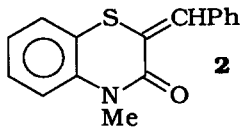
1,4-Dihydrobenzothiazines are compounds of considerable pharmacological interest. Indeed, some of them have been described as potential medicinal agents,[1a-f] others have been reported to exhibit antiinflammatory activity[2] and blood pressure reducing properties on animals.[3] Herbicide activity has also been shown by some dihydrobenzothiazine derivatives.[4]

1,4-Dihydrobenzothiazines are usually prepared from acyclic precursors.[1a] Such a synthetic strategy has the drawback that each time different precursors are required for the construction of the thiazine ring. Benzothiazine derivatives can also be prepared by ring expansion of benzothiazoles and benzothiazolines.[5] Here again, suitable precursors are needed each time and yields are often not high. A more convenient method for preparation of dihydrobenzothiazines involves the functionalization of simple and easily available precursors containing the thiazine ring.[6]

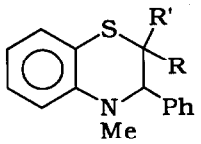
We have recently reported the stereoselective synthesis of 2-alkylidene-3,4-dihydro-3-oxo-2H-1,4-benzothiazines based on the lithiation of the dihydrobenzothiazinone ring and subsequent aldol-type condensation.[7] In the present paper we describe the preparation of some 2-acyl-1,4-dihydrobenzothiazines, using 2-benzylidene-4-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine **2** as the precursor.[6] The lithiation reaction of 2-acetyl-4-methy-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine **3a** has also been studied as a route for further functionalization of the heterocyclic ring.



Ia : R = H
Ib : R = $CHPh_2$

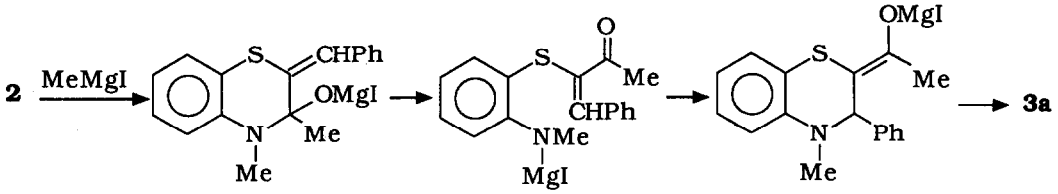


2



3a: R = COMe; R' = H
3b: R = $CH_2CH{=}CH_2$; R' = H
3c: R = $CH_2C(Me){=}CH_2$; R' = H
3d: R = $CH(Me)CH{=}CH_2$; R' = H
3e: R = COMe; R' = Me
3f: R = COEt; R' = Me
3g: R = $C(Me)(Bu^t)OH$; R' = H
3h: R = $COPr^i$; R' = Me
3i: R = COMe; R' = Bz
3k: R = $COCH{=}CHC_6H_5$; R' = H
3l: R = $COCH{=}CHC_6H_3Cl_2$; R' = H
3j: R = $C(Me)(Bu^n)OH$; R' = H

As reported,[7] lithiation of N-methyldihydrobenzothiazinone **1a** and subsequent reaction with benzaldehyde followed by acetylation and elimination under basic conditions, led stereoselectively to the benzylidene derivative **2** (Z/E : 9/1). We have now found that (Z)-benzylidene **2** undergoes exclusive 1,4-addition upon treatment with PhMgBr to give the diphenylmethyl dihydrobenzothiazinone **1b**. In contrast, the reaction of **2** with MeMgI furnishes 2-acetyldihydrobenzothiazine **3a**. Its formation could be explained by assuming a 1,2-addition of MeMgI to **2** leading to the intermediate (**A**), that cleaves to the α,β-unsaturated ketone (**B**). Subsequent intramolecular 1,4-addition would produce **3a** upon protonation of the enolate (**C**).



(A) **(B)** **(C)**

The small coupling constant between the two methynic hydrogens of the heterocyclic ring (J= 2.1 Hz) matches well the *trans* geometry of **3a** in view of the fact that comparable values have been reported for other 1,4-dihydrobenzothiazine derivatives,[8] and lower values of $J_{H2\text{-}H3}$ have been reported for dihydrobenzothiazines bearing 2-H and 3-H in a *cis* arrangement.[9] Moreover, the trans configuration of **3a** has been confirmed by NOE difference spectroscopy (Fig. 1). The doublets at δ 5.08 and 3.58 can be straightforwardly assigned to the methynic protons of the thiazine ring on the basis of chemical shift considerations, as it is also confirmed by the detection of dipolar interactions with N-Me and acetyl Me. In turn, the N-Me resonance is unambiguously determined from the dipolar interaction with one *ortho* proton of the fused aromatic ring. The *ortho* protons of the monosubstituted aromatic ring give dipolar interactions with

N-Me and both the methynic protons. A further diagnostic interaction is found between these latter protons. They, therefore, must be in reciprocal *gauche* orientation, as it is also documented by the small (2.1 Hz) reciprocal scalar constant. No interaction is found between acetyl Me and the *ortho* protons of the monosubstituted aromatic ring. They are, therefore, on different sides of the azathio ring and *anti* oriented. The reverse attribution would require the detection of some dipolar interaction. The conformational preference is supported by force field and AMI semiempirical geometry optimization.[10]

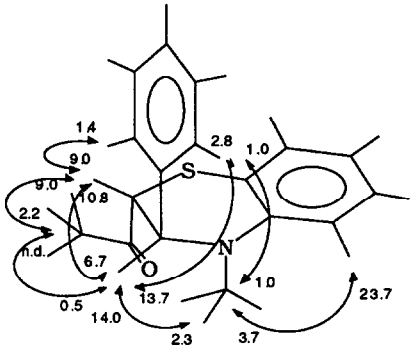


Fig.1 NOE interaction diagram for **3a**
The numbers at the tip of the arrows give the % enhancements uponsaturation of the connected nucleus. n.d. = not detected. is. = isochronous

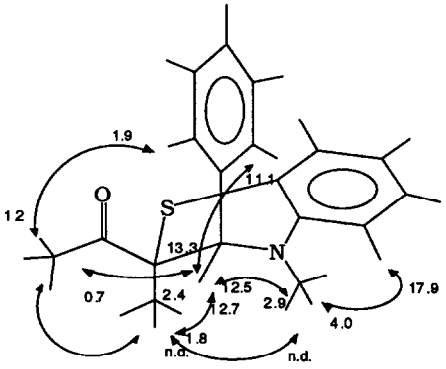
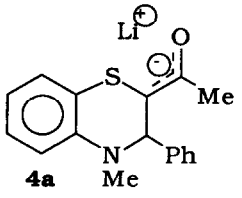
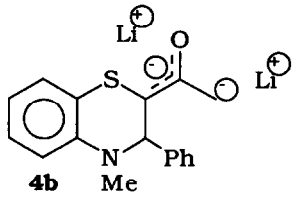


Fig. 2 Noe interaction diagram for **3e**.
The numbers at the tip of the arrows give the % enhancements upon saturation of the connected nucleus. n.d. = not detected. is. = isochronous

Further support to the structure of **3a** was provided by X-Ray crystallography (Fig. 3).
The stereoselective formation of **3a** in the reaction between **2** and MeMgI could be rationalized by assuming that the protonation of the enolate (C) occurs from the same side of the phenyl group in order to put it *trans* to the acetyl group. Attempts to methylate the enolate (C) with MeI failed as **3a** was recovered. Comparable results were obtained when benzylidene **2** was reacted with allylic Grignard reagents. Indeed, the reaction of **2** with allylmagnesium bromide, methallylmagnesium chloride and crotylmagnesium choride furnished satisfactory to good yields of dihydrobenzothiazine derivatives **3b**, **3c** and **3d** respectively, all having a trans geometry as suggested by the coupling constants between the two hydrogens in 2- and 3-position.



4a



4b

The acidity of the methynic hydrogen in the 2-position of the heterocyclic moiety of **3a** encouraged us to explore the possibility of further elaboration of the benzothiazine ring for the preparation of more substituted derivatives. Lithiation of **3a** with lithium diisopropylamide (LDA) at -78°C produced a dark red solution most likely due to lithium enolate **4a**. Its formation has been proved by trapping it with methyl iodide to give compound **3e**. It was very interesting to note that methylation of **4a** proceeded with excellent diastereoselection furnishing compound **3e**, in which the acetyl and the phenyl groups set up *cis* each other. Such a stereoselection could be rationalised by assuming that enolate **4a** undergoes the electrophilic attack of MeI from the less sterically hindered site thus putting the acetyl group *cis* with respect to phenyl group. It is worth noting the different stereochemistry of the protonation and the methylation reaction of enolate **4a**. The stereochemistry of **3e** has been assigned on the basis of the NOE difference spectroscopy (Fig. 2). The methyl resonance at δ 2.97, 1.89 and 1.6O can be assigned to Me-N, Me-CO and Me-C respectively, on the basis of the relative downfield shift and also of the measured NOE interactions with the methynic proton at δ 4.59. The Me-N group also exhibits a strong interaction with the adjacent *ortho* proton of the fused aromatic ring, resonating at d 6.74. A small but diagnostic interaction of the *ortho* protons of the monosubstituted phenyl ring is observed with the Me-CO group, but not with the Me-C group, thus implying the relative orientations shown in Figure 2.

The lithiation of **3a** followed by methylation with MeI also yielded a small amount of a product that was identified as the dimethylation product **3f**, most likely formed from the dianion **4b**. Compound **3e** was formed almost exclusively when **3a** was first treated with potassium t-butoxide in dimethylformamide(DMF) and then with MeI. Lithiation of **3a** with t-BuLi in THF at -78°C followed by addition of MeI provided a mixture of **3e** and the alcohol **3g** to be ascribed to a nucleophilic attack of t-BuLi to the carbonyl group. Lithiation of **3a** with lithium bis(trimethylsilyl)amide and subsequent addition of MeI led to compound **3e** as the main product together with small percentages of di- and tri-methylation compounds **3f** and **3h**. Trapping of **4a** with benzyl bromide yielded the benzylation product **3i**, as well as a small amount of the alcohol **3j**, which is most likely due to the addition to the carbonyl of n-BuLi used as an excess in the preparation of LDA. Finally, lithiation of **3e** with LDA followed by addition of excess MeI led to a mixture of mono- and di-methylation products **3f** and **3h**.

Thus, in the metallation-alkylation reaction of 1,4-dihydro-2-acetylbenzothiazines the alkylation takes place mainly on the heterocyclic ring α to sulfur, regardless of the metallating agent. Only in the absence of hydrogens in the 2-position did the lithiation-alkylation reaction occur at the methyl of the acetyl group. In no case was alkylation obseved at position 3, that would arise from the relevant metallated intermediate.[11] In contrast, lithiation of **3a**, carried out under the usual conditions (LDA, THF, -78°C) and followed by addition of benzaldehyde, gave rise to the formation of the aldol-type condensation product **3k**. Similarly, the reaction with 2,6-dichlorobenzaldehyde furnished compound **3l**.

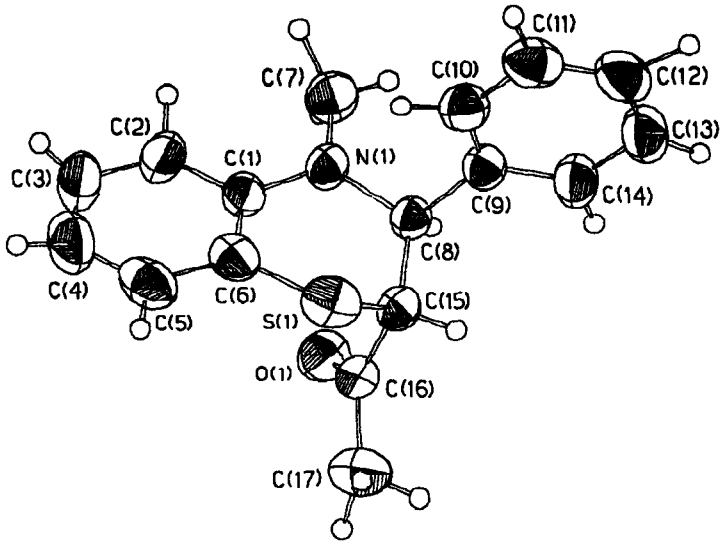


Fig. 3: ORTEP view of **3a** with thermal ellipsoids at 40% probability.

Experimental

^{1}H NMR spectra were recorded on a Varian EM 360A, a EM 390 and a Varian XL-200 MHZ and a Bruker AC 200 and 400 MHz spectrometers ; chemical shifts are reported in parts per million (δ) from internal standard using $CDCl_3$ as solvent. NOE spectra (in $CDCl_3$) have been obtained as reported.[12] IR spectra were recorded on a Perkin-Elmer spectrometer model 598 and refer to films. GC analyses were carried out with a Hewlett-Packard MP-5890 series II gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.). Boiling points were uncorrected. Flash chromatographies were performed with Merck 230-400 mesh silica gel.

Materials: Tetrahydrofuran (THF) and diethyl ether of commercial grade were purified by distillation (twice) from sodium wire in a N_2 atmosphere. Petroleum ether refers to the 40-60°C boiling fraction. Allylic halides and all other chemicals were of commercial grade and used without further purification or eventually distilled prior to use. Allylic Grignard reagents were prepared according to the procedure reported for 1-methyl-2-propenylmagnesium bromide.[13] Elemental analyses were performed on Carlo Erba C,H,N analyser.

Reaction of (Z)-2-benzylidene-3,4-dihydro-3-oxo-2H-4-methyl-1,4-benzothiazine 2 with phenylmagnesium bromide.

To a stirred ether (50 ml) solution of **2** (1.0g, 3.7 mmol) was added dropwise a ether solution of 1.3M PhMgBr at room temperature under a N_2 atmosphere. The reaction mixture was quenched with aqueous NH_4Cl after 18h at room temperature and extracted with CH_2Cl_2(3x25ml). Drying over $MgSO_4$ and solvent

evaporation under reduced pressure left an oily residue (1.2g) that was purified by flash chromatography. The main eluted compound (1.0g) was characterized as **2-diphenylmethyl-4-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1b**; 78% yield, mp 164-5°C (C_2H_5OH). IR (nujol) ν: 1660 cm^{-1}(CO). ^1H NMR ($CDCl_3$, 60MHz) δ: 3.4(s, 3H); 4.1-4.6(m, 2H); 7.2-7.7 (m, 14H). (Anal. Calc. for $C_{22}H_{12}NOS$: H, 5.54; C, 76.49; N, 4.05. Found: H, 5.49; C, 76.35; N, 4.15.)

Reaction of (Z)-2 with methylmagnesium iodide.

3.98g (15 mmol) of benzylidene **2** in 130 ml of THF were treated, under stirring and a N_2 atmosphere at room temperature, with 6 ml of 3.7M MeMgI (22.2 mmol) in THF. After 24h the reaction mixture was quenched with aqueous NH_4Cl and extracted with CH_2Cl_2 (3x30ml). Drying over $MgSO_4$ and evaporation of the solvent under reduced pressure left an oily residue (5g). TLC indicated the presence of one main product together with some starting benzylidene **2**. The residue was then purified by column chromatography (silica gel, ether/petroleum ether: 1/4 as eluent) to give 3.2g, 80% yield of **2-acetyl-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3a.** mp 83-4°C (EtOH). IR (CH_2Cl_2) ν: 1710 cm^{-1}(CO). ^1H NMR($CDCl_3$, 200 MHz) δ: 2.27(s,3H); 2.94(s,3H); 3.58(d,1H,J=2.1Hz); 5.08(d,1H, J=2.1Hz); 6.68-6.79(m,2H); 7.15-7.32(m,7H). ^{13}C NMR($CDCl_3$, 200 MHz) δ: 27.32; 38.51; 54.30; 63.89; 111.53; 113.68; 116.90; 127.13; 127.69; 127.96; 128.45; 128.76; 142.86; 144.33; 203.05. Anal. Calcd. for $C_{17}H_{17}NOS$: H, 6.05; C, 72.05; N, 4.94. Found: H, 6.15; C, 72.25; N, 4.84.

Reaction of 2 with 2-methyl-2-propenylmagnesium chloride.

To a solution of **2** (0.5g, 1.9 mmol) in 30 ml of THF at -78°C, under stirring and in a N_2 atmosphere was added dropwise a THF solution of 0.6M 2-methyl-2-propenylMgCl (3.7 ml, 2.23 mmol). After 1.5 h at -78°C, the reaction mixture was allowed to warm to RT and kept overnight. Quenching with sat aqueous solution of NH_4Cl, extraction with CH_2Cl_2 (3x25 ml), drying over $MgSO_4$ and evaporation of the solvent under reduced pressure left an oily residue (0.55g), that was purified by flash chromatography (silica gel, ether/petroleum ether: 1/4 as eluent) to give 0.5g, 81% yield of **2-(3-methyl-3-butenoyl)-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3c**: oil, IR(neat) ν: 1710 cm^{-1}(CO). ^1H NMR ($CDCl_3$, 60 MHz) δ: 1.65(s,3H); 3.00(s,3H); 3.44(s,2H); 3.78(d, 1H,3Hz); 4.5-5.1 (m, 2H); 5.13(d,1H,3Hz). Anal. Calcd. for $C_{20}H_{21}NOS$: H, 6.54; C,74.27; N, 4.33. Found: H, 6.44; C, 74.04; N, 4.43.

Reaction of 2 with allylmagnesium bromide.

The reaction was carried out as described above for 2-methyl-2-propenylmagnesium chloride and furnished **2-(3-butenoyl)-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3b** : oil, 63% yield. IR (neat) ν : 1710 cm^{-1}(CO). ^1H NMR ($CDCl_3$, 60 MHz) δ: 3.0 (s,3H); 3.35-3.55 (m,2H); 3.68 (d,1H, J=2Hz); 5.15 (d,1H, J=2Hz); 5.20-5.40 (m, 2H); 5.50-6.20 (m, 1H); 6.80-7.50 (m,4H); 7.60 (s,5H). Anal. Calcd. for $C_{19}H_{19}NOS$: H, 6.19; C, 73.75; N, 4.53. Found: H, 6.15; C, 73.69; N, 4.43.

Reaction of 2 with 1-methylallylmagnesium bromide.

Reaction carried out as above for allylmagnesium bromide to give **2-(2-methyl-3-butenoyl)-3-phenyl-4-methyl-3,4-dihydro-2H-1,4-benzothiazine 3d**: oil, 67% yield. IR (neat) ν: 1710 cm^{-1}(CO). ^1H NMR ($CDCl_3$, 60MHz) δ: 1.10(d,3H, J=6Hz); 2.93(s,3H); 3.45(m,1H,); 3.70(d,1H, J=2Hz); 5.10(d,1H,

J=2Hz); 5.20-5.35(m,2H); 5.50-5.90(m,1H); 6.70-7.50(m,4H); 7.40(s,5H). Anal. Calcd. for C20H21NOS: H, 6.54; C, 74.27; N, 4.33. Found: H, 6.51; C, 74.12; N, 4.21.

Metallation of 2-acetyl-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3a with lithium diisopropylamide (LDA) and reaction with electrophiles.

To a THF (5ml) solution of diisopropylamine (0.3 ml, 2.12 mmol) was added a hexane 2.4N solution (0.885 ml, 2.12 mmol) of n-BuLi at about 0°C under stirring and a N_2 atmosphere. The mixture was then cooled to -78°C and a THF (10 ml) solution of **3a** added dropwise. The resulting yellow reaction mixture was kept under stirring at -78°C for 30 min and then treated with 0.177 ml (2.12 mmol) of methyl iodide in THF (2ml). After 30 min at -78°C, the reaction mixture was allowed to warm to RT and retained for 24h. Quenching with a sat aqueous solution of NH4Cl, extraction with ether (3x25 ml), drying over $MgSO_4$ and evaporation of the solvent under reduced pressure left a solid residue that was a mixture of two main compounds which could be separated by column chromatography(silica gel, ether/petroleum ether: 3/7 as eluent). The first eluted compound (0.039g, 7.5% yield) was identified as **2,4-dimethyl-3-phenyl-2-propanoyl-3,4-dihydro-2H-1,4-benzothiazine 3f:** oil, IR (neat) ν : 1712 cm^{-1}(CO). ^{1}HNMR (CDCl3, 200 MHz) δ: 0.80(t, 3H, J=7Hz); 1.60(s, 3H); 1.71-1.92 (dq, 1H, J=7Hz); 2.25-2.45 (dq, 1H, J= 7Hz); 2.95 (s, 3H); 4.58 (s, 1H); 6.65-6.75 (m, 2H); 7.0-7.30 (m, 7H). Anal. Calcd. for C19H21NOS: H, 6.80; C, 73.28; N, 4.50. Found: H, 6.65; C, 73.15; N, 4.54.

The second eluted compound was **2-acetyl-2,4-dimethyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3e:** 0.334g, 66% yield, mp 125-6°C (EtOH). IR (KBr) ν: 1715 cm^{-1}(CO). ^{1}H NMR (CDCl3, 400MHz) δ: 1.60 (s, 3H); 1.90 (s, 3H); 3.0 (s, 3H); 4.60 (s,1H); 6.65-6.80 (m, 2H); 7.10-7.35 (m, 7H). Anal. Calcd. for C18H19NOS: H, 6.44; C, 72.70; N, 4.71. Found: H, 6.35; C, 72.65; N, 4.60.

Comparable results were obtained when t-BuOK or lithium hexamethyldisilylazide (LHMDS) were used for the metallation reaction of **3a**.

Metallation of 3a with t-BuLi and reaction with MeI.

To 0.2g (0.71 mmol) of **3a** in 10 ml of THF under stirring and N_2 atmosphere at -78°C was added a pentane 1.6N solution of t-BuLi (0.53 ml, 2.44 mmol). After 30 min the reaction mixture was treated with an excess MeI. After 30 min the mixture was allowed to warm to RT and then worked up as usual to give a solid residue (0.28g). Column chromatography (silica gel, ether/petroleum ether: 1/9 as eluent) gave two main products. The first eluted compound (0.04g, 22% yield) was **3e**. The second eluted compound (0.144g, 68% yield) was identified as **2-[2-(2-hydroxy-3,3-dimethyl)-butyl]-4-methyl-3,4-dihydro-2H-1,4-benzothazine 3g**. mp 102-103.5°C (C2H5OH). IR (KBr) ν: 3520 cm^{-1}(CO). ^{1}H NMR (CDCl3, 90MHz) δ: 1.15(s, 9H); 1.30(s, 3H); 3.02 (s,3H); 3.35 (d, 1H, J=2.2Hz); 5.25 (d, 1H, J=2.2Hz); 6.65-6.90(m, 2H); 7.05-7.35 (m, 7H). Anal. Calcd for C21H27NOS: H, 7.98; C, 73.86; N, 4.10. Found: H, 7.84; C, 73.72; N, 4.19.

Metallation of 3a and reaction with benzylbromide.

To the LDA solution (0.71 mmol), prepared as above, was added a THF (10ml) solution of **3a** (0.2g, 0.70 mmol) at -78°C. After 30 min a THF (5ml) solution of benzylbromide (0.15 ml, 0.7 mmol) was added dropwise. After 30 min at -78°C the reaction mixture was allowed to warm to RT and worked up as usual to

give a residue of two main compounds that could be separated by column chromatography (silica gel, ether/petroleum ether: 1/4). The first eluted compound (0.12g, 46%yield) was **2-acetyl-2-benzyl-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3i**: oil, IR (neat) ν: 1710 cm^{-1}(CO). ^1H NMR (CDCl3, 90MHz) δ: 1.43(s, 3H); 2.95(d, 1H, J=13.5Hz); 3.0(s,3H); 3.40(d, 1H, J=13.5Hz); 4.80(s,1H); 6.70-6.90(m,2H); 7.00-7.40(m,7H). Anal. Calcd. for C24H23NOS: H, 6.21; C, 77.18; N, 3.75. Found: H, 6.28; C, 77.08; N, 3.60.

The second eluted compound (0.02g, 6% yield) was **2-[2-(2-hydroxyhexyl)]-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3j**: oil, IR(CCl4) ν : 3520 cm^{-1}(CO)· ^1H NMR (CDCl3, 200 MHz) δ: 0.75(t, 3H); 1.20-1.40 (m, 7H); 1.60-1.80 (m,2H); 2.98 (s, 3H); 3.00(d,1H, J=2.2 Hz); 5.00(d,1H, J=2.2Hz); 6.60-6.75 (m, 2H); 7.0-7.4 (m, 7H). Anal. Calcd. for C21H27NOS: H, 7.97; C, 73.86: N, 4.10. Found: 7.84; C, 73.95; N, 4.21.

Metallation of 3e and reaction with MeI.

0.180 g of **3e** (0.6 mmol) in 5 ml of THF was added dropwise at -78°C to LDA (0.72) mmol) prepared as above. After 30 min the resulting reaction mixture was treated with an excess MeI and allowed to warm to RT. Usual work up furnished a mixture of two main compounds that could be separated by column chromatography (silica gel, ether/petroleum ether : 1/9). The first eluted product (0.050g, 30% yield) was **2,4-dimethyl-3-phenyl-2-(2-methyl)propanoyl-3,4-dihydro-2H-1,4-benzothiazine 3h.** ^1H NMR (CDCl3, 200 MHz) δ: 0.50 (d, 3H, J=6.7 Hz); 1.00 (d, 3H, J=6.7 Hz); 1.60 (s, 3H); 2.60 (hept., 1H, J=6.7 Hz); 2.95 (s, 3H); 4.65(s, 1H); 6.68(m,2H); 7.05-7.30 (m, 7H). Anal. Calcd. forC19H21NOS: H, 6.80; C, 73.28; N, 4.50. Found: 6.75; C, 73.12; N, 4.58. The second eluted compound (0.030g, 19% yield) was **2,4-dimethyl-3-phenyl-2-propanoyl-3,4-dihydro-2H-1,4-benzothiazine 3f.**

Reaction of 4a with aldehydes.

The reaction with benzaldehyde is here described. To a solution of **4a** (0.85 mmol) prepared as above was added dropwise at -78°C a THF (8 ml) solution of benzaldehyde (0.95 mmol). After 30 min the reaction mixture was allowed to warm to RT and after 2h quenched with sat aqueous NH4Cl and worked up as usual to give a residue that was column chromatographed (silica gel, ether/petroleum ether: 3/7). The first eluted compound was characterized as **4-methyl-3-phenyl-2-(3-phenyl)propenoyl-3,4-dihydro-2H-1,4-benzothiazine 3k**: oil, 65% yield. ^1H NMR (CDCl3, 200 MHz) δ: 3.00 (s, 3H); 3.68(d, 1H, J=16 Hz); 3.80(d,1H, J=2.1 Hz); 3.98(d, 1H, J=16 Hz); 5.15 (d, 1H, J=2.1 Hz); 6.30-7.90(m, 14H). Anal. Calcd. for C24H21NSO: H, 5.70; C, 77.60; N, 3.77. Found: H, 5.81; C, 77.51; N, 3.91. The second eluted compound was **3a**.

Similarly, **4a** reacted with 2,6-dichlorobenzaldehyde to give **4-methyl-3-phenyl-2-(3-(2,6-dichlorophenyl))propenoyl-3,4-dihydro-2H-1,4-benzothiazine 3l:** m.p. 134-6°C(EtOH); 72% yield. IR(KBr) ν: 1695 cm^{-1}(CO). ^1H NMR(CDCl3, 200 MHz) δ: 2.87(s, 3H); 3.63(d, 1H, J=2.1Hz); 5.01(d, 1H, J=2.1Hz); 6.60-6.85(m, 2H, cis +trans); 7.06-7.30(m, 12H). Anal. Calcd. for C24H19NOS: H, 5.19; C, 78.02; N, 3.79. Found: 5.31; C, 77.18; N, 3.62.

X-Ray crystallographic data of 2-acetyl-4-methyl-3-phenyl-3,4-dihydro-2H-1,4-benzothiazine 3a.

Table I. Fractional atomic coordinates.

Atom	X/a	Y/b	Z/c
S(1)	0.14374(6)	0.00290(4)	0.38001(5)
O(1)	-0.0216(2)	0.0937(1)	0.0873(2)
N(1)	0.2985(2)	0.1116(1)	0.2091(2)
C(1)	0.2395(2)	0.1670(1)	0.2893(2)
C(2)	0.2587(3)	0.2672(2)	0.2933(2)
C(3)	0.2092(3)	0.3218(2)	0.3775(3)
C(4)	0.1340(4)	0.2830(2)	0.4568(3)
C(5)	0.1083(3)	0.1859(2)	0.4538(2)
C(6)	0.1632(2)	0.1272(2)	0.3725(2)
C(7)	0.3810(3)	0.1570(2)	0.1289(2)
C(8)	0.2491(2)	0.0164(1)	0.1678(2)
C(9)	0.3670(2)	-0.0574(1)	0.1947(2)
C(10)	0.3686(3)	-0.1351(2)	0.1168(2)
C(11)	0.4743(3)	-0.2034(2)	0.1399(3)
C(12)	0.5783(3)	-0.1957(2)	0.2417(3)
C(13)	0.5779(3)	-0.1190(2)	0.3199(3)
C(14)	0.4738(2)	-0.0502(2)	0.2964(2)
C(15)	0.1206(2)	-0.0175(1)	0.2174(2)
C(16)	-0.0176(2)	0.0267(1)	0.1559(2)
C(17)	-0.1491(3)	-0.0182(2)	0.1847(3)
H(2)	0.344(5)	0.296(3)	0.245(4)
H(3)	0.245(5)	0.387(3)	0.381(4)
H(4)	0.111(7)	0.324(4)	0.486(6)
H(5)	0.049(3)	0.158(2)	0.511(2)
H(71)	0.468(5)	0.196(3)	0.177(4)
H(72)	0.322(4)	0.197(2)	0.056(3)
H(8)	0.220(2)	0.021(1)	0.086(2)
H(10)	0.295(3)	-0.144(2)	0.045(2)
H(11)	0.459(5)	-0.240(3)	0.066(4)
H(12)	0.658(4)	-0.256(2)	0.243(3)
H(13)	0.654(4)	-0.107(3)	0.383(3)
H(14)	0.466(3)	0.002(2)	0.339(3)
H(15)	0.111(3)	-0.085(2)	0.209(3)
H(73)	0.424(4)	0.109(2)	0.100(3)
H(171)	-0.244(4)	0.000(2)	0.137(4)
H(172)	-0.145(4)	-0.043(3)	0.260(4)
H(173)	-0.165(4)	-0.077(3)	0.150(4)

Table II. Selected bond distances (Å) and angles (°).

S(1)-C(6)	1.750(2)	C(2)-C(3)	1.366(4)
S(1)-C(15)	1.818(2)	C(3)-C(4)	1.357(5)
O(1)-C(16)	1.208(3)	C(4)-C(5)	1.378(5)
N(1)-C(1)	1.384(3)	C(5)-C(6)	1.400(4)
N(1)-C(7)	1.450(3)	C(8)-C(9)	1.530(2)
N(1)-C(8)	1.459(2)	C(8)-C(15)	1.523(3)
C(1)-C(2)	1.412(3)	C(15)-C(16)	1.518(3)
C(1)-C(6)	1.403(3)	C(16)-C(17)	1.502(4)

C(6)-S(1)-C(15)	95.85(8)	S(1)-C(6)-C(1)	119.9(2)
C(7)-N(1)-C(8)	112.8(2)	N(1)-C(8)-C(15)	114.1(1)
C(1)-N(1)-C(8)	124.5(2)	N(1)-C(8)-C(9)	111.4(1)
C(1)-N(1)-C(7)	119.6(2)	C(9)-C(8)-C(15)	110.2(2)
N(1)-C(1)-C(6)	122.4(2)	C(8)-C(9)-C(14)	121.8(2)
N(1)-C(1)-C(2)	120.6(2)	C(8)-C(9)-C(10)	119.7(2)
C(2)-C(1)-C(6)	117.0(2)	S(1)-C(15)-C(8)	110.8(1)
C(1)-C(2)-C(3)	121.0(2)	C(8)-C(15)-C(16)	114.5(2)
C(2)-C(3)-C(4)	121.7(3)	S(1)-C(15)-C(16)	109.3(1)
C(3)-C(4)-C(5)	119.5(3)	O(1)-C(16)-C(15)	121.9(2)
C(4)-C(5)-C(6)	120.3(3)	C(15)-C(16)-C(17)	116.1(2)
C(1)-C(6)-C(5)	120.4(2)	O(1)-C(16)-C(17)	122.0(2)
S(1)-C(6)-C(5)	119.6(2)		

Crystal data: C17H17NOS, M = 283.4, monoclinic, space group P21/a, a = 9.650(7), b = 13970(6), c = 11205(7) Å, β = 100.39(3)°, U = 1485(1) A^3, Z = 4, Dc = 1.27 g/cm^3, F(000) = 600, Cu Ka = 1.54056 Å, μ = 18.4 cm^{-1}. Crystal size: 0.32x0.90x0.48 mm^3.

The intensities of 3108 reflections were collected up to a θmax = 70° on a computer controlled Siemens AED using the ω-2θ scan technique. The reflection 5-1-3, remeasured every fifty, was chosen as a standard to check the stability of the crystal and the electronics. No absorption correction was applied.

The structure was solved by direct methods using the SHELX86[14] program and refined to a final R value of 5.67%, wR=7.21% for 2496 reflections with I>2s(I). w = $1.000.(s^2(F_O)+0.013901(F_O)^2)^{-1}$. Scattering factors for C,H,N,O,S were taken from the International Tables for X-Ray Crystallography,[15] and both the real and imaginary components of anomalous dispersion were included. All non-hydrogen atoms were refined anisotropically using SHELX76.[16] Hydrogen atoms have been located by means of a DF synthesis and subsequently refined. The atomic fractional coordinates are reported in Table I and Table II shows a list of selected bonds and angles. Geometrical parameters were calculated by PARST.[17]

The two aromatic rings show deviations from planarity, but while the phenyl ring has only a slight distorsion from the ideal geometry, the other one, part of the benzothiazine moiety, presents appreciable displacements (C(3) -0.021(4), C(5) 0.018(2)Å). This distorsion is probably caused by the strains of the neighbouring cyclic moiety. The phenyl and the acetyl groups are in a antiperiplanar conformation with the torsion angle C(9)-C(8)-C(15)-C(16) of 156.8(1)°. The six-membered heterocyclic ring exhibits a twist-boat conformation with puckering parameters q2=0.576(2), q3=0.292(2)Å and ϕ_2 = 149.2(2)°. The phenyl ring forms an angle of 99.18(5)° with the mean LSQ plane of the benzothiazine molecule.

Being absent any atom group allowing hydrogen bonds, the molecular packing is completely determined by van der Waals Interactions.

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