A potent benzylamine analgesic: (-)cis-2(α-dimethylamino-m-hydroxybenzyl)cyclohexanol

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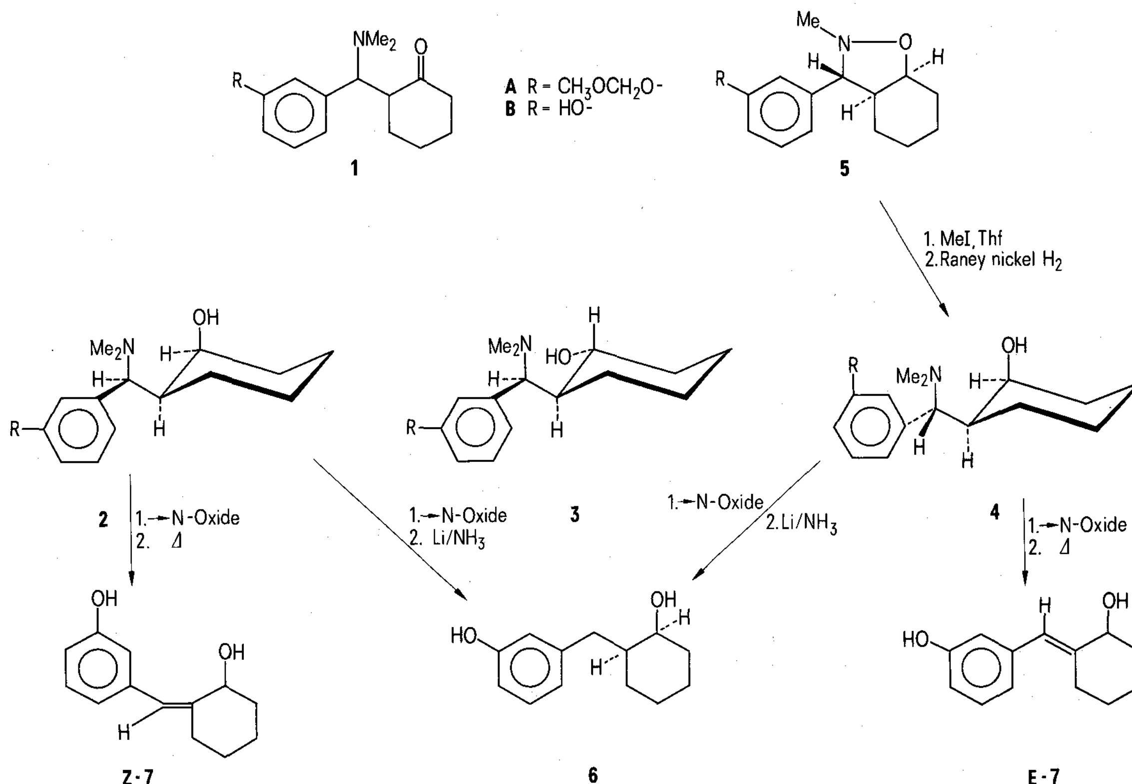
Summary. Synthesis and preliminary biological activity of (-)cis-2(α-dimethylamino-m-hydroxybenzyl)cyclohexanol, a novel analgesic agent is described.

We wish to report the synthesis, stereochemistry and biological activity of (-)cis-2-(α-dimethylamino-m-hydroxybenzyl)cyclohexanol (-) (**2B**), a novel benzylamine with a mixed agonist-antagonist analgesic profile[1].

The racemic form of **2B** was obtained by reduction of the oily, unstable adduct (**1A**) of 2-(3-methoxymethoxybenzylidene)cyclohexanone (b.p. 173-176 °C at 0.3 mm; $\lambda_{max}^{CH_3CH}$ 287 nm [ε 13,000]) and dimethylamine, followed by mild acid hydrolysis of the methoxymethyl protecting group[2]. Reduction of **1A** with $LiAlH_4$ affords a 1:2 mixture of the cis-(**2A**) and trans-(**3A**) isomers arising from reduction of 1 of the 2 theoretically possible amino ketones. This conforms with the early finding of Baltzly and Russell on the reduction of the adducts of secondary amines and benzylidene cyclohexanone[3]. The isomers were separated by chromatography on Woelm neutral grade III alumina using benzene-ether solvent mixtures. **3A** (less polar), PMR ($CDCl_3$): δ 2.28 (6H, s, $N(CH_3)_2$), 3.0 (1H, d, J=3 Hz, $CHN(CH_3)_2$), 3.48 (3H, s, OCH_3), 3.3-3.8 (1H, broad m, $CHOH$)ppm. **2A** PMR ($CDCl_3$): δ 2.1 (6H, s, $N(CH_3)_2$), 3.37-3.7 (overlapping m, $CHOH$ and $CHN(CH_3)_2$), 3.47 (3H, s, OCH_3), 5.17 (2H, s, $-OCH_2O-$) ppm. The cis-stereochemistry of **2A** was inferred initially from PMR-comparisons of the cyclohexane C(1)-proton signal (α to the hydroxyl) in **2A** and **3A**; the narrower signal in **2A** reflecting the lack of 2 large trans diaxial couplings present in **3A**, the cyclohexane ring being assumed in a chair form with the bulky benzylamine function equatorial.

In constrast to reduction with $LiAlH_4$, **1A** with diborane affords an isomer ratio of 3:1 in favor of **2A** and permitted an Eintopfmethode synthesis of **2B** by terminating the reduction with an in situ hydrolysis of boranes and acidic cleavage of the methoxymethyl protecting group. The HCl salt of **2B**, virtually free of the more soluble trans-form, crystallized in 50% overall yield from 2-(3-methoxymethoxybenzylidene)cyclohexanone. **2B**: HCl salt, m.p. 263-265 °C/methanol-acetone:mass spectrum (CI) 250 (MH^+ free base), 232, 205, 150. **3B**: (free base) m.p. 220-225 °C/methanol:PMR (D_6MSO) δ 2.2 (6H, s, $N(CH_3)_2$) ppm: maleate salt, m.p. 182-183 °C/acetone.

A direct correlation with a 3rd isomer **4B**, which from its method of preparation vide infra must be cis and therefore epimeric with **2B** at the benzylic carbon, proved instrumental in the determination of the benzyl carbon stereochemistry. The nitrone, formed between N-methylhydroxylamine and m-methoxymethoxybenzaldehyde[2], undergoes 1,3-dipolar addition to cyclohexene to give the isoxazolidine (**5A**):PMR ($CDCl_3$) δ 2.72 (s, $N-CH_3$) with a GLC-purity of 86%. **5A** was converted without purification to a crystalline methiodide, m.p. 150 °C decomp./methanol-ether. The impurity in the isooxazolidine (**5A**) presumed to be the benzyl epimer and therefore a potential precursor of **2** is lost since it does not separate under the quaternization conditions. Hydrogenation of the methiodide with Raney-Nickel in ethanol containing sodium acetate gave **4A**: fumarate salt, m.p. 156-157 °C/acetone-hexane. Acid



Absolute configuration is not known; as shown (−) **2B** is (−)-(1S,2S)-2-[(S)-α-(dimethylamino)-m-hydroxybenzyl] cyclohexanol.

Route of administration	Analgesia (rat tail flick)[7,8] Morphine ED_{50} mg/kg	(−) **2B** ED_{50} mg/kg (95% confid. levels)	Safety ratio (rats) LD_{50}/ED_{50}	Antagonism[8] of morphine (rats) (−) **2B** ED_{50} mg/kg	Nalorphine ED_{50} mg/kg
i.p.	4.0	2.71 (1.95–3.75)	> 100		
i.m.	1.7	0.76 (0.62–0.94)	> 400	1.2	0.84
p.o.	11	4.31 (3.03–6.14)	> 200		

hydrolysis afforded **4B**: (free base) m.p. 172–173.5 °C/ether-hexane: PMR ($CDCl_3$) δ 2.17 (6H, s, N (CH_3), 4.05 (2H, overlapping 1H, d, J = 12 Hz - $CHN(CH_3)_2$), and 1H, m, CHOH) ppm:HCl salt, m.p. 241–242 °C/acetone-ethanol-hexane.

Attempts to convert **2** and **4** to a common intermediate by catalytic hydrogenolysis of the dimethylamino function were unsuccessful. However, conversion of **2B** and **4B** to their N-oxides with monoperphthalic acid followed by reductive cleavage[4] of either, using lithium in liquid ammonia, afforded the identical racemate (**6**): m.p. 93–96,5 °C/acetone-hexane. **2B** and **4B** can only differ, therefore, in the stereochemistry of the benzyl position and this was inferred from the facile Cope[5] cis-elimination of their N-oxides to give the Z and E isomers of **7** respectively in 98% stereochemical purity. Stereospecific cis-elimination dictates the geometry shown in **2** and **4**. Elimination of the amine function was observed when either N-oxide was stored over long periods, warmed in chloroform, or heated briefly above its melting point. GC-MS analysis of the elimination products was made on a 3 ft, 3% OV-17 glass column, 2 mm ID at 220 °C. The **Z-7** isomer (from **2B** N-oxide) had a retention time of 4.6 min, M^+ 204; R_f[6] 0.48 while the **E-7** isomer (M^+, 204; R_f 0.42) had a retention time of 5.7 min identical to an authentic sample of **E-7** isomer: m.p. 107–110 °C/ether-hexane prepared by acid hydrolysis followed by $NaBH_4$ reduction of 2-(3-methoxy-methoxybenzylidene)cyclohexanone.

Resolution of **2B** proceeded with an efficiency of 78% via the diastereoisomeric tartrate salts. (-) **2B** (-) tartaric acid salt: m.p. 198–200 °C/aqueous acetone; $[\alpha]_D$ − 16.9°. (-) **2B** (free base): m.p. 191–193 °C/acetone-hexane; $[\alpha]_D$ −46.7°. (-) **2B**, HCl salt: m.p. 255–257 °C/acetone-methanol, $[\alpha]_D$−15.31°. (+) **2B**, HCl salt: m.p. 255–257 °C/acetone-methanol, $[\alpha]_D$ + 14.7°.

Biological activity. Analgesic-antagonist activity for (-) **2B** is summarized in the table. In the D'Amour-Smith rat tail flick method[7,8], i.p. route, (+) **2B** and **3B** were inactive as analgesics, the ED_{50} for **4B** was 50 mg/kg. (−) **2B** is under active clinical evaluation.

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Synthesis of N-aryl-N-glycolyl hydroxamic acids: Nonmicrosomal metabolites of nitrosoaromatics[1]

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Summary. A method for the synthesis of N-aryl-N-glycolyl hydroxamic acids is described. This method consists of N-acylation of an arylhydroxylamine by glycolic acid in the presence of dicyclohexylcarbodiimide.

In previous reports it was demonstrated that nitrosoaromatic compounds are converted to N-aryl-N-glycolyl hydroxamic acids by transketolase enzymes[2,3]. This previously unknown type of hydroxamic acid derivative could be involved in the known toxicological properties of nitrosoaromatics, and their known metabolic precursors, the arylamines and nitroaromatics[4]. A further interest in these very unusual metabolites arises from the fact that they are produced by soluble enzymes, and not by microsomal enzymes[2,5].

We have developed an efficient method for the synthesis of this new class of hydroxamic acids, which we now describe for N-(4-chlorophenyl)-N-glycolylhydroxamic acid (**2**). Standard methods which employ acid chlorides or anhydrides for the synthesis of hydroxamic acids[6] could not be employed in the preparation of **2** and related compounds. A previous report on the coupling of carboxylic acids with hydroxylamine by employing dicyclohexylcarbodiimide (DCC)[7] suggested the method which we developed. Critical to the success of this procedure is the saponification of the crude product to convert **3** to **2** before the final isolation is attempted.

To 2.9 g (0.02 moles) of 4-chlorophenylhydroxylamine (**1**) in 50 ml of anhyd. ether at 0 °C was added 8.3 g (0.04 moles) of DCC in 20 ml of anhyd. ether. With stirring and continued cooling was added to this solution 3.0 g (0.04 moles) of glycolic acid in 10 ml of DMF in the course of 15 min. The resulting mixture was stirred with cooling for 15 min, then filtered to remove dicyclohexylurea, which was washed with 20 ml of ether. The ether solution was stirred with 1.6 g (0.04 moles) of NaOH in 30 ml of H_2O for 15 min at 0 °C. This mixture was transferred to a separatory funnel and the 2 phases separated. The ether layer was washed with 10 ml of H_2O, which was then combined with