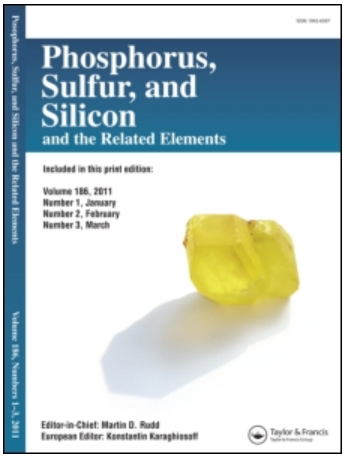

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CHEMICAL BEHAVIOR OF SOME BENZ[b] INDENO[1,2-e] [1,4] THIAZINE DERIVATIVES[1]

by

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ABSTRACT

The study of the chemical behavior of some benz[b] indeno[1,2-e] [1,4] thiazine derivatives was accomplished. Different reactivities were observed for 4*b*,5-dihydrobenz[b]-indeno[1,2-e] [1,4] thiazine-10*a*(11*H*)-ol (**3**) and 5-ethyl-4*b*,5-dihydrobenz[b] indeno[1,2-e]-[1,4] thiazine-10*a*(11*H*)-ol (**5**); **3** is reoxidated to benz[b] indeno[1,2-e] [1,4] thiazine-10*a*(11*H*)-ol (**2**), while **5** undergoes transposition and oxidation to spiro[3-ethylbenzothiazol-2(3*H*), 1′-indan-2′-one] (**6**). Possible pathways for these transformations are discussed.

As reported in a previous paper,[2] 10*a*,11-dihydrobenz[b] indeno[1,2-e] [1,4] thiazine (**13**) undergoes autoxidation by exposure to air yielding the benz[b]-indeno[1,2-e] [1,4] thiazine-10*a*(11*H*)-ol (**2**) together with the isomeric 5,11-dihydrobenz[b] indeno[1,2-e]-[1,4] thiazine-10-oxide.

Moreover, in a study of the autoxidation of 1,4-benzothiazine systems analogous to **13**,[3] hemithioketal compounds similar to **2** were found as unstable intermediates in the transformation of 1,4-benzothiazines into spiroketones. Unexpectedly, the conversion of **2** into the corresponding spiroketone could not be observed.[2]

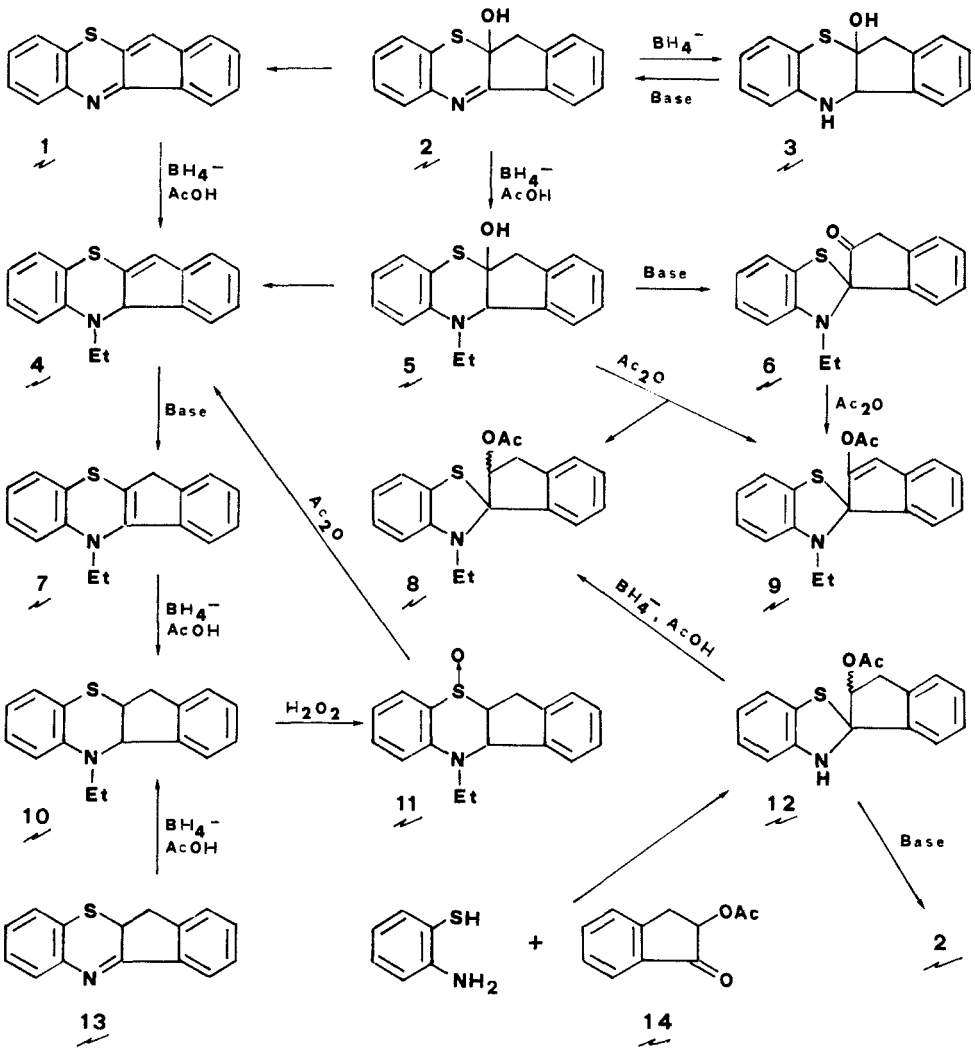
2 was stable enough to undergo $NaBH_4$ reduction into the corresponding dihydro derivative. In fact, by treating **2** with $NaBH_4$ in acetic acid/ethyl alcohol solution, the 4*b*,5-dihydrobenz[b] indeno[1,2-e] [1,4]-thiazine-10*a*(11*H*)-ol (**3**), whose structure is unequivocally demonstrated by its nmr spectrum, is obtained. On the other hand, if the $NaBH_4$ reduction is carried out in neat acetic acid, *N*-alkylation is also observed,[4] and 5-ethyl-4*b*,5-dihydrobenz[b] indeno[1,2-e] [1,4]-thiazine-10*a*(11*H*)-ol (**5**), as proved by its nmr spectrum, is formed as well. Both **3** and **5**, by treatment with bases (KOH in EtOH, *t*-BuOK in *t*-BuOH) undergo some interesting transformations, even at room temperature; namely, under these conditions, **3** is readily and quantitatively reoxidated to **2**, whilst **5** is readily and quantitatively converted in spiro[3-ethylbenzothiazol-2(3*H*),1′-indan-2′-one] (**6**), which, in turn, yields the enol acetate **9** by treatment with hot acetic anhydride. Both structures **6** and **9** are supported by nmr and ir spectral data.

It must be pointed out that if **5** is treated with bases under N_2, the transformation to **6** does not occur, and the product is recovered unchanged. Furthermore, it has been proved that **5** undergoes analogous rearrangement, with ring contraction, also by heating in acetic anhydride; the major product from this reaction is the spirobenzothiazoline **8**, together with small amounts of the enol acetate **9**. The structure of **8** was confirmed by an independent synthesis; the spirobenzothiazoline **12** was prepared by reacting 2-mercaptoaniline with the ketoester **14**, and subsequently transformed into **8** by alkylation.

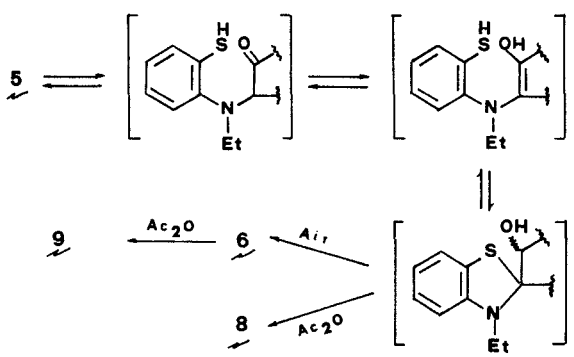
The reported experimental results can be easily interpreted as a whole, assuming that, in the reaction conditions used, both **5** and **3** are in equilibrium with the corresponding chain-tautomer ketones, and therefore, *via* their enolic forms, with the isomeric hydroxyspirobenzothiazolines; these should represent the key intermediates of the transformation, since they can easily undergo oxidation to the corresponding spiroketones (Schemes II and III).

A general pathway, as that outlined for the transformation of **5** into **6** in Scheme II, seems in good agreement with the observed stability of **5** in the absence of oxygen. On the other hand, the simultaneous

SCHEME I



SCHEME II

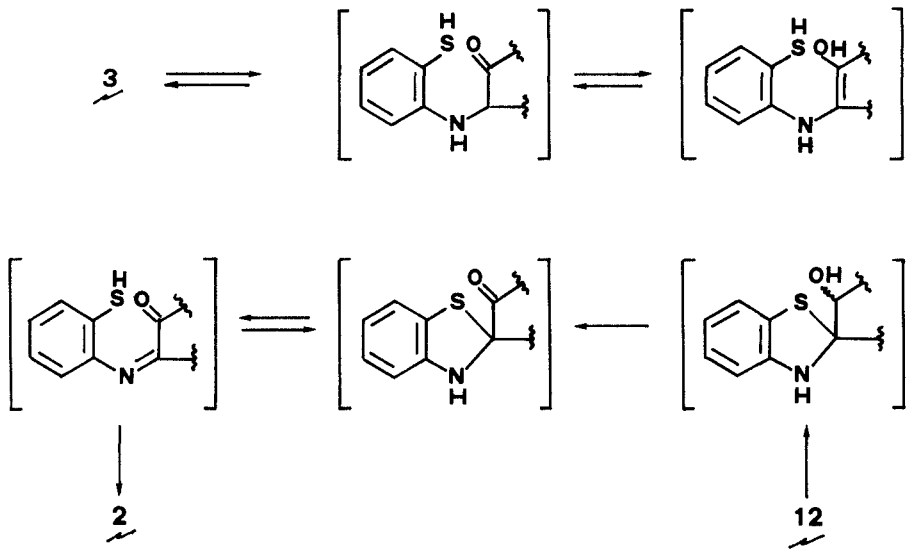


formation of **8** and **9** by treating **5** with acetic anhydride strongly suggests a hydroxyspirobenzothiazoline structure for the intermediate; in fact, under these conditions, the esterification reaction is favoured, even though the competitive oxidation is still present, as shown by the isolation of **9**, from the acetylation of the initially formed **6**.

For the specific conversion of **3** into **2** (Scheme III) also, the intervention of an intermediate with the hydroxyspirobenzothiazoline structure has been experimentally confirmed by the transformation of **12** into **2**, following treatment with base.

The dramatically different behavior of **5** and **3** towards the treatment with bases, which is clearly demonstrated by the reported results, is due, in our opinion, to the different stability of **6** and of the analogous spiroketone, that should be formed from **3** (Scheme III), in the reaction conditions. In fact, only

SCHEME III



for the latter compound a sequence of ring-chain tautomeric equilibria, which eventually yield a stable end-product like hemithioketal **2**, is possible.

2 can be also easily dehydrated to benz[b]indeno-[1,2-e][1,4]thiazine (**1**), by heating in acid solution.[5] **1** undergoes reduction and alkylation by treatment with $NaBH_4$ in neat acetic acid, yielding 5-ethyl-4*b*,5-dihydrobenz[b]indeno[1,2-e][1,4]thiazine (**4**), whose structure was easily inferred by its nmr spectrum. The same product can be also obtained by heating **5** in the presence of molecular sieves. In basic solution, **4** is transformed into 5-ethyl-5,11-dihydrobenz[b]indeno-[1,2-e][1,4]thiazine (**7**), whose enamine structure is confirmed by $NaBH_4$ reduction in acidic medium, to 5-ethyl-4*b*,5,10*a*,11-tetrahydrobenz[b]indeno[1,2-e]-[1,4]thiazine (**10**); **10** was also prepared reducing **13** with $NaBH_4$ in neat acetic acid. **10** could be transformed into **4** as well, *via* sulfoxide **11**; in fact, oxidation with H_2O_2 converts **10** into 5-ethyl-4*b*,5,10*a*,11-tetrahydrobenz[b]indeno[1,2-e][1,4]thiazine-10-oxide (**11**), that yields **4** on heating in acetic anhydride according to a typical Pummerer reaction.

Experimental Section

All melting points were taken on a Kofler apparatus and are uncorrected. Infrared spectra as nujol mulls were determined on a Perkin-Elmer 257 grating spectrophotometer. Nuclear magnetic resonance spectra, unless otherwise stated, were obtained on a Varian HA-100 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (δ = 0 ppm) as internal standard; the hydrogen atoms adjacent to the nitrogen and sulfur atoms were indicated H_a and H_b, respectively. Preparative thin-layer chromatography (PLC) was performed on Merck PF_{254} silica gel coated plates, using a mixture of light petroleum ether/EtOAc (9:1) as solvent. All compounds were analyzed for C, H, N, S and gave analytical results within ±0.3% of the theoretical values.

$NaBH_4$ Reduction of 2 in AcOH/EtOH

$NaBH_4$ (0.25 g) was added portionwise to a stirred suspension of **2**[2] (0.25 g) in a AcOH/EtOH mixture (15 + 5 ml), maintained at room temperature and under N_2. After hydrogen evolution, the colorless solution was evaporated, Et_2O and H_2O added to the residue, the organic layer separated, dried (Na_2SO_4), and evaporated. Crystallization of the residue gave **3** (0.12 g), mp 132–4° (EtOH); ir 3340 (OH), and 3300 cm^{-1} (NH); nmr (60 MHz) δ 7.3–6.5 (8 H, aromatic H), 4.80 (1 H, H_a), 3.95 (2 H, NH + OH, disappeared on deuteration), and 3.7–3.1 ppm (2 H, CH_2).

Treatment of 3 with Alcoholic KOH

A solution of **3** (0.20 g) in EtOH (10 ml) was added to a stirred solution of KOH (0.2 g) in EtOH (20 ml). The reaction mixture becomes immediately dark; after 30 min the solvent was evaporated, Et_2O and H_2O added to the residue, the organic layer separated, dried (Na_2SO_4), and evaporated to give a residue (0.18 g) of essentially pure **2**.

$NaBH_4$ Reduction of 2 in AcOH

$NaBH_4$ (2.5 g) was added portionwise to a stirred suspension of **2** (2.0 g) in neat AcOH (50 ml), maintained under N_2. After solution, further $NaBH_4$ (3.0 g) was added portionwise. After 10 min, H_2O was added until complete precipitation occurred, the solid was collected by suction, washed with H_2O, and dissolved in CH_2Cl_2. The organic solution was dried (Na_2SO_4), and evaporated: crystallization of the residue (2.0 g) gave **5**, mp 129–30° (EtOH); ir 3420 cm^{-1}

(OH); nmr δ 7.3–6.4 (8 H, aromatic H), 4.81 (1 H, H_a); 4.1–3.4 (2 H, N–CH_2), 3.5–3.1 (2 H, CH_2), 2.87 (1 H, OH, disappeared on deuteration), and 1.35 ppm (3 H, CH_3).

Treatment of 5 with Alcoholic KOH

5 (0.20 g) was added to a stirred solution of KOH (0.1 g) in EtOH (30 ml) at room temperature; after 15 min the dark yellow solution was evaporated and Et_2O and H_2O added to the residue. The organic layer was separated, dried (Na_2SO_4), and evaporated. Crystallization of the residue (0.12 g) gave **6**, mp 129–30° (EtOH); ir 1755 cm^{-1} (C=O); nmr (60 MHz, CCl_4) δ 8.1–6.3 (8 H, aromatic H), 4.1–3.1 (2 H, CH_2), 3.6–2.4 (2 H, N–CH_2), and 1.09 ppm (3 H, CH_3). The same reaction performed and worked up under N_2 gave unchanged **5**, even extending the reaction time to 5 hr.

Reaction of 6 with Ac_2O

A solution of **6** (0.10 g) in acetic anhydride (10 ml) was refluxed for 1.5 hr. After cooling, EtOH was added, and the solvent evaporated. PLC of the residue gave **9** (0.10 g), mp 126–7° (EtOH); ir 1770 (C=O), and 1605 cm^{-1} (C=C); nmr (60 MHz) δ 7.9–6.4 (8 H, aromatic H), 6.63 (1 H, vinyl H), 3.2–2.7 (2 H, N–CH_2), 2.08 (3 H, $COCH_3$), and 1.05 ppm (3 H, CH_3).

Reaction of 5 with Ac_2O

A solution of **5** (0.20 g) in acetic anhydride (10 ml) was refluxed for 1 hr. After cooling, EtOH was added, and the solvent evaporated. PLC of the residue gave **8** (0.10 g) and **9** (0.06 g). **8**, mp 123–4° (2-propanol); ir 1730 cm^{-1} (C=O); nmr δ 7.8–6.2 (8 H, aromatic H), 5.62 (1 H, O–CH), 3.5–2.6 (4 H, N–CH_2 + CH_2), 1.88 (3 H, $COCH_3$), and 1.12 ppm (3 H, CH_3); mw 325 (from mass spectrum).

Reaction between 2-Mercaptoaniline and 14

A solution of 2-mercaptoaniline (1.3 g) and **14** (2.0 g) in toluene (100 ml), containing catalytic amounts of *p*-toluenesulfonic acid, was refluxed under N_2 for 10 hr. The solvent was evaporated and the residue chromatographed on 70-325 mesh SiO_2 Merck (250 g) with a mixture of light petroleum ether/EtOAc (9 : 1) as eluent. It was thus isolated, *inter alia*, a solid (0.5 g), ir 3320 (NH) and 1725 cm^{-1} (C=O); mw 297 (from mass spectrum). The nmr spectrum clearly shows the presence of a mixture of two compounds, very likely of the two diastereoisomers corresponding to the structure **12**, which was not separated and used as such in the following reactions:

N-alkylation. $NaBH_4$ (0.8 g) was added portionwise to a solution of the above mixture (0.25 g) in neat AcOH (5 ml). After 5 min, 10% aqueous $NaHCO_3$ and $CHCl_3$ were added, the organic layer was separated, dried (Na_2SO_4), and evaporated. PLC of the residue (light petroleum ether/EtOAc 95 : 5 as solvent) yielded **8** (0.05 g) and its diastereoisomer, mp 120–1° (2-propanol); ir 1740 cm^{-1} (C=O); nmr δ 7.6–6.2 (8 H, aromatic H), 5.8–5.5 (1 H, methine H), 3.3–2.8 (4 H, methylene H), 1.75 (3 H, $COCH_3$), and 1.20 ppm (3 H, CH_3); mw 325 (from mass spectrum).

Treatment with base. A solution of the above mixture (0.10 g) in 3% alcoholic KOH (3 ml) was stirred at room temperature for 10 min. Silica gel chromatography of the reaction mixture yielded **2** (0.08 g).

Treatment of 5 with Molecular Sieves

A stirred mixture of **5** (0.70 g), type 5A, 1/8″ pellet BDH molecular sieves (3.0 g) and toluene (30 ml) was refluxed under N_2 for 2 hr, the solid was filtered off, and the filtrate evaporated. PLC of the residue gave unchanged **5** (0.30 g), and **4** (0.20 g), bp 91–2° (0.04 Torr); ir 1600 cm^{-1} (C=C); nmr (60 MHz) δ 7.9–7.1 (8 H, aromatic H), 6.65 (1 H, vinyl H), 4.52 (1 H, H_a), 3.1–2.7 (2 H, N–CH_2), and 0.85 ppm (3 H, CH_3).

$NaBH_4$ Reduction of 1 in AcOH

$NaBH_4$ (0.3 g) was added portionwise during 3 min to a stirred solution of **1**[5] (0.10 g) in neat AcOH (10 ml). After 2 min, 2 *N* NaOH and Et_2O were added, the organic layer was separated, dried (Na_2SO_4), and evaporated. PLC of the residue gave **4** (0.02 g), and **7** (0.03 g) (see below).

Isomerization of 4 into 7

A solution of **4** (0.28 g) in 3% alcoholic KOH (3 ml) was stirred under N_2 at room temperature for 10 min. The precipitate formed (0.20 g) was collected by vacuum and crystallized from EtOH: **7**, mp 136–7°; ir 1605 cm^{-} (C=C); nmr δ 7.4–6.7 (8 H, aromatic H), 3.89 (2 H, N–CH_2), 3.28 (2 H, CH_2), and 1.30 ppm (3 H, CH_3).

$NaBH_4$ Reduction of 7 in AcOH

$NaBH_4$ (1.0 g) was added portionwise to a stirred solution of **7** (0.10 g) in neat AcOH (10 ml), maintained under N_2. After 10 min, 2 *N* NaOH and CH_2Cl_2 were added, the organic layer was separated, dried (Na_2SO_4), and evaporated. PLC of the residue gave **10** (0.08 g), mp 108–9° (EtOH); nmr (60 MHz) δ 7.6–6.6 (8 H, aromatic H), 5.20 (1 H, H_a), 4.2–3.5 (3 H, N–CH_2 + H_b), 3.6–2.7 (2 H, CH_2), and 1.36 ppm (3 H, CH_3).

$NaBH_4$ Reduction of 13 in AcOH

$NaBH_4$ (1.5 g) was added portionwise to a stirred solution of **13**[2] (0.50 g) in neat AcOH (10 ml), maintained under N_2. After 10 min, H_2O was added until complete precipitation occurred. The solid (**10**) was collected by vacuum and dried under vacuum (0.50 g).

Oxidation of 10 into 11

A 33% solution of H_2O_2 (0.8 ml) was added dropwise to a solution of **10** (1.8 g) in acetic acid (30 ml). After stirring at room temperature for 6 hr, the solution was concentrated, neutralized with NH_4OH, and extracted with CH_2Cl_2. The organic layer was separated dried (Na_2SO_4), and concentrated. On crystallization of the residue **11** was obtained (1.6 g), mp 186–7° (MeOH); ir 1045 cm^{-1} (S → O); nmr δ 7.7–6.7 (8 H, aromatic H), 4.92 (1 H, H_a), 3.8–3.5 (2 H, N–CH_2), 3.5–3.1 (3 H, H_b + CH_2), and 1.29 ppm (3 H, CH_3).

Treatment of 11 with Ac_2O

A stirred mixture of **11** (0.4 g) and acetic anhydride (20 ml) was refluxed for 15 min. After cooling, EtOH was added, and the solvent evaporated. PLC of the residue gave **4** (0.2 g).

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