Oxazoline Chemistry Part III. Synthesis and Characterisation of [2-(2'-anilinyl)-2-oxazolines] and Some Related Compounds

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Received January 2, 2003

The syntheses and characterisation of a series of chiral and achiral 2-(aminophenyl)-2-oxazolines and some related compounds is reported. All of the derivatives have been produced by a one-step procedure involving the treatment of isatoic anhydride (*i.e*. [2*H*]-3,1-benzoxazine-[1*H*]-2,4-dione: **1**) or its 5-chloro analogue with a slight excess of appropriate amino-alcohols. In most cases, anhydrous $ZnCl_2$ is shown to be an effective Lewis acid catalyst for this reaction at reflux temperature in high boiling aromatic solvents (PhCl or PhMe). Oxazolines have been readily formed using *rac*-2-amino-1-butanol, (*S*)-phenylglycinol, 2-methyl-2-amino-1-propanol and *(1S,2R)* or *(1R,2S)-cis*-1-amino-2-indanol; yields range from 85% to 22%. The use of aminoalcohols such as 2-ethanolamine, (±)-2-amino-1-phenyl-1-propanol or 3-amino-1-propanol (to give the corresponding 4,5-dihydro-1,3-oxazine) results in poor yields. The use of other Lewis acid catalysts (silicic acid, $Cd(acac)_2 \cdot 2H_2O$, $CuCl_2 \cdot 2H_2O$, $InCl_3$) or higher temperatures did not improve the yields with these latter two substrates. Benzoxazoles and N-substituted benzoxazoles can also be obtained in reasonable yields from **1** using 2-aminophenol (36%) or 2-amino-3-hydroxypyridine (45%).

J. Heterocyclic Chem., **40**, 513 (2003).

Introduction.

The oxazoline group represents an important class of organic heterocycles. Oxazolines have found utility as protecting groups in carboxylic acid chemistry [1], as a directing group in *ortho*-metallation reactions [2], as chiral auxiliaries in asymmetric synthesis [3] and as ligands in transition metal and main group coordination chemistry [4]. The oxazoline ring is also found in a number of (bio-active) natural products [5] and synthetic drugs [6]. The sub-class of oxazolines containing a secondary amino-group have found application in a number of diverse roles including acting as lead compounds for new drugs [7a-7g], or pesticides [7h-7i], as modifiers of macromolecular supports [8-9], as chiral ligands for asymmetric catalysis [10] and for the derivatisation of soluble inorganic frameworks such as gold nanoparticles [11].

Our interests are centred on the design and synthesis of new and easily accessible oxazoline ligands for transition metal ion coordination and medicinal chemistry [12-13] and the amino-oxazoline class of compounds represent an integral part of this endeavour. The oxazoline ring represents one of these potential metal-binding agents. Our use of the anilinyl-derivatives is based on four unique properties of this class of oxazolines (Figure 1):

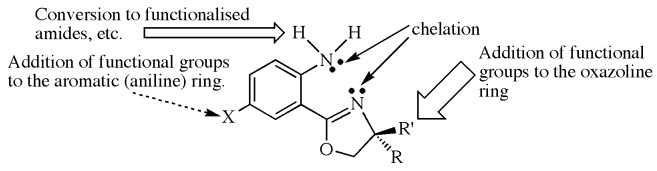
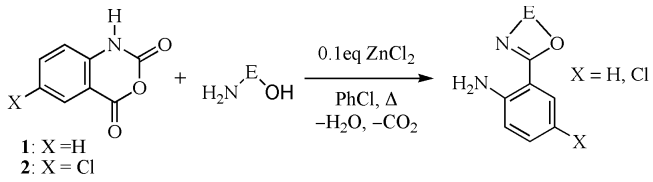


Figure 1

(i) ease of variation of groups on the oxazoline portion of the molecular framework; (ii) facile derivatisation of the $-NH_2$ group (*e.g*., conversion to an amide) to modify the reactivity or function [11] of the oxazoline; (iii) coordination of both the N-atom of the oxazoline [4] and the $-NH_2$ group to form a six-membered (chelate) ring [13]; and (iv) modification of the aniline ring by aryl-halide activation at position 5 (*e.g*., Stille, Heck or Sonogara chemistry). We set out to investigate a general synthesis of amino-oxazolines (eq. 1) using isatoic anhydride (*i.e*. [*2H*]-3,1-benzoxazine-[*1H*]-2,4-dione: **1**) or its 5-chloro analogue (**2**) and a variety of amino-alcohols [14]. This would allow us to evaluate the general accessibility of this class of ligand precursors. A few of these [8,15-16] and related compounds [17] have been previously synthesised by a number of different routes. These protocols include inorganic clay promoted addition of amino-alcohols to **1** [8], Lewis acid-catalysed addition of amino-alcohols to (expensive) 2-cyanoanilines [16], ring closure of (2-anilinyl)amidoalcohols using ethanolic KOH [17b] or phosphites [17a] and *ortho*-metallation of aryl-oxazolines followed by reaction with sodium azide and subsequent treatment with $NaBH_4$ [17f]. We have chosen to use the Lewis acid method in combination with **1** due to the availability of the required catalyst ($ZnCl_2$), ease of handling of the reagents, simple work-up procedures and the low cost of **1** relative to other precursors such as 2-cyanoaniline.

In several cases, we have found that purification of the resulting oxazoline (Table 1) can be accomplished without the need for further separation *via* column chromatography. In this report, we detail the synthesis of a number of anilinyl-appended oxazolines, benzoxazoles and a simple

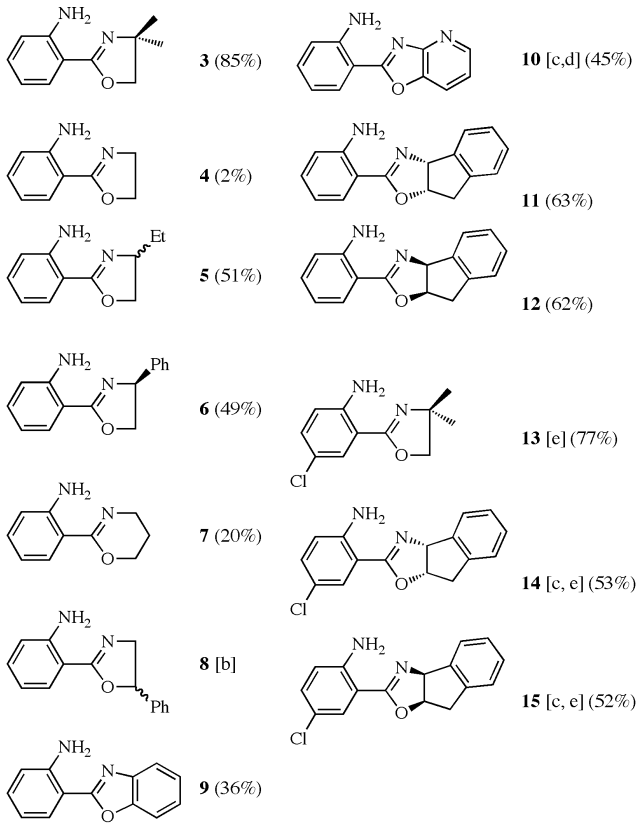


1: X =H
2: X = Cl

4,5-dihydro-1,3-oxazine. This work expands on our brief communication in this area [11] and compliments recent work on the use of **1** for the synthesis of modified oxazoline derivatives [8]. In this regard, Gajare *et al*. have reported the use of **1** for the production of a variety of 2-(2'-anilinyl)-2-oxazolines using a kaolitinic clay [8] as the Lewis acid promoter (eq. 1). We report herein the use of readily available $ZnCl_2$ as Lewis acid catalyst [12,18] for the reaction depicted in eq. 1. In addition, we have expanded the scope of the reaction [8,11] to include the production of heteroatom-substituted benzoxazoles, chiral oxazolines derived from enantiopure *cis*-1-amino-2-indanols [19] and aryl-halide compounds whose skeletal structure is that of 2-(2'-amino-5'-chlorophenyl)-2-oxazoline.

Table 1

2-Anilinyl-2-Oxazolines and related compounds synthesised [a] herein (isolated yields in parentheses)



[a] GeneralConditions: isatoic anhydride, 1.2 equiv. amino-alcohol, 10 mol% $ZnCl_2$, PhCl as reaction medium, reflux temperature; [b] product could not be obtained pure, yield estimated (NMR) as 10-15%; [c] produced using PhMe as solvent; [d] yield 42% with PhCl as solvent; [e] 5-chloroisatoic anhydride used.

Results and Discussion.

The general synthetic reaction is shown in eq. 1. Typically, a portion of **1** (or **2**) was suspended in chlorobenzene (PhCl) or toluene (PhMe) and the mixture was then treated with a slight excess (1.2 equiv) of the appropriate amino-alcohol under argon. To this was added the zinc catalyst followed by heating. Gas (presumably CO_2) evolution was often observed as the mixture was heated and in some cases water was also observed as insoluble droplets in the reaction vessel. After appropriate work-up procedures (see Experimental section), the resulting crude material was isolated, often in the form of a light brown oil or solid. Yields in most cases were in the range of 35-85% (Table 1), not unlike the clay catalysed or amino-benzonitrile protocols [8,16].

We had particular trouble with the simplest oxazoline (*i.e*., **4**) derived from 2-aminoethanol. Yields were invariably poor with this substrate (<5%) and a large number of other, yet unidentified, products were formed. Isolation was also problematic and tedious due to the number of side-products. Unlike a recent report to the contrary however [8], we were able to isolate **4** as a solid with a mp virtually identical to that reported for this material over 60 years ago by Leffler and Adams [15]. Our attempts to produce this material with other Lewis acid catalysts [18] (silicic acid, $Cd[acac]_2 \cdot 2H_2O$, $CuCl_2 \cdot 2H_2O$, $InCl_3$) did not yield any of required product. The related amino-alcohol, 3-aminopropanol, also gave low yields of the corresponding 4,5-dihydro-1,3-oxazine (**7**: 20%) and the oxazoline derived from (±)-2-amino-1-phenyl-1-propanol (**8**) could not be analytically purified. These results suggest that side-product formation may be an inherent property when isatoic anhydrides are employed as cyanoaniline surrogates. This is perhaps not altogether surprising when one considers the highly reactive nature of the imino-ketene derived from **1** (or **2**) *via* loss of CO_2 (**A**: Figure 2) [14,17a,20]. In this regard, some intriguing aspects of the chemistry of **1** have been previously reported by Menger and Kaiserman [20b].

One characteristic of all three of the amino-alcohols that gave unacceptable yields of the corresponding ring product is that they are all unsubstituted at the sp^3 C atom

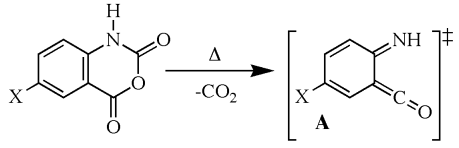


Figure 2: The Imino Ketene (**A**) Derived from **1** (X =H).

located alpha to N. The sluggish reactivity of this class of amino-alcohols to cyclisation is a well-document phenomenon, regardless of the promoters used to affect ring closure [1] and appears to also be the case here. This observation may be explained in relation to the "Thorpe-Ingold" effect [21] wherein under entropic control, substituents on a ring increase the rate, or equilibrium constant, for a ring-forming process. The low yield observed for **7** is likely a kinetic manifestation of the difficulty in forming a six (*i.e.*, the 4,5-dihydro-1,3-oxazine) *versus* a five-membered (oxazoline) ring.

We were pleased to find that enantiopure *cis*-1-amino-2-indanols react readily under the above conditions and give good yields of the corresponding oxazolines (**11**, **12**, **14**, **15**). Also, 5-chloroisatoic anhydride (**2**) can be substituted for **1** with only a slight drop in yield of the desired products (**13-15**). Benzoxazoles (**9**, **10**) are also accessible by this method (eq. 1) [8]. The pyridine derivative **10** opens a gateway to investigate multidentate metal binding of the compound *via* the $-NH_2$ group and the N-atoms of both the benzoxazole and pyridine rings.

We are currently investigating the coordination chemistry of this entire group of oxazolines and their derivatives and shall report these findings in due course [13,22].

Conclusions.

The synthesis of a variety of 2-anilinyl substituted oxazolines and benzoxazoles has been accomplished in a simple one-step procedure using isatoic anhydrides and amino-alcohols with $ZnCl_2$ as catalyst. The products are generally obtained in moderate to good yields. This methodology seems to be best suited for reactions involving amino-alcohols with carbon-containing substituents on the α-C atom to N [1,21]. The advantages of the methodology reported herein *versus* other methods include:

(*i*) a simple "one-pot" reaction; (*ii*) use of a cheap, common and well-defined (homogeneous) Lewis acid catalyst ($ZnCl_2$); (*iii*) chromatography can be avoided in some cases; (*iv*) substituted isatoic anhydrides and enantiopure amino-indanols can be used; (*v*) oxazolines, benzoxazoles and benz-5-*N*-oxazoles have all been shown to be accessible by this method; and (*vi*) isatoic anhydrides are considerably cheaper than the other common precursor to this class of compounds, amino-benzonitriles.

EXPERIMENTAL

General.

All reactions involving **1** or **2** were carried out under an atmosphere of dry air or argon gas. All reagents were purchased commercially or supplied by Sepracor Canada Ltd. and used as received. PhCl was dried by storage over 4 Å molecular sieves. 2-Ethanolamine and PhMe were purchased in dry form in Sure-Seal® bottles (Aldrich) and handled by syringe using standard Schlenk techniques. Petroleum ether (pet. ether) was of the 65-70 ºC boiling-point range. Zinc dichloride was dried by repeated heating under vacuum to the melt (Bunsen burner) followed by cooling to room temperature (RT) under an atmosphere of dry argon gas. Flash chromatographic separations were carried out using 230-400 mesh silica gel (Silicycle, Inc.) with compressed air as the carrier gas. Melting points were determined on a Mel-Temp II or Büchi melting point apparatus and are uncorrected. IR spectra were recorded as thin films on NaCl plates or as KBr pellets using a Perkin Elmer 683 IR spectrometer. Optical rotation measurements were made on a Bellingham + Stanley Ltd. model ADP220 Polarimeter using a 1 dm path length optical cell. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded in deuteriochloroform ($CDCl_3$) solution at RT by a Bruker AC-250 NMR spectrometer located at the ARMRC in Halifax, Nova Scotia or by a Bruker Avance 300 MHz NMR spectrometer located at ACMA in Wolfville, Nova Scotia. Spectra are referenced to TMS (δ = 0.00 ppm) as internal standard. Long relaxation times prevented the observation of some *ipso*-^{13}C resonances as noted. Elemental analyses measurements were performed by Mr. Keith Pringnitz and Mr. A. MacKenzie at the Lakehead University Centre for Analytical Services (LUCAS) located in Thunder Bay, Ontario, Canada.

Syntheses.

General.

All reactions were carried out as detailed below for compound **3** (except where noted) using the appropriate amino-alcohol. Characterisation by IR, mp and ^1H NMR spectroscopy was used to confirm the identity of the known compounds (**3**, **4**, **6** and **9**) [8,15-16] and these data were consistent within experimental error. Any other data reported herein (*e.g.*, ^{13}C NMR chemical shifts) for these known compounds is information that has not been previously disclosed by other authors.

2-(2'-Anilinyl)-4,4-dimethyl-2-oxazoline (**3**).

Compound **1** (10.0 g: 61 mmol, 96% purity: Aldrich) was placed in a two-necked round-bottomed flask under an atmosphere of argon gas and the flask was then charged with 150 mL of PhCl. The contents were then stirred at room temperature for 5 min. using a Teflon stirbar. To this mixture was added (*via* syringe) 2-methyl-2-amino-1-propanol (7.6 g, 85 mmol) followed by solid anhydrous $ZnCl_2$ (0.8 g, 10 mol%) in a single portion. The mixture was then stirred and slowly heated to reflux temperature during which time gas evolution was noted. After 18 h, the flask was cooled to room temperature and then all volatile components were removed by rotary evaporation with a bath temperature of 60-70 ºC. To the resulting brown oil was added CH_2Cl_2 (75 mL) and 80 mL of 10% aq. NaCl. The layers were separated and the aqueous portion extracted twice with CH_2Cl_2 (75 mL) and once with EtOAc (75 mL). The combined organic layers were then dried ($MgSO_4$), filtered and evaporated to give the crude light brown solid. Recrystallisation of this material from boiling 95% EtOH gave compound **3** in the form of colourless crystals (mp 103-105 ºC, lit. [8] 103.6-106 ºC). Yield: 9.9 g (85%). ^1H NMR was identical within experimental error to that found in [8]. $^{13}C\{^1H\}$ nmr: 28.8, 67.8, 77.4, 109.3, 115.6, 116.0, 129.5, 131.9, 148.5, 162.1.

2-(2'-Anilinyl)-2-oxazoline (**4**).

Light brown solid (mp 54-56 ºC; lit. [15] 55-56 ºC). Yield 2%. Purified first by column chromatography of the crude oil using 85/15 EtOAc/hexanes as eluent (R_f = 0.60). The resulting isolated oil [8] was re-dissolved in hot pet. ether and precipitated at –20 °C in the form of beige coloured crystals. ^{1}H NMR was identical within experimental error to that found in [8]. $^{13}C\{^1H\}$ nmr: 14.7, 54.9, 65.8, 109.2, 115.7, 116.0, 129.6, 131.9, 148.5 (N=C[R]-O-: not observed).

rac-2-(2'-Anilinyl)-4-ethyl-2-oxazoline (**5**).

Compound **5** was obtained as a yellow oil, produced from (±)-2-amino-1-butanol and was purified by flash column chromatography. Yield: 51%. R_f (EtOAc/pet. ether: 1/1) = 0.83. ^{1}H nmr: 1.00 (t, J = 15 Hz, 3H, CH_3), 1.63 (m, 2H, CH_2), 3.92 (m, 1H, CH), 4.27 (m, 2H, OCH_2), 6.01 (br s, 2H, NH_2), 6.66 (m, 2H, ArH), 7.19 (m, 1H, ArH), 7.67 (m, 1H, ArH). $^{13}C\{^1H\}$ nmr: 10.3, 29.0, 68.2, 70.5, 109.2, 115.7, 116.0, 129.6, 131.9, 148.6 (N=CO: not observed).

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N 14.72. Found: C, 69.07; H, 7.56; N, 14.99%.

(*S*)-2-(2'-Anilinyl)-4-phenyl-2-oxazoline (**6**).

Produced from (*S*)-glycinol, and obtained as a white solid (mp 70-72 ºC; lit. [16] 71 ºC). Yield: 49%. Recrystallised from CH_2Cl_2/pet. ether (1/1) at –20 °C and the resulting powder was washed with further pet. ether and then dried in air. ^{1}H NMR was identical within experimental error to that found in [16].

2-(2'-Anilinyl)-4,5-dihydro-1,3-oxazine (**7**).

Obtained as a yellow solid (mp 59-62 ºC). Yield: 20%. Crude material was first purified by gravity filtration through silica (60-200 mesh) using EtOAc as solvent and the resulting material was recrystallised from CH_2Cl_2/pet. ether (1/1) at –20 °C. ^{1}H nmr: 1.71 (m, 2H, CH_2), 3.50 (m, 2H, CH_2), 3.65 (m, 2H, CH_2), 4.99 (br s, 2H, -NH_2), 5.26 (s, 0.5H, CH_2Cl_2 [inclusion solvent]), 6.60 (m, 2H, ArH), 7.16 (m, 1H, ArH), 7.30 (m, 1H, ArH). $^{13}C\{^1H\}$ nmr: 32.0, 36.8, 59.7, 116.0, 117.3, 127.4, 132.3, 148.5, 170.4.

Anal. Calcd. for $C_{10}H_{12}N_2O$•0.25(CH_2Cl_2): C, 62.35; H, 6.38; N, 14.19. Found: C, 61.62; H, 6.71; N 14.35%.

Attempted Preparation of *rac*-2-(2'-Anilinyl)-5-phenyl-2-oxazoline (**8**).

1.7 g Each of **1** and (±)-1-phenyl-2-aminoethanol (Fluka) were used and an orange waxy oil was obtained. Attempts to purify this crude material (chromatography/recrystallisation) were not successful. The yield, estimated by (solely) nmr spectroscopy, was in the range of 10-15% (see text).

2-(2'-Anilinyl)-2-benzoxazole (**9**)

This compound was obtained as a white solid (mp 106-108 ºC; lit. [8]: this compound has been previously reported as a dark, viscous oil). Yield: 36%. The crude red coloured oil was subjected to separation by flash chromatography using 1/1 EtOAc/pet. ether and the fractions with R_f = 0.70 were collected and evaporated to dryness. The solid thus obtained was recrystallised from CH_2Cl_2/pet. ether (1/1) at low temperature (–20 °C). IR: 1620 cm^{-1}. ^{1}H nmr: 6.15 (br s, 2H, -NH_2), 6.74 (m, 2H, ArH), 7.28 (m, 3H, ArH), 7.51 (m, 1H, ArH), 7.67 (m, 1H, ArH), 8.03 (m, 1H, ArH). $^{13}C\{^1H\}$ nmr: 108.7, 110.3, 116.3, 116.8, 119.4, 124.3, 124.7, 128.8, 132.4, 141.9, 147.9, 149.3, 163.2.

Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N 13.32. Found: C, 73.81; H, 5.05; N, 13.10%.

Preparation of 2-(2'-Anilinyl)-2-benz-5-*N*-oxazole (**10**).

This compound was obtained as light yellow cubic-shaped crystals (mp 103-105 ºC). Yield: 45%. This material was extracted from the crude reaction mixture using EtOAc only (3 × 75 mL) and recrystallised in four portions from hot 80% aq. EtOH. IR: 1630 cm^{-1}; ^{1}H nmr: 5.61 (br s, 2H, -NH_2), 6.66 (m, 2H, ArH), 7.05 (m, 1H, ArH), 7.27 (m, 1H, ArH), 7.35 (m, 1H, ArH), 7.62 (m, 1H, ArH), 7.75 (m, 1H, ArH). $^{13}C\{^1H\}$ nmr: 113.2, 117.0, 117.8, 122.6, 128.1, 128.5, 134.0, 138.9, 140.4, 145.0, 149.7, 169.9.

Anal. Calcd. for $C_{12}H_9N_3O$•1.6(H_2O): C, 60.04; H, 5.12; N 17.50. Found: C, 60.08; H, 4.84, N, 17.19 %.

(+)-Indanyl-(2'-aminophenyl)-2-oxazoline (**11**).

This compound was obtained as a white solid (mp 143-144 ºC) [21]. Yield: 63%. R_f (EtOAc/pet. ether: 1/1) = 0.84; $[\alpha]_D$ (c 0.011, 299 K, EtOAc) = +127 (±7)°; IR: 1650 cm^{-1}; ^{1}H nmr: 7.67 (d, J = 7.9 Hz, 1H), 7.50 (d, br, J = 3 Hz, 1H), 7.16 (m, 2H), 6.62 (m, 2H), 6.05 (br, s, 3H), 5.77 (m, 1H), 5.36 (m, 1H), 3.44 (m, 3H). $^{13}C\{^1H\}$ nmr: 39.8, 77.0, 81.2, 109.5, 115.7, 116.0, 125.4, 125.5, 127.4, 128.4, 129.7, 132.1, 139.9, 142.5, 148.6, 164.2.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N 11.19. Found: C, 76.90; H, 5.69; N, 10.89%.

(-)-Indanyl-(2'-aminophenyl)-2-oxazoline (**12**).

This compound was obtained as an off-white solid (mp 143-144 ºC) [21]. Yield 62%. $[\alpha]_D$ (c 0.012, 298 K, EtOAc) = –134 (±9)°. ^{1}H nmr identical to **11**.

2-(2'-Amino-5'-chlorophenyl)-4,4-dimethyl-2-oxazoline (**13**).

This compound was obtained as an off-white solid (mp 63-64 ºC). Yield 77%. Recrystallised from CH_2Cl_2/pet. ether (1/1) at –20 °C. IR: 1632 cm^{-1}; ^{1}H nmr (300 MHz): 1.35 (s, 6H, CH_3), 3.98 (s, 2H, CH_2), 6.12 (br s, 2H, -NH_2), 6.59 (m, 2H, ArH), 7.11 (m, 1H, ArH), 7.64 (m, 1H, ArH). $^{13}C\{^1H\}$ nmr: 29.7, 68.1, 77.5, 110.2, 116.9, 120.3, 128.8, 131.7, 147.1, 161.1.

Anal. Calcd. for $C_{11}H_{13}N_2OCl$: C, 58.80; H, 5.83; N 12.47. Found: C, 58.37; H, 5.77; N, 12.41%.

(+)-Indanyl-(2'-amino-5'-chlorophenyl)-2-oxazoline (**14**).

This compound was obtained as an off-white solid (mp 175-176 ºC) [21]. Yield 52%. $[\alpha]_D$ (c 0.0053, 298 K, THF) = +25 (±10)°. IR: 1630 cm^{-1}; ^{1}H nmr: 3.48 (m, 2H, CH_2), 5.37 (m, 1H, CH), 5.78 (m, 1H, CH), 6.06 (br s, 2H, -NH_2), 6.57 (m, 1H, ArH), 7.10 (m, 1H, ArH), 7.27 (m, 3H, ArH), 7.49 (m, 1H, ArH), 7.66 (m, 1H, ArH). $^{13}C\{^1H\}$ nmr: 39.7, 77.0, 81.5, 116.9, 120.4, 124.7, 125.4, 125.5, 127.5, 128.5, 129.0, 131.9, 139.8, 142.1, 147.1, 163.5.

Anal. Calcd. for $C_{16}H_{13}N_2OCl$: C, 67.49; H, 4.60; N 9.84. Found: C, 67.55; H, 4.90; N, 10.04%.

(-)-Indanyl-(2'-amino-5'-chlorophenyl)-2-oxazoline (**15**).

This compound was obtained as an off-white solid (mp 173-174 ºC). Yield 53%. ^{1}H NMR identical to **14**.

Acknowledgements.

This work was supported by an award from Research Corporation. The authors are also indebted to the support of Acadia University, The Nova Scotia Department of Human

Resources, The Canadian Institutes for Health Research (CIHR), and The Natural Science and Engineering Research Council of Canada (NSERC). Mr. Kurt E. Kershaw is thanked for technical assistance in our attempts to purify compound **8**. Sepracor Canada Ltd. provided a generous donation of enantiopure 1-amino-2-indanols that were used in this work. Prof. J. T. Banks (Acadia U.) is thanked for fruitful discussions and support. RAG would also like to thank CNC/IUPAC for an international travel grant to present some of these results at the XXth ICOMC (Corfu, Greece, July, 2002). This paper is dedicated to Professor Elmer C. Alyea (University of Guelph), my undergraduate research mentor, on the occasion of his retirement.

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