SHORT PAPER

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Crystal structure of (*R**,*S**)-3-(hydroxy-phenyl-methyl)- 2-methyl- and 2-(4-methoxybenzyl)-2,3-dihydroisoindol-1-ones[†]

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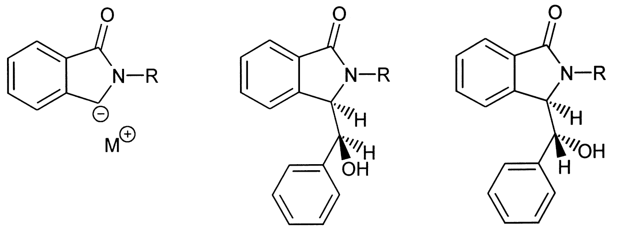
Quenching of lithiated isoindolin-1-ones with benzaldehyde gives rise almost exclusively to the *erythro* (*R**,*S**) adducts.

Keywords: isoindolinones, lithiation, diastereoselection

As a part of our continuing program on the synthesis and chemistry of isoindolin-1-ones[1–3] we have been investigating diastereoselectivity in the addition of achiral metallated isoindolinone derivatives **1a,b** to carbonyl compounds. In so doing two pairs of *erythro* (*R**,*S**) and *threo* (*R**,*R**) isomers, **2a,b** and **3a,b** respectively, may be formed with a non enolizable aldehyde such as benzaldehyde (Scheme 1). In related systems Seebach has shown that addition of aldehydes to a lithiated tetrahydroisoquinoline pivalamide gave a mixture of both *erythro* and *threo* diastereomers, whereas the exclusive formation of the *erythro* isomer required transmetallation with $MgBr_2$ prior to addition.[4] The use of the BF_3 complex of the *N*-alkyl derivatives before subjection to the metallation-quenching with benzaldehyde sequence did not dramatically alter the diastereoisomeric ratio.[5] We did not find the same trend with the metallated lactams **1a,b**. Indeed, the lithiated isoindolin-1-ones **1a,b** (M = Li) afforded almost exclusively one diastereomer. In order to determine the structural character and conformation of the racemic adducts **2a,b** or **3a,b** we therefore investigated their crystal structure by X-ray diffraction (Figs 1 and 2).



1 **2** *erythro* **3** *threo*

a R = CH_3
b R = CH_2-C_6H_4-OCH_3(*p*)
M = metal

Scheme 1

The title compounds were synthesised by metallation of the parent isoindolin-1-ones[3] with LHMDS in THF at –90°C. Subsequent trapping with benzaldehyde and usual work up afforded the crude adducts which could be equally well recrystallised from hexane–toluene, acetone–hexane and EtOH, but only EtOH gave crystals satisfactory for X-ray analysis.

The X-ray crystal analysis allowed the unambiguous assignment of the *erythro* (*R**,*S**) configuration to the racemic hydroxyalkylation adducts **2a** and **2b.** Interestingly the X-ray structure of **2b** showed that the two crystallographically independent molecules in the cell differ only by a slight rotation of the methyl group.

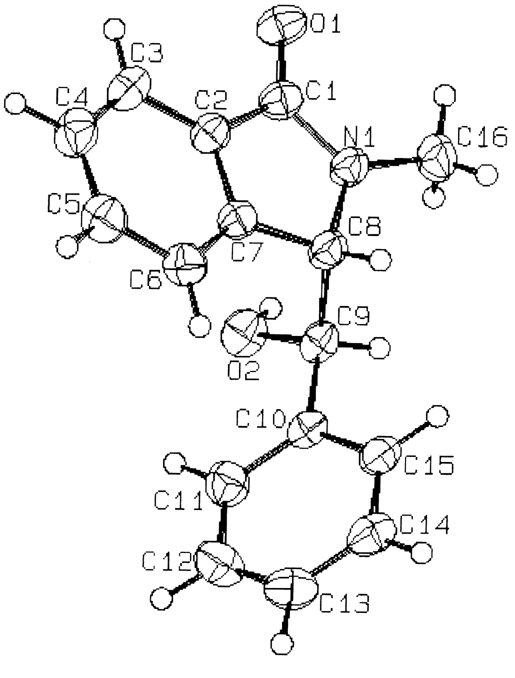


Fig. 1 Crystal structure of (*R**,*S**)-3-(hydroxy-phenyl-methyl)-2-methyl-2,3-dihydroisoindol-1-one **2a**.

Experimental

To a solution of the parent isoindolin-1-one (1 mmol) in THF (20 ml) cooled at –90°C was added by syringe under argon LHMDS (1.1 ml, 1.1 mmol, 1M solution in THF) over a period of 10 min. The orange solution of **1a,b** in THF was stirred for an additional 15 min and a solution of benzaldehyde (117 mg, 1.1 mmol) in THF (5 ml) was then added dropwise at –90°C. The solution was warmed to room temperature, then quenched with saturated aqueous NH_4Cl and extracted with $CHCl_3$ (3 × 30 mL). The combined organic phases were washed successively with water and brine and then dried (Na_2SO_4). Evaporation of the solvents left a crude residue which was purified by recrystallization from EtOH to afford **2a,b**.

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

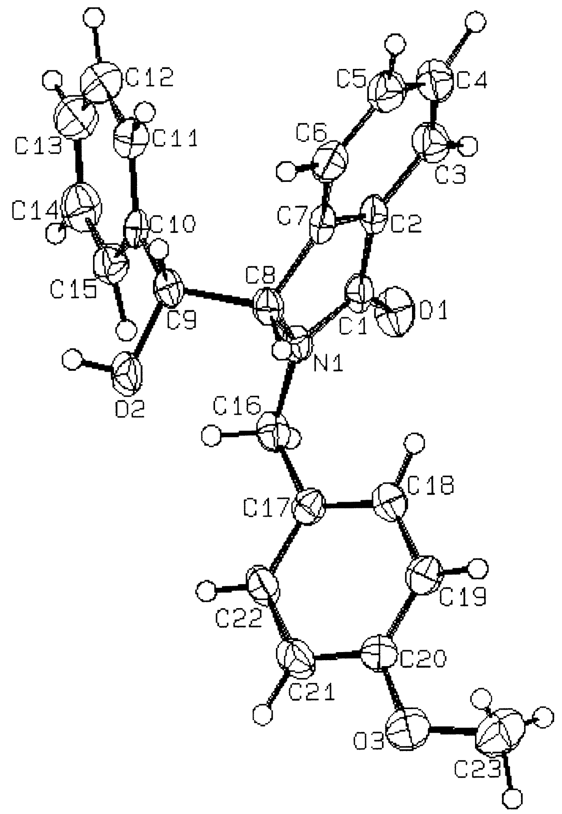

Fig. 2 Crystal structure of (*R**,*S**)-3-(hydroxy-phenyl-methyl)-2-(4-methoxy-benzyl)-2,3-dihydroisoindol-1-one **2b**.

(R,S*)-3-(Hydroxy-phenyl-methyl)-2-methyl-2,3-dihydroisoindol-1-one* **2a:** m.p. 213–214 °C; ^{1}H NMR (DMSO-d_6, δ ppm, *J* Hz): 3.14 (3H, s), 4.86 (1H, d, *J* 2.9), 5.32 (1H, dd, *J* 2.9, 4.5), 5.71 (1H, d, *J* 4.5), 6.68–6.72 (1H, m), 7.00-7.40 (8H, m); ^{13}C NMR (DMSO-d_6, δ ppm) 29.2, 67.8, 71.8, 123.1, 124.3, 127.3, 128.1, 128.7, 128.8, 131.2, 134.1, 141.8, 143.2, 168.7; Crystal data: $C_{16}H_{15}NO_2$, M_r = 253.29, F(000) = 536, colourless crystal, monoclinic system, a = 9.873(2), b = 12.260(3), c = 10.824(2) Å, α = 90, β = 96.585(5), γ = 90°, V = 1301.5(5) Å^3, Space group P2(1)/*c*, Z = 4, D_c = 1.293 g/cm^3, μ(Mo Kα) = 0.85 cm^{-1}.

(R,S*)-3-(Hydroxy-phenyl-methyl)-2-(4-methoxybenzyl)-2,3-dihydroisoindol-1-one* **2b**: m.p. 165–166°C; ^{1}H NMR (DMSO-d_6, δ ppm, *J* Hz): 3.72 (3H, s), 4.45 (1H,d, *J* 14.8), 4.62 (1H, d, *J* 2.7), 5.18 (1H, d, *J* 14.8), 5.37 (1H, dd, *J* 2.7, 4.4), 5.82 (1H, d, *J* 4.4), 6.80–7.58 (13H, m); ^{13}C NMR (DMSO-d_6, δ ppm) 45.1, 56.7, 65.6, 73.0, 115.7, 124.2, 125.3, 128.3, 128.9, 129.4, 130.6, 131.0, 131.3, 132.3, 134.4, 142.1, 143.9, 160.2, 169.4; Crystal data: $C_{23}H_{21}NO_3$, M_r = 359.41, F(000) = 1520, colourless crystal, monoclinic system, a = 15.451(4), b = 9.917(3), c = 25.340(7) Å, α = 90, β = 91.682(5), γ = 90°, V = 3881.2(18) Å^3, Space group P2(1)/n, Z = 8, D_c = 1.230 g/cm^3, μ(Mo Ka) = 0.81 cm^{-1}.

The intensity data were collected on a Bruker AXS SMART three-circle diffractometer with graphite monochromatised Mo Ka radiation (λ=0.71073 Å) and equipped with a CCD two-dimensional detector. Collection with ω and φ scans.

The structures were solved by direct methods and expanded using Fourier maps. All non hydrogen atoms were refined anisotropically. Hydrogen atoms positions were refined but their temperature coefficients were fixed to 1.2 times the U_{eq} of the atoms they are bound to. The SHELXTL[6] crystallographic software package was used for all calculations.

For **2a**, 3122 independent reflections were used –13< h <13, –17< *k* <16, –15< l < 14 , θ max = 30°, R_1 = 0.055, R_{w_2} = 0.1277; the estimated standard deviations for non-hydrogen atoms were in the range 0.002–0.004 Å for the bond lengths and 0.2–0.3° for the bond angles.

For **2b**, 8040 independent reflections were used –22< h <22, –13< k <13, –35< l < 36 , θ max = 31°, R_1 = 0.064, R_{w_2} = 0.1384; the estimated standard deviations for non-hydrogen atoms were in the range 0.004–0.009 Å for the bond lengths and 0.3–0.7 ° for the bond angles.

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