Reaction of 2,2'-Dithiodianiline with 2-Alkyl-1,3-diketones. Synthesis and Chemical Behaviour of Some 2-Acyl-2*H*-1,4-benzothiazines

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The reactions of 2,2'-dithiodianiline **1** with 2-alkyl-1,3-diketones **2a-d** have been employed in order to synthesize 2-acyl-2*H*-1,4-benzothiazines. In the cases of **2a,b** the expected 2-acyl-2*H*-1,4-benzothiazines, *i.e.* **3a,b** were obtained, whereas the reactions of **1** with the 1,3-diketones **2c,d** afforded the α-ketosulfide **12** and the 1,4-benzothiazine **17**, respectively. The products **3a,b** underwent the hydrolytic C_2-C_3 bond cleavage of the thiazine nucleus to give the α-ketosulfides **6** and **11**, respectively. Such an hydrolytic process explains the formation of the compound **12** in the reaction of **1** with **2c**. The formation of **17** in the case of **2d** is considered to be formed through a rearrangement involving the 1,3-sulfur shift of the preformed 1,4-benzothiazine **3d**.

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1,4-Benzothiazine compounds exhibit a number of pharmacological activities. These properties together with other uses, their syntheses and reactions have been recently reviewed [1]. In previous works [2-4] we described the synthesis of 1,4-benzothiazine compounds by the reactions of 2,2'-dithiodianiline either with enolizable ketones or with electron deficient alkynes. At this purpose some useful synthetic variants have been proposed [5,6]. However, by using these procedures as well as the other known methods [1] 2-acyl-4*H*- and not 2-acyl-2*H*-1,4-benzothiazines have so far been prepared. In order to synthesize the latter compounds our study was extended to the reaction of 2,2'-dithiodianiline **1** with 1,3-diketones **2a-d.**

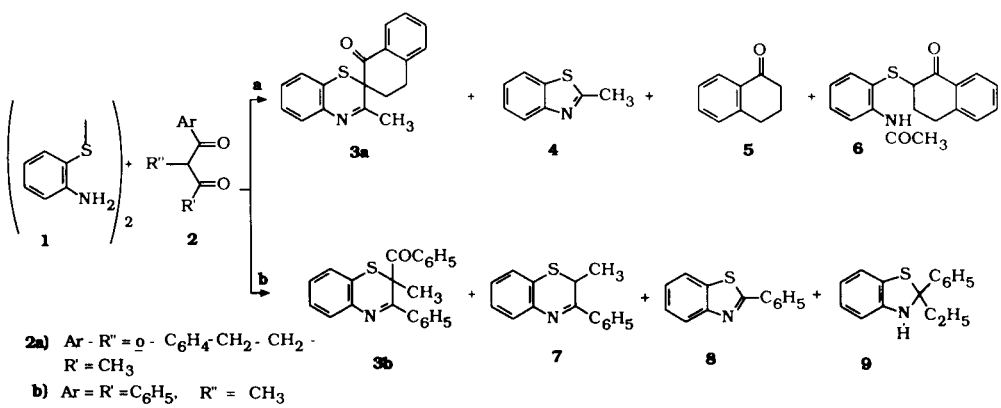
By reacting in toluene solution the disulfide **1** with the 1,3-diketones **2a,b** under nitrogen and in the presence of *p*-toluenesulfonic acid as the catalyst, complex reaction mixtures were obtained in both cases. By column chromatography it was possible to isolate the expected 2-acyl-2*H*-1,4-benzothiazines **3a** and **3b** (Scheme I) whose structures are fully demonstrated by microanalytical and spectral data. In addition, we isolated the α-ketosulfide **6** and the compounds **4, 5, 7, 8** and **9.**

Interestingly, we found that the 2-acyl-2*H*-1,4-benzothiazine **3a** by treatment with silica-gel in petroleum ether/-ethyl acetate 9:1 mixture gives rise to the compound **6.** The foregoing result indicates that the 1,4-benzothiazine **3a** undergoes an hydrolytic ring opening. Such an hydrolysis involves the C_2-C_3 bond cleavage of the thiazine nucleus which apparently proceeds *via* the aminoalcohol intermediate **10** as shown in Scheme II.

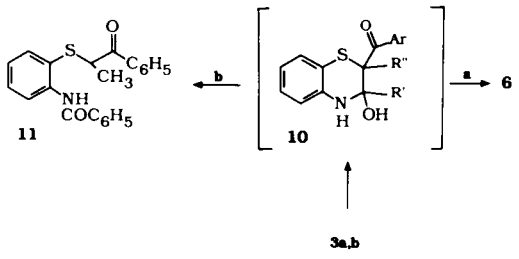
Similarly, the compound **3b** when treated with aqueous hydrochloric acid in ethanol underwent the hydrolytic ring opening to give the α-ketosulfide compound **11.**

From the reaction of 2,2'-dithiodianiline **1** with diketone **2c** in toluene by column chromatography we isolated the α-ketosulfide **12** and compounds **4, 13** and **14** (Scheme III). The structure of compound **12** deduced by spectral and microanalytical data was further confirmed from its sodium borohydride reduction to the sulfide **15** which in turn was deacylated to give compound **16.** Although compound **16** was chromatographically homogeneous the ^{1}H-nmr spectrum clearly revealed it as a 2:1 mixture of *cis* and *trans* diastereomers. The formation of the compound **12** can be accounted for by assuming that a complete

Scheme I



Scheme II



a Ar-R''= o-$C_6H_4CH_2CH_2$
R' = CH_3

b Ar=R''= C_6H_5
R' = CH_3

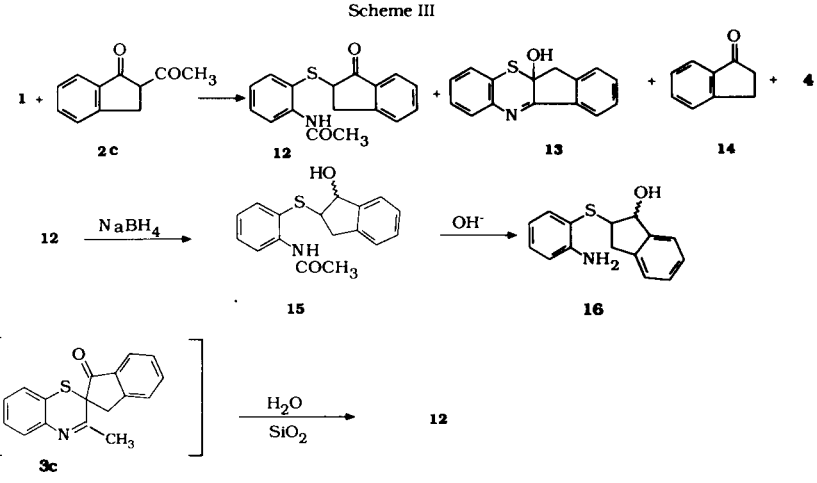
silica-gel catalyzed hydrolysis of the expected spirobenzothiazine compound **3c** occurs.

As for hydrolysis of spiro-2-acyl-2*H*-1,4-benzothiazines **3a** and **3c** it is apparent that the ring size of the cycloalkyl moiety affects the extent of the hydrolysis process. The absence of a spiro ring and the presence of a more conjugate imine system could explain the quite drastic reaction conditions required to hydrolyze **3b**.

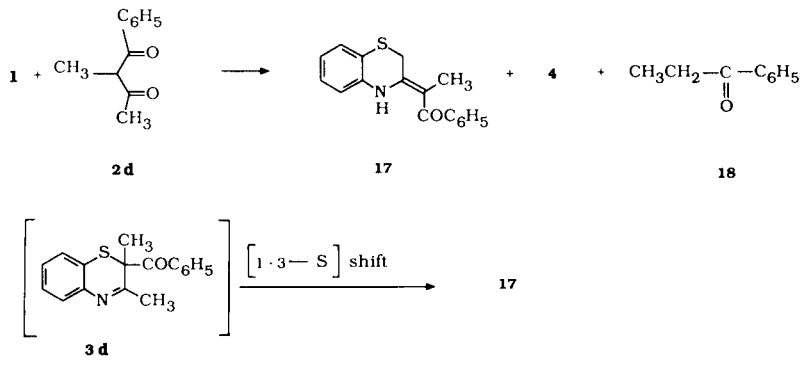
From the reaction of disulfide **1** with diketone **2d** in toluene 1,4-benzothiazine **17** together with the known compounds **4** and **18**, were isolated. The formation of 1,4-benzothiazine **17** can be accounted for by assuming that it could arise from the expected 2-benzoyl-2,3-dimethyl-2*H*-1,4-benzothiazine **3d**. This compound could undergo an intramolecular acid-catalyzed rearrangement involving the 1,3-sulfur shift as previously reported [7,8] for structurally related compounds such as 2-alkoxycarbonyl-3-alkyl-2*H*-1,4-benzothiazines (Scheme IV).

Finally, the formation of the compounds **4, 5, 7, 8, 9, 13, 14, 18** remains to be rationalized. Taking into account that i) 2,3-dihydrobenzothiazoles **B** can undergo thermal decomposition [9] affording benzothiazoles and ketones, **C** and **D** respectively; ii) 2-alkyl-1,4-benzothiazines **F** undergo autoxidation giving rise to their 1-oxide derivatives **H** together with the hemithioketal isomers **I** [10], we believe that the formation of the above mentioned products occurs starting from 2,3-dihydrobenzothiazole **B**. This last compound and the 1,4-benzothiazine **A**, are the expected products of the reaction between 2,2'-dithiodianiline and enolizable ketones such as 1,3-diketones **2a-d** (Scheme V).

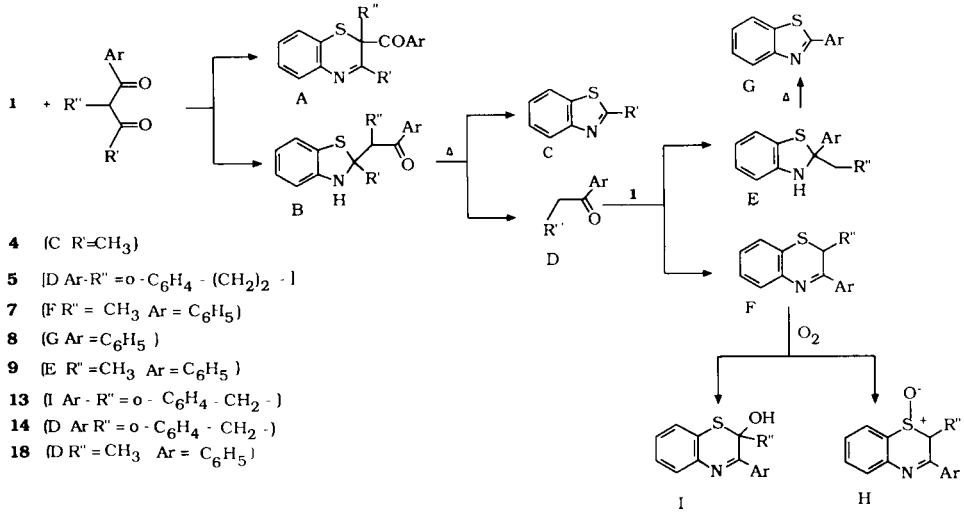
Scheme III



Scheme IV



Scheme V



4 (C R'=CH_3)

5 [D Ar-R" =o-C_6H_4-$(CH_2)_2$-]

7 (F R" = CH_3 Ar = C_6H_5)

8 (G Ar = C_6H_5)

9 (E R" = CH_3 Ar = C_6H_5)

13 (I Ar-R" = o-C_6H_4-CH_2-)

14 (D Ar R" = o-C_6H_4-CH_2-)

18 (D R" = CH_3 Ar = C_6H_5)

In conclusion, our data demonstrate that the reaction of 2,2'-dithiodianiline **1** with 2-alkyl-1,3-diketones leads to 2-acyl-2*H*-1,4-benzothiazines which could be in some instances not isolated suffering from a rearrangement to 3-(1-acylalkylylidene)-3,4-dihydro-2*H*-1,4-benzothiazine or an hydrolytic ring cleavage involving the C_2-C_3 bond breaking of the thiazine nucleus. Moreover it has been found that, starting from 1-aryl-2,3-dialkyl-1,3-diketones, 2-aroyl-3-alkyl-2*H*-1,4-benzothiazines and not 2-alkylcarbonyl-3-aryl-2*H*-1,4-benzothiazines are regioselectively formed.

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are uncorrected. The ir spectra were taken on a Perkin-Elmer 257 instrument. The pmr spectra were recorded on a Varian EM-390 instrument operating at 90 MHz or on a Varian XL-200 instrument. Chemical shifts are given in δ from tetramethylsilane as the internal standard. Gas-mass analysis has been carried out on a Hewlett-Packard 5995 C-GC/MS instrument. Preparative tlc on Carlo Erba SIF_{254} silica gel plates (2 mm thickness) and column chromatography on silica gel (Merck 70-325 mesh) were carried out using light petroleum ether (bp 40-70°)-ethyl acetate (9:1 v/v) as eluent. The yields are based on disulfide **1** used. All the reactions were carried out under nitrogen.

Reaction of 2,2'-Dithiodianiline (**1**) with 1,3-Diketone **2a**.

A solution of 2,2'-dithiodianiline **1** (2.48 g, 0.01 mole) and 2-acetyltetral-1-one **2a** (3.76 g, 0.02 mole) in toluene (150 ml) containing catalytic amounts of *p*-toluenesulfonic acid as catalyst was refluxed for 5 hours with azeotropic removal of the water by a Dean-Stark apparatus. After cooling and evaporation of the solvent at reduced pressure, the residual oil was separated by column chromatography to give **4** [11], **5** [11], **3a** and **6** in 40, 51, 43, and 11% yield, respectively.

3-Methyl-2*H*-1,4-benzothiazine[2-spiro-2'-tetral-1'-one] (**3a**).

This compound was obtained as a pale yellow solid (isopropyl alcohol), mp 148-149°; ir (potassium bromide): ν 1670 (CO), 1625 (C=C) cm^{-1}; pmr (deuteriochloroform): δ 2.0-3.2 (m, 4H, CH_2CH_2), 2.23 (s, 3H, CH_3), 7.0-7.6 (m, 7H, phenyl protons), 8.03 (dd, 1H, phenyl proton); ms: m/e 293 (M^+, 100).

Anal. Calcd. for $C_{18}H_{15}NOS$: C, 73.70; H, 5.15; N, 4.78. Found: C, 73.58; H, 5.08; N, 4.81.

N-Acetyl-2-(2-aminophenylthio)tetral-1-one (**6**).

This compound was obtained as a yellow oil; ir (neat): ν 3300 (NH), 1680 (CO) cm^{-1}; pmr (deuteriochloroform): δ 1.8-3.3 (m, 4H, CH_2CH_2), 2.23 (s, 3H, CH_3), 3.73 (dd, 1H, -SCHCO), 6.7-7.7 (m, 6H, phenyl protons), 8.0 (dd, 1H, phenyl proton), 8.4 (dd, 1H, phenyl proton), 9.2 (br s, 1H, NH); ms: m/e 311 (M^+, 57), 205 (32), 144 (58), 121 (61), 115 (57), 97 (27), 93 (100).

Anal. Calcd. for $C_{18}H_{17}NO_2S$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.20; H, 5.38; N, 4.48.

Reaction of 2,2'-Dithiodianiline (**1**) with 1,3-Diketone **2b**.

2,2'-Dithiodianiline **1** (2.48 g, 0.01 mole) and 1,3-diphenyl-2-methyl-1,3-propandione **2b** (4.74 g, 0.02 mole) were allowed to react as described in the above reported reaction. Evaporation of the solvent under reduced pressure and column chromatography of the residue yielded two fractions. Analysis of the first eluted fraction by gc/ms revealed it to correspond to a mixture of **8** [11], **9** [11], and **7** [11] in 76, 15 and 30% yield, respectively. The second eluted fraction was **3b** in 25% yield.

2-Benzoyl-2-methyl-3-phenyl-2*H*-1,4-benzothiazine (**3b**).

This compound was obtained as a white solid (methanol), mp 92-94°; ir (potassium bromide): ν 1675 (CO), 1595 cm^{-1}; pmr (deuteriochloroform): δ 1.9 (s, 3H, CH_3), 6.9-7.4 (m, 10H, phenyl protons), 7.5-7.7 (m, 2H, phenyl protons), 7.8-8.2 (m, 2H, phenyl protons); ms: m/e 343 (M^+, 14), 238 (100).

Anal. Calcd. for $C_{22}H_{17}NOS$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.58; H, 4.96; N, 4.08.

Reaction of 2,2'-Dithiodianiline (**1**) with 1,3-Diketone **2c**.

2,2'-Dithiodianiline **1** (2.48 g, 0.01 mole) and 2-acetylindan-1-one **2c** (3.48 g, 0.02 mole) were allowed to react as described in the above reported reaction. Evaporation of the solvent under

reduced pressure and column chromatography of the residue yielded **4** [11], **14** [11], **13** [12], and **12** in 81, 76, 12 and 47% yield, respectively.

N-Acetyl-2(2-aminophenylthio)indan-1-one **12**.

This compound was obtained as a yellow-green oil; ir (potassium bromide): ν 3320 (NH), 1700 (CO) cm^{-1}; pmr (deuteriochloroform): δ 2.30 (s, 3H, CH_3), 2.9-3.7 (m, 3H, $CHCH_2$), 6.7-7.8 (m, 7H, phenyl protons), 8.3 (dd, 1H, phenyl proton), 9.2 (br s, 1H, NH); ms: m/e 297 (M^+, 15), 222 (11), 167 (62), 131 (30), 125 (100).

Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.78; H, 5.03; N, 4.46.

Reaction of 2,2'-Dithiodianiline (**1**) with 1,3-Diketone **2d**.

2,2'-Dithiodianiline **1** (2.48 g, 0.01 mole) and 1-phenyl-2-methyl-1,3-butandione **2d** were allowed to react as described in the above reported reaction. Evaporation of the solvent under reduced pressure and column chromatography of the residue yielded **18** [11], **4** [11], and **17** in 65, 66 and 42% yield, respectively.

3-(1-Benzoylethylidene)-3,4-dihydro-2*H*-1,4-benzothiazine (**17**).

This compound was obtained as a yellow solid, mp 136-137°; ir (potassium bromide): ν 1590, 1580, 1530 cm^{-1}; pmr (deuteriochloroform): δ 1.95 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 6.7-7.6 (m, 9H, phenyl protons), 13.7 (br s, 1H, NH); ms: m/e 281 (M^+, 100).

Anal. Calcd. for $C_{17}H_{15}NOS$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.88; H, 5.47; N, 5.01.

Hydrolysis of the 1,4-Benzothiazine **3a**.

A mixture of compound **3a** (0.2 g, 0.7 mmole) in light petroleum ether/ethyl acetate 9:1 (50 ml) and silica gel (10 g) was stirred at room temperature for 3 days and then filtered. The filtrate was evaporated and purified on preparative tlc affording the sulfide **6** in 70% yield.

Hydrolysis of the 1,4-Benzothiazine **3b**.

A mixture of compound **3b** (0.1 g, 0.3 mmole) in ethanol (10 ml) and dilute hydrochloric acid (1:1 v/v) was stirred at room temperature for 2 days. Evaporation of the solvent and purification of the resulting residue by preparative tlc gave compound **11** in 90% yield. This compound was obtained as a yellow oil; ir (Nujol): ν 3360 (NH), 1680 (CO) cm^{-1}; pmr (deuteriochloroform): δ 1.53 (d, J = 8 Hz, 3H, CH_3), 4.63 (q, J = 8 Hz, 1H, CH), 6.8-7.9 (m, 13H, phenyl protons), 8.53 (dd, 1H, phenyl proton), 9.3 (br s, 1H, NH); ms: m/e 361 (M^+, 20), 105 (100).

Anal. Calcd. for $C_{22}H_{19}NO_2S$: C, 73.11; H, 5.30; N, 3.88. Found: C, 73.02; H, 5.18; N, 3.81.

N-Acetyl-2-(2-aminophenylthio)indan-1-ol (**15**).

To a solution of compound **12** (0.3 g, 1.0 mmole) in ethanol (30 ml) at room temperature sodium borohydride (2 g, 0.05 mole) was added in small portions with stirring. After 30 minutes the reaction mixture was diluted with water, then extracted with chloroform. Removal of the solvent from the organic solution dried over sodium sulfate gave a residue which was purified by preparative tlc affording compound **15** (75% yield) as a pale yellow solid, mp 147-148°; ir (potassium bromide): ν 3280 (OH), 3240 (NH), 1675, 1660 cm^{-1}; pmr (deuteriochloroform): (200 MHz) δ 2.17 (s, 3H, CH_3), 2.65 (d, 1H, OH), 3.0-3.3 (m, 2H, CH_2), 3.7-3.8 (m, 1H, S-CH), 4.96 (dd, 1H, CHOH), 6.9-7.7 (m, 7H, phenyl protons), 8.35 (d, 1H, phenyl proton), 9.1 (br s, 1H, NH); ms: m/e 299 (M^+, 5), 167 (34), 125 (100).

Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.12; H, 5.65; N, 4.71.

2-(2-Aminophenylthio)indan-1-ol (**16**).

To a solution of compound **15** (0.1 g, 0.3 mmole) in ethanol (10 ml) was added a solution of potassium hydroxide (0.2 g, 3.5 mmoles) in ethanol (5 ml). The reaction mixture was refluxed for 40 hours and then the solvent was evaporated under reduced pressure. Preparative tlc of the residue afforded the compound **16** as a white solid (yield 95%), mp 89-90°; ir (potassium bromide): ν 3420 (OH), 3330 (NH), 1675 cm^{-1}; pmr (deuteriochloroform): δ 2.8-3.5 (m, 2H, CH_2), 3.7-4.0 (m, 1H, CHS-), 4.2 (br s, 3H, NH_2 + OH), 4.96 (d, 0.66 H, CHOH), 5.10 (d, 0.33 H, CHOH), 6.6-6.9 (m, 2H, phenyl protons) 7.1-7.6 (m, 6H, phenyl protons); ms: m/e 257 (M^+, 18), 125 (100).

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.96; H, 5.80; N, 5.46.

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