# Synthesis and Stereochemistry of Indano[1,2-*d*][1,3]oxazines and Thiazines, New Ring Systems

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A set of structurally varied indano[1,2-*d*][1,3]oxazines and thiazines, which are new ring systems, were prepared by ring-closure reactions of amino alcohols **4**-**6**. The reactions of *cis*- and *trans*-1-amino- and *cis*-1-benzylamino-2-hydroxymethylindane (**4**-**6**) with 1 equivalent of an aromatic aldehyde in methanol at room temperature resulted in three-component equilibria (**15a-g**), or a Schiff base (**16**), or a ring-closure product alone (**17a-c**), respectively, depending on the substitution or configuration of the starting amino alcohol. The ring-chain tautomeric equilibria can be described by an equation of Hammett type.

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## Introduction.

Cyclic $\beta$-amino acids can be used as starting substances for the preparation of different heterocycles, potential pharmacons and synthons of natural products or their analogues, also used as building blocks in drug research [1-4]. (1*R*,2*S*)-2-Aminocyclopentanecarboxylic acid (cispentacin) is an antifungal antibiotic [5-9], while many 1,2- and 1,3-amino alcohols and their derivatives play important roles in the synthesis of pharmacologically active compounds [10-14]. The applications of *cis*-1-amino-2-indanol in asymmetric syntheses have been reviewed [15], and its (1*S*,2*R*) enantiomer is a key component of an HIV protease inhibitor, Indinavir [16,17].

Our present aim was to prepare *cis*- and *trans*-1-amino-2-hydroxymethylindane from 1-aminoindane-2-carboxylic acid derivatives (new cispentacin benzologues) and to examine the chemistry and stereochemistry of indane-fused 1,3-oxazines and thiazines.

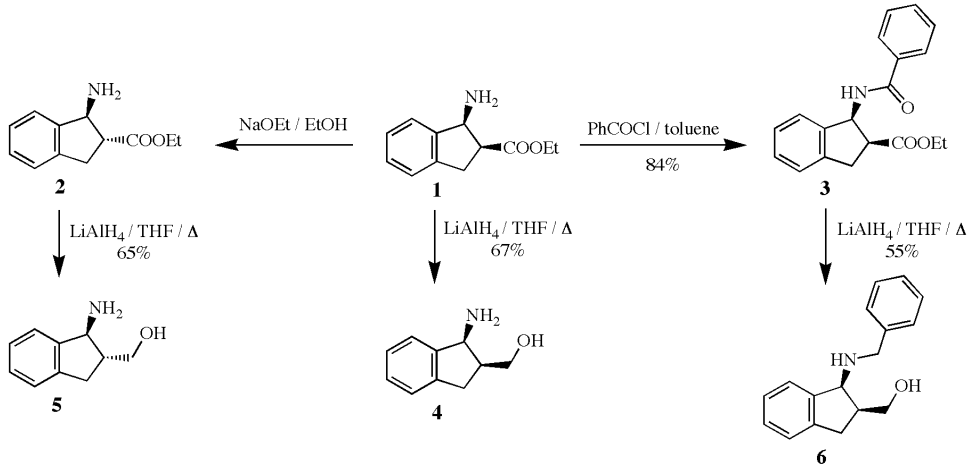
## Results and Discussion.

In our earlier work, racemic ethyl *cis*- and *trans*-1-aminoindane-2-carboxylate (**1** and **2**) were prepared from indene by chlorosulfonyl isocyanate addition, followed by ring opening and isomerization [18]. The *cis*- and *trans*-unsubstituted and *cis*-*N*-benzyl-substituted 1,3-amino alcohols **4**-**6** were prepared by $LiAlH_4$ reduction or by benzoylation followed by reduction, respectively (Scheme 1).

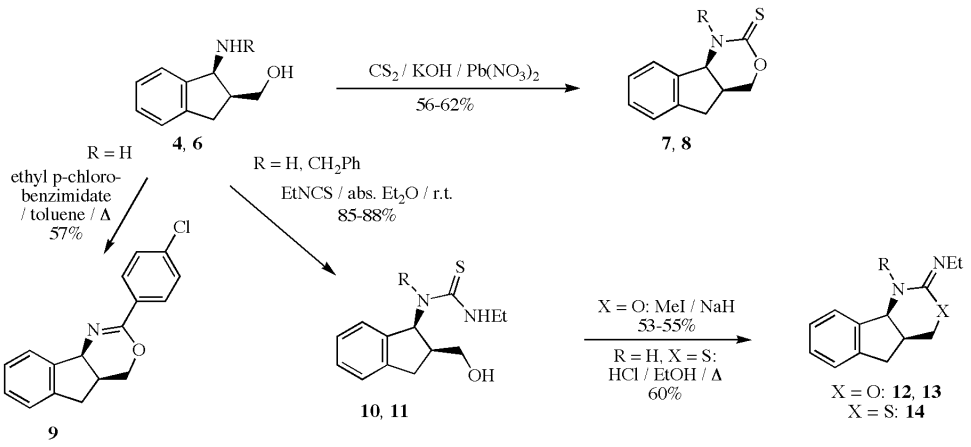
For the preparation of 2-thioxo-1,3-oxazines **7** and **8** the most common method is the reaction of the appropriate 1,3-amino alcohols **4** and **6** with carbon disulfide, followed by cyclization of the resulting thiourea with lead(II) nitrate. Cyclization of the corresponding 1,3-amino alcohol **4** with ethyl *p*-chlorobenzimidate resulted in the dihydro-1,3-oxazine **9**. The synthesis of heterocycles **12**-**14** started from adducts of the corresponding amino alcohols **4** and **6** with ethyl isothiocyanate. Treatment of thioureas **10** and **11** with methyl iodide followed by alkali treatment led to the elimination of methyl mercaptan, resulting in the oxazines **12** and **13** in good yields. Treatment of thiourea **10** with ethanolic hydrogen chloride under reflux, followed by treatment with alkali provided thiazine **14** (Scheme 2).

The *cis* amino alcohol **4** was condensed in methanolic solution with seven substituted aromatic aldehydes with

Scheme 1



Scheme 2

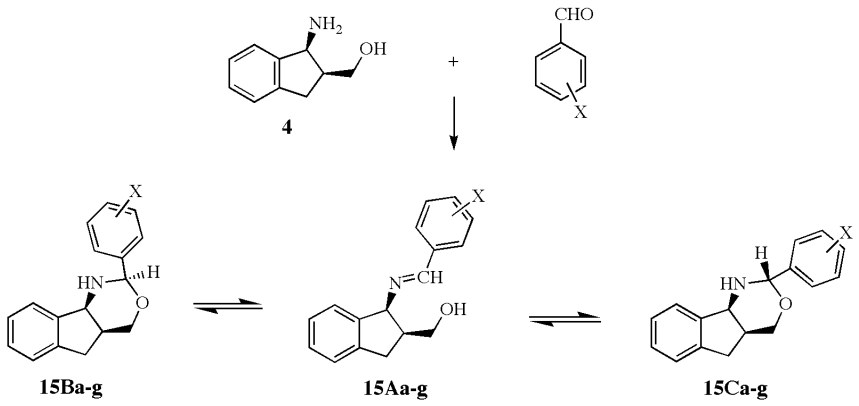



different electronic characters. The reactions reached completion within a few hours, even at room temperature. After evaporation and purification, well-defined products **15a-g** were obtained, which existed as three-component tautomeric mixtures in deuteriochloroform solution. For the tautomeric equilibria to be reached, the substances were allowed to stand for 24 h in deuteriochloroform (Scheme 3). The relative configurations of the various structures **15A**,**B**,**C** were determined *via* NOESY spectra, on the basis of observation of NOE correlation's between the NH-C*H*Ar-O and the NH-C*H*-CH hydrogen atoms.

oxazines. When eq. (1) was applied to the log $K_X$ values, good linear correlations were obtained *vs* the Hammett-Brown parameter ($\sigma^+$) of the substituent X on the 2-phenyl group for compounds **15a**-**g** (Tables 1 and 2, Figure 1). The tautomeric ratios are based on the integration of the **15B** and **15C** ring form NH-C*H*Ar-O and the **15A** chain form N=CH proton singlets.

The linear regression analysis data in Table 2 show that, as customary among 2-aryl-substituted tetrahydro-1,3-oxazines, the value of $\rho$ is positive in each case; *i.e.* an electron-withdrawing substituent on the 2-aryl ring

Scheme 3




X = *p*-$NO_2$: **a**; *m*-Br: **b**; *p*-Cl: **c**; H: **d**; *p*-Me:**e**; *p*-OMe: **f**; *p*-$NMe_2$: **g**

Comparative studies were carried out earlier on the ring-chain tautomerism of a wide range of 2-aryl-substituted tetrahydro-1,3-oxazines [19-24]. For all these series, the following equation is valid:

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (1)$$

where $K_X$ = [ring]/[chain] and $\rho$ is a constant characteristic of the ring system. In deuteriochloroform solution at ambient temperature, $\rho$ is 0.76 for tetrahydro-1,3-

favours the ring-closed tautomer. The proportion of the ring form for the *trans*-2-aryl-1,3-*O,N* heterocycles **15C** varies within a somewhat wider range (10.7-54%) than that for the corresponding *cis*-2-aryl-1,3-*O,N* heterocycles **15B** (9.2-41.7%). The relative configuration of the ring-closed products does not seem to influence the value of $\rho$: *cis*- and *trans*-2-aryl-1,3-*O,N* heterocycles have very similar values of $\rho$ (0.78 and 0.81).

Table 1

Proportions (%) of Ring Forms (**B** and **C**) in Tautomeric Equilibria for Compounds **15a-g** in Deuteriochloroform at 300 K

| Compound | X | σ+ | **B** (%) | **C** (%) |
|---|---|---|---|---|
| **15a** | *p*$NO_2$ | 0.79 | 41.7 | 54.0 |
| **15b** | *m*Br | 0.05 | 39.3 | 49.8 |
| **15c** | *p*Cl | 0.114 | 35.8 | 50.5 |
| **15d** | H | 0 | 35.1 | 41.5 |
| **15e** | pMe | -0.31 | 29.6 | 35.9 |
| **15f** | *p*OMe | -0.77 | 22.9 | 28.2 |
| **15g** | *p*$NMe_2$ | -1.7 | 9.2 | 10.7 |

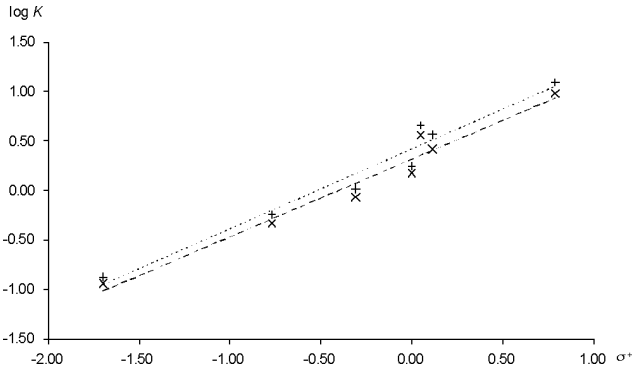



Figure 1. Plots of log $K_X$ *vs* σ+ for Compounds **15a-g**: **B** (X), **C** (+) in deuteriochloroform.

Table 2

Linear Regression Data for Compounds **15a-g**

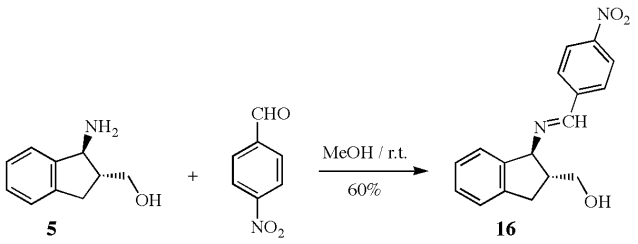
| | **B** | **C** | [20] |
|---|---|---|---|
| Intercept | 0.32 | 0.42 | 0.22 |
| Slope | 0.78 | 0.81 | 0.72 |
| Corr. coeff | 0.981 | 0.979 | 0.991 |
| No. of points | 7 | 7 | 6 |

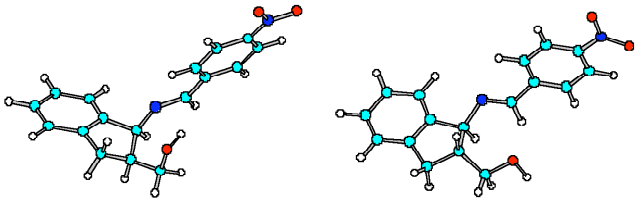
[20] The data for the corresponding cyclopentane-fused tetrahydro-1,3-oxazines

When the *trans*-amino alcohol **5** was condensed in methanol with *p*-nitrobenzaldehyde a well-defined product was obtained, which exists solely as the open, Schiff base form **16** (Scheme 4). In this case, the OH group is too far from the N=CH bond (4.5 Å), and intramolecular proton transfer is not possible without energy transfer (Figure 2).

When the *N*-benzylamino alcohol **6** was condensed with aldehydes in methanolic solution at room temperature only one diastereomer **17a-c** was observed in deuteriochloroform of the product at 300 K (Scheme 5). The product formed is stabilized by aromatic-aromatic interactions (Figure 3).

Scheme 4

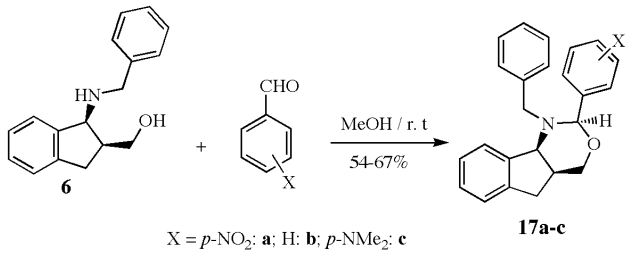


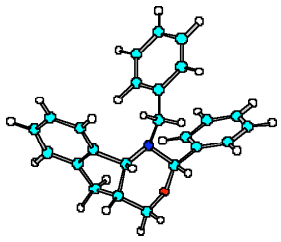
**15Ad** **16**

Figure 2. Stereoview of typical minimum energy molecular structures for **15Ad** and **16**.

Scheme 5




X = *p*-$NO_2$: **a**; H: **b**; *p*-$NMe_2$: **c**



**17b**

Figure 3. Stereoview of typical minimum energy molecular structure for **17b**.

## EXPERIMENTAL

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel $60F_{254}$ plates were used for TLC: the eluent was toluene–methanol 4:1. The $^1H$- and $^{13}C$ nmr spectra were

recorded in deuteriochloroform solution in 5 mm tubes, at room temperature, on a Bruker *Avance* DRX 400 spectrometer at 400.13 ($^1$H) and 100.61 ($^{13}$C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Compounds **1** and **2** were prepared by following literature methods [18].

Ethyl *cis*-1-Benzoylaminoindane-2-carboxylate (**3**).

Ethyl *cis*-2-aminoindane-1-carboxylate hydrochloride (4.84 g, 20 mmol) was allowed to react with benzoyl chloride (3.0 mL, 24 mmol) under Schotten-Baumann acylation conditions. After 2 h, the toluene phase was separated and dried ($Na_2SO_4$) and the solvent was evaporated off to yield a snow-white, crystalline product. Yield 5.18 g (84%), mp 151-153 °C (*n*-hexane); $^1$H nmr (deuteriochloroform): δ 1.19 (3H, t, J = 7.1 Hz, $COOCH_2$-C*H*$_3$), 3.23 (1H, dd, J = 8.6, 16.4 Hz, 3-H), 3.41 (1H, dd, J = 5.8, 16.4 Hz, 3-H), 3.70 (1H, ddd, J = 5.8, 8.3 Hz, 2-H), 4.03-4.15 (2H, m, $COOCH_2$-$CH_3$), 6.05 (1H, t, J = 8.6 Hz, 1-H), 6.97 (1H, d, J = 9.1 Hz, 4'-H), 7.18-7.25 (2H, m, 3'-H, 5'-H), 7.33-7.53 (4H, m, 4-H, 5-H, 6-H, 7-H), 7.73-7.80 (2H, m, 2'-H, 6'-H); $^{13}$C nmr (deuteriochloroform): δ 14.3, 34.8, 48.0, 55.6, 61.2, 124.7, 125.0, 127.2, 127.6, 128.7, 128.8, 131.9, 134.5, 141.1, 141.7, 167.1, 173.9.

*Anal*. Calcd. for $C_{19}H_{19}NO_3$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.47; H, 6.31; N, 4.71%.

General Procedure for Amino Alcohols **4**-**6**.

To a slurry of $LiAlH_4$ (1.7 g, 45 mmol) in 50 mL of dry THF, amino ester **1** or **2** (3.07 g, 15 mmol) or N-benzoyl amino ester **3** (4.64 g, 15 mmol) in 20 mL of THF was added dropwise at 0 °C. After stirring and refluxing for 4 h (the end of the reduction was detected by means of TLC), the mixture was decomposed with 2 mL of water under ice cooling. The inorganic material was filtered off and washed with THF. After drying and evaporation, the resulting oils were crystallized from *n*-hexane and recrystallized from diisopropyl ether.

*cis*-1-Amino-2-hydroxymethylindane (**4**).

Compound **4** was obtained in 67 % yield (1.63 g), mp 83-84 °C, lit. mp [25]: 81-83 °C; $^1$H nmr (deuteriochloroform): δ 2.67-2.97 (3H, m, 2-H, 2 x 3-H), 3.72-3.85 (2H, m, C*H*$_2$-OH), 4.59 (1H, d, J = 7.1 Hz, 1-H), 7.17-7.24 (3H, m, 4-H, 5-H, 6-H), 7.28-7.34 (1H, m, 7-H); $^{13}$C nmr (deuteriochloroform): δ 33.3, 44.3, 58.6, 63.7, 124.0, 125.2, 127.1, 128.2, 141.8, 146.1.

*Anal*. Calcd. for $C_{10}H_{13}NO$ (163.22): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.42; H, 8.21; N, 8.72%.

*trans*-1-Amino-2-hydroxymethylindane (**5**).

Compound **5** was obtained in 65% yield (1.59 g), mp 92-93 °C; $^1$H nmr (deuteriochloroform): δ 2.27-2.39 (1H, m, 2-H), 2.52-2.58 (1H, m, 3-H), 2.94 (1H, dd, J = 8.1, 15.6 Hz, 3-H), 3.88-4.00 (2H, m, C*H*$_2$-OH), 4.17 (1H, d, J = 8.8 Hz, 1-H), 7.17-7.28 (4H, m, 4-H, 5-H, 6-H, 7-H); $^{13}$C nmr (deuteriochloroform): δ 33.1, 52.7, 61.8, 66.4, 122.9, 124.9, 126.9, 127.6, 141.7, 146.9.

*Anal*. Calcd. for $C_{10}H_{13}NO$ (163.22): C, 73.59; H, 8.03; N, 8.58. Found: C, 73.51; H, 8.11; N, 8.61%.

*cis*-1-Benzylamino-2-hydroxymethylindane (**6**).

Compound **6** was obtained in 55% yield (2.09 g), mp 45-48 °C; $^1$H nmr (deuteriochloroform): δ 2.68-2.78 (1H, m, 2-H), 2.87 (2H, d, J = 7.6 Hz, 2 x 3-H), 3.80 (1H, dd, J = 7.6, 11.6 Hz, C*H*$_2$-OH), 3.89 (1H, dd, J = 4.3, 11.6 Hz, C*H*$_2$-OH), 4.00 (2H, d, J = 2.8 Hz, NH-C*H*$_2$-Ph), 4.34 (1H, d, J = 7.1 Hz, 1-H), 7.17-7.30 (5H, m, Ph), 7.31-7.38 (4H, m, 4-H, 5-H, 6-H, 7-H); $^{13}$C nmr (deuteriochloroform): δ 33.5, 44.4, 52.9, 63.6, 65.0, 124.2, 125.5, 126.8, 127.8, 128.3, 128.7, 128.9, 139.4, 143.3, 144.2.

*Anal*. Calcd. for $C_{17}H_{19}NO$ (253.35): C, 80.60; H, 7.56; N, 5.53. Found: C, 80.52; H, 7.31; N, 5.61%.

General Procedure for the Synthesis of 1,3-Oxazine-2-thiones **7** and **8**.

Amino alcohol **4** (0.51 g, 3.16 mmol) or **6** (0.8 g, 3.16 mmol) in a solution (2 mL) of potassium hydroxide (0.22 g) was cooled to 0 °C, carbon disulfide (0.26 g) in dioxane (1.6 mL) was added and the mixture was stirred for 5 min. Potassium hydroxide (0.11 g) in water (2 mL) and then an aqueous solution (6 mL) of lead(II) nitrate (1.1 g) were added, followed by stirring at 60 °C for 10 min. The precipitated lead sulfide was filtered off, washed with hot water and extracted with hot ethanol. The aqueous filtrate and the ethanolic extracts were combined and evaporated to dryness. The crystalline product was recrystallized from diisopropyl ether–ethyl acetate.

*cis*-4,4a,5,9b-Tetrahydro-*1H*-indano[1,2-*d*][1,3]oxazine-2-thione (**7**).

Compound **7** was obtained in 62% yield (0.4 g), mp 160-161 °C; $^1$H nmr (deuteriochloroform): δ 2.81 (1H, d, J = 16.1 Hz, 5-H), 2.96-3.07 (1H, m, 4a-H), 3.21 (1H, q, J = 7.8 Hz, 5-H), 3.88-3.98 (1H, m, 4-H), 4.41 (1H, dd, J = 4.8, 11.3 Hz, 4-H), 4.93 (1H, d, J = 7.1 Hz, 9b-H), 7.20-7.30 (3H, m, 6-H, 7-H, 8-H), 7.42-7.48 (1H, m, 9-H); $^{13}$C nmr (deuteriochloroform): δ 32.9, 33.9, 58.9, 68.7, 125.1, 125.7, 127.9, 129.2, 139.9, 140.5, 187.8.

*Anal*. Calcd. for $C_{11}H_{11}NOS$ (205.28): C, 64.36; H, 5.40; N, 6.82. Found: C, 63.42; H, 5.51; N, 6.69%.

*cis*-1-Benzyl-4,4a,5,9b-tetrahydro-2-thioxo-*1H*-indano[1,2-*d*]-[1,3]oxazine (**8**).

Compound **8** was obtained in 56% yield (0.52 g), mp 133-137 °C; $^1$H nmr (deuteriochloroform): δ 2.81-2.94 (2H, m, 4a-H, 5-H), 2.97-3.07 (1H, m, 5-H), 3.85 (1H, dd, J = 7.8, 11.6 Hz, 4-H), 3.93-4.01 (2H, m, 4-H, N-C*H*$_2$-Ph), 4.08 (1H, d, J = 12.8 Hz, N-C*H*$_2$-Ph), 4.67 (1H, d, J = 6.3 Hz, 9b-H), 7.20-7.40 (8H, m, Ph, 6-H, 7-H, 8-H), 7.48 (1H, d, J = 7.6 Hz, 9-H); $^{13}$C nmr (deuteriochloroform): δ 33.3, 43.6, 49.5, 60.6, 63.7, 125.9, 126.6, 127.5, 129.4, 129.5, 129.9, 130.5, 131.0, 135.7, 144.6, 150.2.

*Anal*. Calcd. for $C_{18}H_{17}NOS$ (295.41): C, 73.19; H, 5.80; N, 4.74. Found: C, 73.32; H, 5.59; N, 4.85%.

*cis*-2-(4-Chlorophenyl)-4,4a,5,9b-tetrahydroindano[1,2-*d*][1,3]-oxazine (**9**).

Amino alcohol **4** (0.17 g, 1.02 mmol) and ethyl *p*-chlorobenzimidate (0.19 g, 1.02 mmol) were dissolved in toluene (20 mL), one drop of ethanol saturated with hydrogen chloride was added and the mixture was refluxed. The progress of the reaction was monitored by TLC. After the reaction was complete (6-8 h), the mixture was evaporated to dryness and the residue was recrystallized from diethyl ether. Yield 0.16 g (57%), mp 130-133 °C; $^1$H nmr (deuteriochloroform): δ 2.67 (1H, dd, J = 2.0, 16.1 Hz, 5-H), 2.82-2.91 (1H, m, 4a-H), 3.20 (1H, dd, J = 7.6, 16.1 Hz, 5-H), 3.70 (1H, t, J = 10.6 Hz, 4-H), 4.30 (1H, dd, J = 5.5, 10.8 Hz, 4-H), 5.09 (1H, d, J = 6.6 Hz, 9b-H), 7.18-7.26 (3H, m, 6-H, 7-H, 8-H), 7.33 (2H, d, J = 8.6 Hz, 3'-H, 5'-H), 7.58 (1H, d, J = 6.8 Hz, 9-H), 7.90 (2H, d, J = 8.6 Hz, 2'-H, 6'-H); $^{13}$C nmr (deuteriochloroform): δ 33.6, 34.6, 60.2, 65.9, 125.5, 125.9, 127.5, 128.1, 128.6, 129.2, 132.4, 136.6, 139.3, 146.1, 155.8

*Anal*. Calcd. for $C_{17}H_{14}ClNO$ (283.76): C, 71.96; H, 4.91; Cl, 12.49; N, 4.94. Found: C, 72.12; H, 5.13; Cl, 12.41; N, 4.78%.

General Synthesis for Thioureas **10** and **11**.

Amino alcohol **4** (0.81 g, 5 mmol) or **6** (1.25 g, 5 mmol) was dissolved in dry diethyl ether (20 mL) and a 10% excess of ethyl isothiocyanate was added (0.47 g, 5.5 mmol). The mixture was allowed to stand for 24 h at room temperature. After evaporation, the resulting crystalline thiourea adducts were recrystallyzed from diisopropyl ether.

*cis*-1-Ethyl-3-(2-hydroxymethylindan-1-yl)-thiourea (**10**).

Compound **10** was obtained in 85% yield (1.06 g), mp 164-166 °C; $^1$H nmr (deuteriochloroform): δ 1.22 (3H, t, J = 7.3 Hz, NH-$CH_2$-C*H*$_3$), 2.67 (1H, q, J = 8.3, 3-H), 2.81 (1H, dd, J = 6.8, 13.4 Hz, 2-H), 2.95 (1H, q, J = 7.8 Hz, 3-H), 3.35 (2H, bs, NH-C*H*$_2$-$CH_3$), 3.70 (2H, d, J = 6.3 Hz, C*H*$_2$-OH), 5.95 (1H, d, J = 6.0 Hz, 1-H), 7.18-7.25 (3H, m, 4-H, 5-H, 6-H), 7.39 (1H, d, J = 6.8 Hz, 7-H); $^{13}$C nmr (deuteriochloroform): δ 14.2, 33.5, 38.8, 46.3, 61.4, 62.6, 125.1, 125.4, 127.5, 128.9, 141.0, 143.5, 184.1.

*Anal*. Calcd. for $C_{13}H_{18}N_2OS$ (250.37): C, 62.37; H, 7.25; N, 11.19. Found: C, 62.22; H, 7.11; N, 11.25%.

*cis*-1-Benzyl-3-ethyl-1-(2-hydroxymethylindan-1-yl)-thiourea (**11**).

Compound **11** was obtained in 88% yield (1.49 g), mp 119-120 °C; $^1$H nmr (deuteriochloroform): δ 0.94 (3H, t, J = 7.3 Hz, NH-$CH_2$-C*H*$_3$), 2.66 (1H, dd, J = 13.9, 19.1 Hz, 3-H), 2.94-3.09 (2H, m, 2-H, 3-H), 3.42-3.67 (3H, m, NH-C*H*$_2$-$CH_3$, C*H*$_2$-OH), 3.75 (1H, dd, J = 2.8, 11.6 Hz, C*H*$_2$-OH), 4.09 (1H, d, J = 15.6 Hz, N-C*H*$_2$-Ph), 4.28 (1H, d, J = 16.9 Hz, N-C*H*$_2$-Ph), 5.57 (1H, s, 1-H), 6.94-7.39 (9H, m, 4-H, 5-H, 6-H, 7-H, Ph); $^{13}$C nmr (deuteriochloroform): δ 14.2, 35.1, 41.5, 47.8, 50.3, 62.4, 66.7, 125.2, 126.2, 127.0, 128.1, 2 x 129.0, 129.2, 134.9, 140.6, 144.3, 183.0.

*Anal*. Calcd. for $C_{20}H_{24}N_2OS$ (340.49): C, 70.55; H, 7.10; N, 8.23. Found: C, 70.29; H, 7.31; N, 8.45%.

General Procedure for 2-Ethyliminooxazines **12** and **13**.

Thiourea compound **10** (0.45 g, 1.8 mmol) or **11** (0.61 g, 1.8 mmol) was suspended in methanol (10 mL) and methyl iodide (1 mL) was added. After stirring at room temperature for 2 h, the reaction mixture was evaporated and the product was dissolved in 20 mL of dry THF. This solution was added dropwise to a suspension (55-65% oily dispersion) of NaH (0.7 g,) in 30 mL of dry THF under nitrogen. The reaction mixture was heated on an oil bath (60 °C) for 5 h, until no starting material could be observed by TLC. A few drops of water were carefully added to the reaction mixture in order to decompose the excess sodium hydride, and the solvent was evaporated off. Ice-cold water (25 mL) was added to the residue, which was then extracted with chloroform (3 x 40 mL). The organic phase was dried over $Na_2SO_4$ and the solvent was evaporated off. The residue was crystallized from diethyl ether and recrystallized from *n*-hexane.

*cis*-2-Ethylimino-4,4a,5,9b-tetrahydro-1*H*-indano[1,2-*d*][1,3]-oxazine (**12**).

Compound **12** was obtained in 53% yield (0.22 g), mp 60-63 °C; $^1$H nmr (deuteriochloroform): δ 1.13 (3H, t, J = 7.1 Hz, N-$CH_2$-C*H*$_3$), 2.58 (1H, dd, J = 2.0, 15.9 Hz, 4a-H), 2.72-2.82 (1H, m, 5-H), 3.09-3.25 (3H, m, 5-H, 2 x 4-H), 3.60 (1H, t, J = 10.3 Hz, N-C*H*$_2$-$CH_3$), 4.07 (1H, dd, J = 5.3, 10.3 Hz, N-C*H*$_2$-$CH_3$), 4.88 (1H, d, J = 6.8 Hz, 9b-H), 7.16-7.25 (3H, m, 6-H, 7-H, 8-H), 7.52 (1H, d, J = 7.3 Hz, 9-H); $^{13}$C nmr (deuteriochloroform): δ 15.3, 33.3, 35.3, 36.4, 59.4, 66.0, 125.2, 125.5, 127.2, 127.4, 139.6, 146.3, 152.4.

*Anal*. Calcd. for $C_{13}H_{16}N_2O$ (216.29): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.27; H, 7.61; N, 12.75%.

*cis*-1-Benzyl-2-ethylimino-4,4a,5,9b-tetrahydro-1*H*-indano[1,2-*d*]-[1,3]oxazine (**13**).

Compound **13** was obtained in 55% yield (0.30 g), mp 77-81 °C; $^1$H nmr (deuteriochloroform): δ 0.98 (3H, t, J = 7.1 Hz, N-$CH_2$-C*H*$_3$), 3.00-3.22 (5H, m, 2 x 4-H, 4a-H, 2 x 5-H), 4.08 (1H, dd, J = 2.5, 10.8 Hz, N-C*H*$_2$-$CH_3$), 4.23 (1H, d, J = 15.6 Hz, N-C*H*$_2$-Ph), 4.36 (1H, dd, J = 3.0, 10.8 Hz, N-C*H*$_2$-$CH_3$), 4.70 (1H, d, J = 8.8 Hz, N-C*H*$_2$-Ph), 5.24 (1H, d, J = 15.4 Hz, 9b-H), 7.13-7.25 (3H, m, 6-H, 7-H, 8-H), 7.27-7.45 (6H, m, 9-H, Ph), $^{13}$C nmr (deuteriochloroform): δ 17.0, 34.6, 38.7, 39.9, 50.8, 61.0, 67.3, 125.3, 125.6, 126.8, 127.3, 128.3, 128.6, 128.8, 138.3, 141.6, 142.8, 152.4.

*Anal*. Calcd. for $C_{20}H_{22}N_2O$ (306.48): C, 78.40; H, 7.24; N, 9.14. Found: C, 78.52; H, 7.52; N, 9.35%.

*cis*-2-Ethylimino-4,4a,5,9b-tetrahydro-1*H*-indano[1,2-*d*][1,3]thiazine (**14**).

Thiourea **10** (0.63 g, 2.5 mmol) was refluxed for 1 h in ethanol (25 mL) containing 10% dry hydrogen chloride. The solvent was evaporated off, and the residue was neutralized with 10% aqueous sodium carbonate and extracted with chloroform (3 x 30 mL). After drying and evaporation off the organic solution, a crystalline product was obtained, which was recrystallized from methanol–diisopropyl ether. Yield 0.35 g (60%), mp 82-84 °C; $^1$H nmr (deuteriochloroform): δ 1.17 (3H, t, J = 7.3 Hz, N-$CH_2$-C*H*$_3$) 2.69-2.81 (4H, m, 4-H, 4a-H, 2 x 5-H), 3.17-3.45 (3H, m, 4-H, N-C*H*$_2$-$CH_3$), 5.14 (1H, d, J = 6.3 Hz, 9b-H), 7.16-7.24 (3H, m, 6-H, 7-H, 8-H), 7.50 (1H, d, J = 7.1 Hz, 9-H), $^{13}$C nmr

Table 3

Physical Data on Compounds **15a-g**

| Comp. | M.p. (°C) | Yield (%) | Formula | M.W. chain (**A**) | δN=C*H*Ar ring (**B**) | δN-C*H*Ar-N ring (**C**) | δN-C*H*Ar-N |
|---|---|---|---|---|---|---|---|
| **15a** | 113-115 | 61 | $C_{17}H_{16}N_2O_3$ | 296.33 | 8.53 | 5.25 | 5.10 |
| **15b** | oil | ~100 | $C_{17}H_{16}BrNO$ | 330.23 | 8.37 | 5.14 | 4.99 |
| **15c** | 71-74 | 51 | $C_{17}H_{16}ClNO$ | 285.78 | 8.39 | 5.14 | 4.70 |
| **15d** | 83-87 | 58 | $C_{17}H_{17}NO$ | 251.33 | 8.45 | 5.18 | 5.03 |
| **15e** | 73-76 | 52 | $C_{18}H_{19}NO$ | 265.36 | 8.39 | 5.14 | 4.99 |
| **15f** | 103-106 | 50 | $C_{18}H_{19}NO_2$ | 281.36 | 8.37 | 5.13 | 4.98 |
| **15g** | 129-133 | 62 | $C_{19}H_{22}N_2O$ | 294.40 | 8.30 | 5.05 | 4.90 |

(deuteriochloroform); δ 15.1, 29.0, 36.0, 37.3, 37.4, 63.3, 125.0, 125.3, 126.9, 127.4, 139.6, 146.1, 148.5.

Anal. Calcd. For $C_{13}H_{16}N_2S$ (232.35): C, 67.20; H, 6.94; N, 12.06. Found: C, 67.37; H, 7.01; N, 12.22%.

General Procedure for the Reactions of Amino Alcohols with Aromatic Aldehydes to form **15a-g**, **16**, **17a-c**.

To a solution of the appropriate amino alcohol **4**-**6** (1.2 mmol) in 20 mL of absolute methanol, an equivalent amount of aromatic aldehyde was added (liquid aldehydes were freshly distilled), and the mixture was allowed to stand at ambient temperature for 1 day. The solvent was then evaporated off and the evaporation was repeated after the addition of 10 mL of benzene. The crystalline products were collected by filtration and recrystallized from diisopropyl ether–ethyl acetate. The oily product **15b** was dried in a vacuum desiccator for 24 h.

*trans*-1-(4-Nitrobenzylideneamino)indane-2-methanol (**16**).

Compound **16** was obtained in 60% yield (0.21 g), mp 133-134 °C; $^1$H nmr (deuteriochloroform): δ 2.83-2.92 (2H, m, 2 x 3-H), 3.20-3.31 (1H, m, 2-H), 3.78-3.88 (2H, m, C$H_2$-OH), 4.88 (1H, d, J = 6.3 Hz, 1-H), 7.02 (1H, d, J = 7.6 Hz, 4-H), 7.17-7.32 (3H, m, 5-H, 6-H, 7-H), 7.97 (2H, d, J = 8.8 Hz, 2'-H, 6'-H), 8.27 (2H, d J = 8.6 Hz, 3'-H, 5'-H), 8.55 (1H, s, N=C*H*); $^{13}$C nmr (deuteriochloroform): δ 34.3, 50.1, 64.3, 77.4, 124.0, 124.5, 125.3, 126.9, 128.3, 129.3, 141.7, 142.5, 143.0, 149.3, 159.3.

*Anal*. Calcd. For $C_{17}H_{16}N_2O_3$ (296.33): C, 68.91; H, 5.44; N, 9.45. Found: C, 68.67; H, 5.21; N, 9.22%.

(2*R**,4a*S**,9b*S**)-1-Benzyl-2-(4-nitrophenyl)-1,2,4,4a,5,9b-hexahydroindano[1,2-*d*][1,3]oxazine (**17a**).

Compound **17a** was obtained in 67% yield (0.31 g), mp 164-166 °C; $^1$H nmr (deuteriochloroform): δ 2.36 (1H, d, J = 15.9 Hz, 4a-H), 2.84 (1H, dd, J = 6.0, 15.6 Hz, 5-H), 3.00-3.09 (1H, m, 5-H), 3.48 (1H, t, J = 11.6 Hz, N-C$H_2$-Ph), 3.68 (1H, d, J = 14.6 Hz, 4-H), 3.86 (1H, d, J = 14.6 Hz, 4-H), 4.26 (1H, dd, J = 7.1, 11.6 Hz, N-C$H_2$-Ph), 4.49 (1H, d, J = 6.0 Hz, 9b-H), 5.49 (1H, s, 2-H), 7.17-7.24 (3H, m, 6-H, 7-H, 8-H), 7.26-7.34 (3H, m, 9-H, Ph), 7.40 (2H, d, J = 7.6 Hz, Ph), 7.62 (1H, d, J = 7.6 Hz, Ph), 7.77 (2H, d, J = 8.56 Hz, 2'-H, 6'-H), 8.21 (2H, d, J = 8.8 Hz, 3'-H, 5'-H); $^{13}$C nmr (deuteriochloroform): δ 30.3, 33.2, 50.8, 64.5, 69.9, 87.1, 123.6, 124.2, 126.0, 127.3, 127.4, 127.5, 128.0, 128.1, 128.6, 129.6, 141.7, 142.0, 147.1, 147.7.

Anal. Calcd. For $C_{24}H_{22}N_2O_3$ (386.45): C, 74.59; H, 5.74; N, 7.25. Found: C, 74.71; H, 5.62; N, 7.42%.

(2*R**,4a*S**,9b*S**)-1-Benzyl-2-phenyl-1,2,4,4a,5,9b-hexahydroindano[1,2-*d*][1,3]oxazine (**17b**).

Compound **17b** was obtained in 54% yield (0.22 g), mp 117-119 °C; $^1$H nmr (deuteriochloroform): δ 2.33 (1H, d, J = 15.9 Hz, 4a-H), 2.81 (1H, dd, J = 6.6, 16.1 Hz, 5-H), 2.97-3.07 (1H, m, 5-H), 3.46 (1H, t, J = 11.6 Hz, N-C$H_2$-Ph), 3.81 (1H, d, J = 14.6 Hz, 4-H), 3.86 (1H, d, J = 15.1 Hz, 4-H), 4.23 (1H, dd, J = 7.6, 11.8 Hz, N-C$H_2$-Ph), 4.45 (1H, d, J = 6.3 Hz, 9b-H), 5.45 (1H, s, 2-H), 7.14-7.38 (9H, m, 6-H, 7-H, 8-H, 9-H, Ph), 7.43 (2H, d, J = 8.1 Hz, 3'-H, 5'-H), 7.56 (2H, d, J = 7.6 Hz, 2'-H, 6'-H), 7.63 (1H, d, J = 7.3 Hz, 4'-H); $^{13}$C nmr (deuteriochloroform): δ 30.4, 33.2, 50.5, 64.3, 69.9, 87.8, 124.4, 125.8, 126.4, 126.9, 127.2, 127.6, 127.7, 128.2, 128.4, 128.5, 139.7, 140.5, 141.7, 142.6.

*Anal*. Calcd. For $C_{24}H_{23}NO$ (341.46): C, 84.42; H, 6.79; N, 4.10. Found: C, 84.37; H, 6.91; N, 4.22%.

(2*R**,4a*S**,9b*S**)-1-Benzyl-2(4-dimethylaminophenyl)-1,2,4,4a,5,9b-hexahydroindano[1,2-*d*][1,3]oxazin (**17c**).

Compound **17c** was obtained in 59% yield (0.27 g), mp 205-207 °C; $^1$H nmr (deuteriochloroform): δ 2.32 (1H, d, J = 15.6 Hz, 4a-H), 2.80 (1H, dd, J = 6.6, 17.1 Hz, 5-H), 2.92 (6H, s, N$Me_2$) 2.97-3.03 (1H, m, 5-H), 3.45 (1H, t, J = 11.6 Hz, N-C$H_2$-Ph), 3.78 (1H, d, J = 14.9 Hz, 4-H), 3.94 (1H, d, J = 14.9 Hz, 4-H), 4.20 (1H, dd, J = 6.6, 11.3 Hz, N-C$H_2$-Ph), 4.43 (1H, d, J = 5.5 Hz, 9b-H), 5.39 (1H, s, 2-H), 7.08-7.65 (13H, m, 6-H, 7-H, 8-H, 9-H, 2'-H, 3'-H, 5'-H, 6'-H, Ph); $^{13}$C nmr (deuteriochloroform): δ 30.6, 33.4, 41.1, 50.5, 64.4, 70.0, 88.1, 112.8, 124.6, 125.9, 2 x 127.0, 127.3, 127.7, 128.4, 128.6, 141.0, 141.9, 143.0, 149.3, 154.2.

*Anal*. Calcd. For $C_{26}H_{28}N_2O$ (384.53): C, 81.21; H, 7.34; N, 7.29. Found: C, 81.34; H, 7.05; N, 7.42%.

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