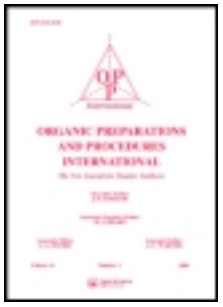

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A FACILE SYNTHESIS FOR RACEMIC AND OPTICALLY ACTIVE 1-AMINOINDANS

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A FACILE SYNTHESIS FOR RACEMIC AND OPTICALLY ACTIVE 1-AMINOINDANS

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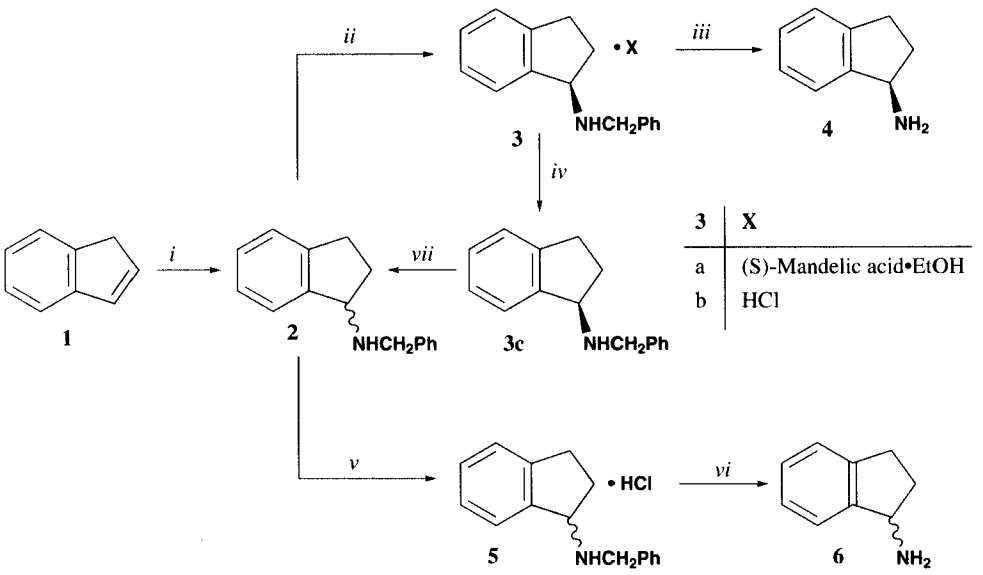
In the course of development work for new central nervous system drugs, we found that a key intermediate, 1-aminoindan and particularly optically active 1-aminoindan, is not readily available in commercial quantities. We therefore developed a facile synthesis suitable for both racemic and enantiomerically pure 1-aminoindans.[1] 1-Aminoindan has previously been prepared by reduction of indanone oxime either with metal,[2] metal-hydride[3] or catalytic hydrogenation.[4] The disadvantage of

these methods *inter alia* is the relatively high price of indanone. Other methods for the preparation of 1-aminoindan include reaction of 1-chloroindan with ammonia[5] or of 1-indanyl-isothiocyanate with 4-methyl-1,2-benzenedithiol.[6] We report here an efficient synthesis of racemic 1-aminoindan starting from indene (**1**), which is transformed to racemic N-benzyl-1-aminoindan (**2**), the key intermediate of this process (see scheme). We developed a process and determined the conditions for regioselective hydrogenolysis. Thus, only one of the two available benzylic bonds is cleaved[13] to give almost exclusively aminoindan and toluene.



i) a) HCl_g b) $PhCH_2NH_2$/toluene *ii*) (S)-Mandelic acid/ethanol *iii*) Pd/C, 3 At H_2/ethanol
iv) NaOH/H_2O *v*) 32% HCl/isoropanol *vi*) Pd/C, 3 At H_2/ethanol *vii*) Pd/C, NaOH, 0.5 At H_2/ethanol

Optically active 1-aminoindan is an expensive compound and there is no suitable synthetic procedure available in the literature by which it can be manufactured on a commercial scale. Nevertheless, it has been prepared by diastereomeric salt formation (S isomer precipitated with N-acetyl-L-leucine[7] and R isomer with (R)-N-acetyl-(3,4-dimethoxyphenyl)alanine[8]), by an enzymatic process[9] and by enantioselective synthesis.[10]

It is known that the secondary amine, N-propargyl-1-aminoindan, is readily resolved by diastereomeric salt formation[11] in contrast to the primary amine, 1-aminoindan. We thus reasoned that the secondary amine intermediate (**2**) in our racemic aminoindan process, would be a useful handle for optical resolution. Racemic N-benzyl-1-aminoindan (**2**) is in fact readily resolved with optically active mandelic acid and smoothly hydrogenolyzed to give 1-aminoindan with high enantiomeric purity. The use of mandelic acid for the optical resolution is advantageous since both enantiomers of mandelic acid are readily available. The synthesis of S-1-aminoindan is thus accomplished using the same method described below except that (R)-mandelic acid is used.

Reaction conditions for high stereoselectivity were developed for the hydrogenolysis of optically active benzylaminoindan, so that almost no racemization occurred (ee = >96%). Nevertheless, using the same catalyst as for the hydrogenolysis, but by modifying the reaction conditions (primarily pH and hydrogen pressure), we were able to racemize, in high yield, the unwanted isomer of N-benzyl-1-aminoindan. The ability to recycle the unwanted isomer as a racemic mixture has a dramatic impact on the economics of the process. The racemization (**3c**→**2**) is also unaffected by the configuration of the starting enantiomer.

In conclusion, we have developed a novel, efficient synthesis of 1-aminoindan starting with indene which is also ideally suited for the preparation of either enantiomer in high optical purity.

EXPERIMENTAL SECTION

Mps were taken on a Thomas Hoover apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were measured with a Bruker AM-300 spectrometer. Chemical shifts are given in δ units and *J* values are given in Hz. IR spectra were recorded on a Perkin Elmer FT-IR 1600 unit. Mass spectra were determined with a low resolution Finnigan 4000 instrument. Optical rotations were obtained on Jasco polarimeter D-370. Elemental analyses were performed at the Microanalytical Laboratory of the Hebrew University, Jerusalem.

Racemic N-Benzyl-1-aminoindan (2).- HCl gas (25 g) was introduced into neat indene (tech., 90%, 100 g., 0.775 moles) at 30-40° during 2.5 h to give 1-chloroindan.[12] The excess HCl was removed *in vacuo*. Toluene (250 mL) and benzylamine (274 g, 2.56 moles, 3.3 equivalents) were added and the mixture was refluxed for 6 h. After cooling to 25°, 400 mL of water was added and the mixture was acidified to pH 2.3 with 66% H_2SO_4. The phases were separated, 250 mL of toluene were added to the aqueous layer and the pH was brought to 6.3 with 47% NaOH solution. The phases were separated and the aqueous phase was re-extracted with 100 mL toluene at pH 6.6. The combined organic layers were washed with 200 mL of water and the toluene was removed *in vacuo* to give 135 g of an oily liquid containing 113.8 g (66%) of **2** (determined by HPLC). A small amount was purified for characterization[14] by distillation (bp. 164°/2 mmHg). ^{1}H NMR ($CDCl_3$): δ 1.54 (br s, 1H, NH), 1.80-1.92 (m, 1H, indan ring), 2.35-2.47 (m, 1H, indan ring), 2.73-2.86 (m, 1H, indan ring), 2.95-3.06 (m, 1H, indan ring), 3.89 (dd, ν_A=3.88, ν_B=4.07, 2H, benzylic CH_2), 4.28 (t, *J* = 6.9, 1H, CH α to the amine group), 7.15-7.40 (m, aromatic ring protons). ^{13}C NMR ($CDCl_3$): δ 30.3 (CH_2 indan ring), 33.6 (CH_2 indan ring), 51.3 (CH_2 benzyl group), 62.7 (CH indan ring), 124.1 (CH aromatic), 124.7 (CH aromatic), 126.2 (CH aromatic), 126.8 (CH aromatic), 127.3 (CH aromatic), 128.1 (CH aromatic), 128.3 (CH aromatic), 140.7 (C aromatic), 143.7 (C aromatic), 145.3 (C aromatic). Mass spectrum (CI, ammonia) *m/Z* [MH^+]: 224.2.

R-(+)-N-Benzyl-1-aminoindan-(S)-mandelate Monoethanolate (3a).- To a solution of **2** (61.6 g, 0.276 moles) in 208 mL absolute ethanol at 50°, was added dropwise a solution of (S)-mandelic acid (22.2 g, 0.146 moles, 0.53 equivalents) in absolute ethanol (100 mL). The reaction was heated to reflux, cooled slowly to 10° and kept at this temperature for an additional hour. The crystals were

collected by filtration, washed with 30 mL ethanol and were recrystallized in 260 mL absolute ethanol. The crystalline compound was collected by filtration, washed with 20 mL cold ethanol and dried in a vacuum oven at 50° to yield **4a** (46.5 g, 80%), mp. 94-97°. $[\alpha]_D^{20}$ = +40.1° (c = 1.5 in acetone). ^{1}H NMR (acetone-d_6): δ 1.11 (t, J = 6.9, 3H, CH_3 of ethanol), 2.08-2.30 (m, 2H, indan ring), 2.66-2.78 (m, 1H, indan ring), 2.96-3.08 (m, 1H, indan ring), 3.55 (q, J = 6.9, 2H, CH_2 of ethanol), 3.89 (s, 2H, benzylic CH_2), 4.46 (dd, J_1 = 8, J_2 = 5, 1H, CH α to the amine group), 4.75 (s, 1H, CHOH), 7.21-7.45 (m, 14H, aromatic rings protons). Mass spectrum (CI, ammonia) *m/Z* [MH^+]: 224.1 for benzyl aminoindan, [MNH_3^+]: 170.1 for mandelic acid.

Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.03; H, 7.51; N, 3.35

The absolute configuration of this compound was determined by a single crystal X-ray diffraction analysis.

R-(+)-N-Benzyl-1-aminoindan Hydrochloride (3b).- **3a** (46.5 g, 0.11 moles), was suspended in a mixture of 117 mL of water and 80 mL of toluene, stirred vigorously and basified to pH 13-14 with 47% NaOH solution. The extraction was repeated with another portion of 37 mL of toluene. Volatiles were removed *in vacuo* from the combined organic layer to give approximately 28 g of a colourless oil. The oil was dissolved in 270 mL of isopropanol, the mixture was heated to 65° and treated with 12.3 mL of 32%HCl solution. The batch was heated to reflux and cooled to 10° over 3 h. The hydrochloride salt was collected by filtration and washed with isopropanol and dried in a vacuum oven at 50° to constant weight to yield 28.5 g of **3b** (quantitative yield), mp. 203-205°. $[\alpha]_D^{20}$ +13.3° (c = 2.0 in ethanol). IR: (KBr) 2887, 2775 (broad, NH_2^+), 1581, 1458, 1423, 699, 755, 742 (aromatic). ^{1}H NMR (D_2O): δ 2.30-2.44 (m, 1H, indan ring), 2.45-2.55 (m, 1H, indan ring), 2.97-3.10 (m, 1H, indan ring), 3.15-3.25 (m, 1H, indan ring), 4.28 (s, 2H, benzylic CH_2), 4.90 (dd, J_1 = 8, J_2 = 5, 1H, CH α to the amine group), 7.35-7.55 (m, aromatic rings protons). ^{13}C NMR (D_2O): δ 29.0 (CH_2 indan ring), 30.4 (CH_2 indan ring), 49.5 (CH_2 benzyl group), 63.1 (CH indan ring), 125.9 (CH aromatic), 126.1 (CH aromatic), 126.6 (CH aromatic), 129.8 (CH aromatic), 130.1 (CH aromatic), 130.2 (CH aromatic), 130.7 (CH aromatic), 131.4 (C aromatic), 136.7 (C aromatic), 145.9 (C aromatic). Mass spectrum (CI, methane) *m/Z* [MH^+]: 224.2, [$MC_2H_5^+$]: 252.2, [$MC_3H_5^+$]: 264.3.

Anal. Calcd for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98; N, 5.39; Cl, 13.65

Found: C, 73.90; H, 7.02; N, 5.25; Cl, 13.94

R-(-)-1-Aminoindan (4).- R-(+)-N-benzyl-1-aminoindan hydrochloride (**3b**, 40 g, 0.154 moles) was suspended in 216 mL of absolute ethanol and hydrogenated in the presence of 5% Pd/C (J.M. type 440, 1.2 g dry catalyst, 3% on a dry basis) at 70° and 2.5-3.0 atmospheres of hydrogen pressure during 6 h. After filtration of the catalyst the volatiles were removed by evaporation *in vacuo*. The solid residue was partitioned between 200 mL of water and 100 mL of toluene. The pH of the aqueous phase was adjusted to 6.3 with a solution of 10% NaOH and the phases were separated. To the aqueous phase 100 mL of toluene were added and the pH was adjusted to 12-13 with a solution of 47% NaOH. The organic phase was separated and the aqueous phase reextracted with 100 mL of toluene. The combined organic phases were evaporated *in vacuo* and the residue was fractionally distilled[16] (bp. 117-119°/20

mmHg) with Hempel column (7.5 cm long and 15 mm diameter, filled with hollow glass rings) to give 15 g (73% yield) of **4**, $[\alpha]_D^{20}$ -16.3° (c = 1.5 in methanol). The product was identical to a commercial sample (Aldrich, 44,534-7) as confirmed by IR, ^{1}H NMR and optical rotation. The optical purity was found to be >99% as determined by HPLC system equipped with chiral column.

N-Benzyl-1-aminoindan Hydrochloride (5).- Racemic N-Benzyl-1-aminoindan (**2**, 200 g, 0.895 moles), and 600 mL of isopropanol were heated to 60°. A solution of 32% HCl (91 mL) was added dropwise to reach pH 1.2 with a concomitant temperature rise to 75°. The mixture was cooled slowly to 10°, held for 1 h at 10°, filtered, washed with 100 mL of cold isopropanol and dried to give 216.4 g of **5** (93% yield), mp. 180-183°; IR and HPLC were identical to **3b**.

1-Aminoindan (6).- As for **4**, from N-Benzyl-1-aminoindan hydrochloride (**5**).

Preparation of racemic N-Benzyl-1-aminoindan (2) by Racemization of R-(+)-N-Benzyl-1-Aminoindan Hydrochloride (3b).- R-(+)-N-Benzyl-1-aminoindan hydrochloride (**3b**, 36.5 g, 0.14 moles) was added to 230 mL of water, the pH was adjusted to 13-14 by 10% NaOH solution and the basic amine was extracted twice with 50 mL of toluene. The toluene phase was washed with 20 mL of water and removed in a rotavapor under vacuum to give 32.3 g of crude R-(+)-N-Benzyl-1-aminoindan base (**3c**) which were placed in a pressure reactor. Ethanol (300 mL), solid NaOH (1.07 g, 0.2 equivalent) and catalyst (Pd/C J.M. 440, 5% by weight calculated on a dry material basis) were added into the reactor, hydrogen (0.5 atm) was introduced and the mixture was heated to 90° for 4 h. The catalyst was taken away by filtration, the solvent was removed *in vacuo*, water (150 mL) was added and the pH was adjusted to 13-14 with 10% NaOH solution. The mixture was extracted with toluene (3x50 mL), the organic phase was washed with 30 mL of water and the solvent was removed to give 29 g (93% yield) of **2**. The racemization was confirmed by chiral HPLC analysis resulting in an ee of 1.2%.

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15. This extraction removes benzylamine due to the pKa difference from **2**.

16. The fractional distillation removes benzylamine impurity based on bp. difference. In 20 mmHg benzylamine boils at 90° while **4** boils at 120°.

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