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LARGE SCALE SYNTHESIS AND ABSOLUTE CONFIGURATION OF (-)-3-PPP, A SELECTIVE DOPAMINE AUTORECEPTOR AGONIST

SETH-OLOV THORBERG* and LARS GAWELL
Astra Läkemedel AB, Research and Development Laboratories,
CNS-Medicinal Chemistry
S-151 85 Södertälje, Sweden

and

INGEBORG CSÖREGH
Department of Structural Chemistry, Arrhenius Laboratory,
University of Stockholm, S-106 91 Stockholm, Sweden

and

J L G NILSSON
Apoteksbolaget, Central Laboratory, Box 3045, S-171 03 Solna, Sweden

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Abstract - A large scale synthesis for (-)-3-PPP has been developed. The racemic methoxy compound 1 was prepared in a three step procedure in 63% yield. This was resolved as a diastereomeric salt by crystallization of the (-)-di-p-toluoyltartrate. Two crystallizations gave the pure (-)-enantiomer 2 in 50% of the theoretical yield and with an enantiomeric excess of >95%. Demethylation using aqueous HBr gave (-)-3-PPP, (3). Compound 2 was also prepared in a stereoselective synthesis from S-(-)- N-propyl-2- chloromethylpyrrolidine 4. By X-ray crystallography it was shown that (-)-3-PPP has the S-configuration at the chiral carbon.

Recently Hjorth *et al.*[1] described the pharmacological properties of 3-(3-hydroxy-phenyl)- N-propylpiperidine (3-PPP, UH 106). The compound was characterized as a selective dopamine (DA) autoreceptor agonist devoid of any appreciable postsynaptic DA-mimetic activity. After resolution[2] of the racemic compound, further studies[3] proved that this selectivity was confined to the (-) enantiomer of 3-PPP.

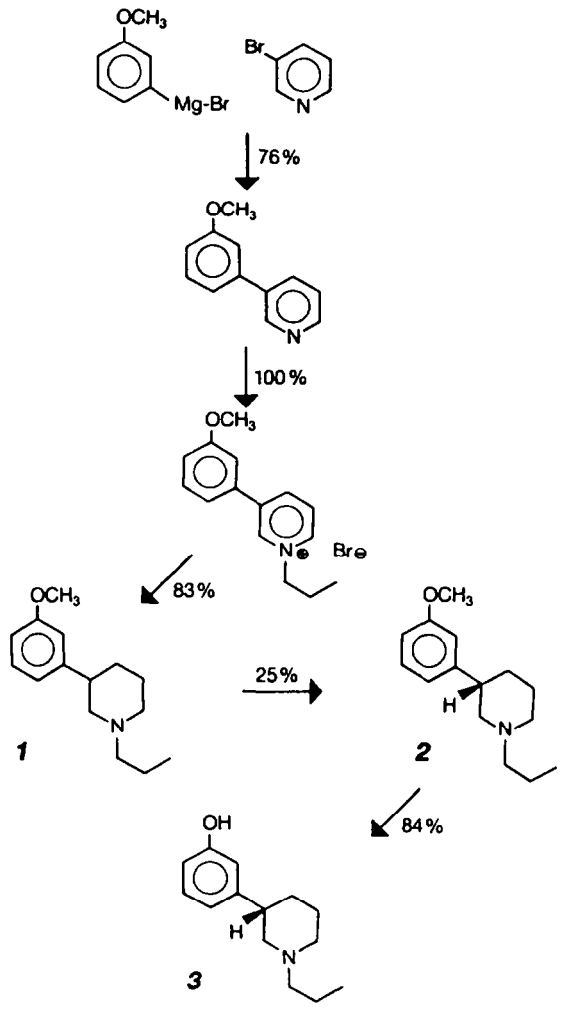
In this paper we describe a method for large scale synthesis of the (-) enantiomer and determination of the absolute configuration of the active enantiomer via a stereoselective synthesis and by X-ray crystallography.

Large scale synthesis

Racemic 3-PPP was originally synthesized by Hacksell *et al*[4] but alternative preparation methods have also been published[5 6]. Resolution methods have been reported by Wikström *et al*[2] and Arnold *et al*[7].

The initial step in our large scale synthesis is a Ni-catalyzed coupling of the Grignard reagent from 3-bromoanisole with 3-bromopyridine (Scheme 1) following essentially the method described by Hacksell *et al*[4]. The crude product was converted to the quaternary pyridinium salt using 1-bromopropane followed by catalytic hydrogenation. The racemic 3-(3-methoxyphenyl)-N-propyl-piperidine (1) was obtained in an overall yield of 63%.

Scheme 1.



In the following resolution the (-)di-p-toluoyl-L-tartaric acid salt of 1 was recrystallized twice from aqueous ethanol giving the desired enantiomer 2 in 50% yield. The compound has an enantiomeric excess of >95% determined by comparing the optical rotation of the salt with known mixtures of the two pure enantiomers (Fig. 1). The final step involves the demethylation in hydrobromic acid followed by isolation of (-)3-PPP (3) as the hydrochloride salt.

Since the resolution methods [2-7] so far reported appear to be either too laborious or too expensive for large scale synthesis, the above method offers a short efficient large scale synthesis with good economy.

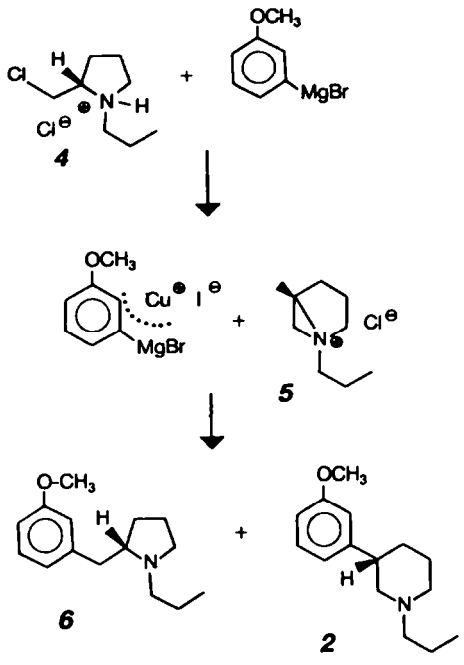
Preparation of (-)3-PPP via stereoselective synthesis

As an alternative to the resolution method for the preparation of (-) 3-PPP we attempted a stereoselective synthesis.

S-(-)-N-propyl-2-chloromethylpyrrolidine hydrochloride (4) (Scheme 2) can be conveniently obtained from naturally occuring L-proline (S-configuration) in analogy with the method described by Hammer et al[8]. The free base of this type of structure is known to undergo molecular rearrangement to its corresponding 1-alkyl-1-azabicyclo [3.1.0] hexane derivative[8-10] 5. The aziridinium ion can react with a nucleophile to form a 3-piperidine or a 2-methyl-pyrrolidine

derivative. Hammer et al[8] have proven that the nucleophile attack is 100% stereospecific and the ring opening of the intermediate aziridinium ion with nucleophiles at both the primary and secondary positions proceeds only by an S_N2 mechanism.

Scheme 2.



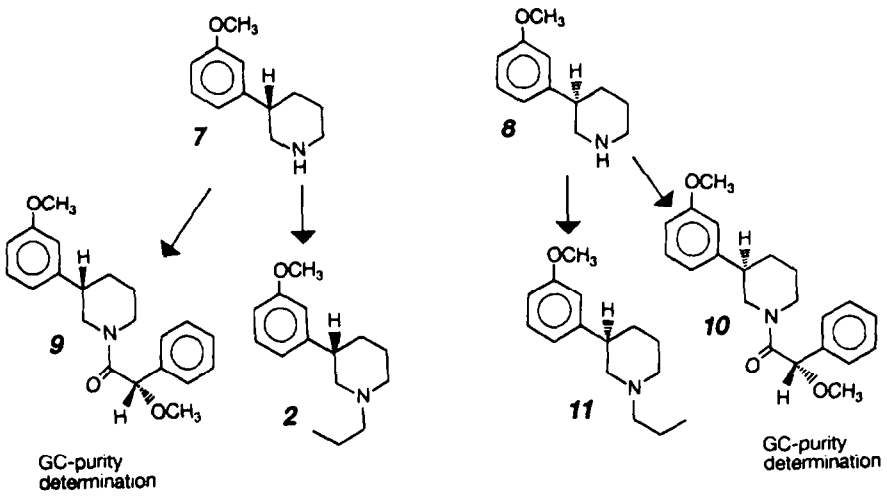
Inspection of a molecular model of 5 indicated no difference in steric hindrance for reaction at the carbon-atoms in positions 2 or 3. Using an appropriate Grignard reagent as a nucleophile we therefore expected to obtain the desired product 2 in an acceptable yield.

The aziridinium intermediate was formed from the hydrochloride of 4 using one mole of 3-methoxyphenyl magnesium bromide as base. Addition of another mole of the Grignard reagent gave no coupling products. Also the use of 3-methoxyphenyllithium as base and nucleophile failed. However, by adding a catalytic amount of cuprous cyanide or cuprous iodide to the reaction mixture, the nucleophile attack was successfully initiated. This method gave the two expected products in a total yield of 82%. The major isomer in the mixture turned out to be the pyrrolidine derivative 6 in 82% yield while the desired compound 2 was present in 18%.

Determination of optical purity

Pure enantiomers of the secondary amines 7 and 8 (Scheme 3) were prepared as described by Wikström et al[2] and their purity was estimated with a capillary gas-chromatographic method using the diastereomeric S-(+)-O-methyl-mandelic acid amides 9 and 10. The optically pure amines were propylated[2] yielding 2 and its corresponding (+)-enantiomer 11. Two diastereomeric salts were then prepared using the two enantiomers 2 and 11 viz (-)-di-p-toluoyl-L-tartrate of 2 and (+)-di-p-toluoyl-D-tartrate of 11. The optical rotation was then determined for known mixtures of the two salts and the rotation was plotted in a diagram against the molar fraction of the two salts (Fig. 1). This diagram was used for determination of the optical purity during the large scale resolution procedure. After two crystallizations, the (-)-di-p-toluoyl-L-tartrate of 2 had a $[\alpha]_D^{20} = -95°$ indicating an optical purity >95%.

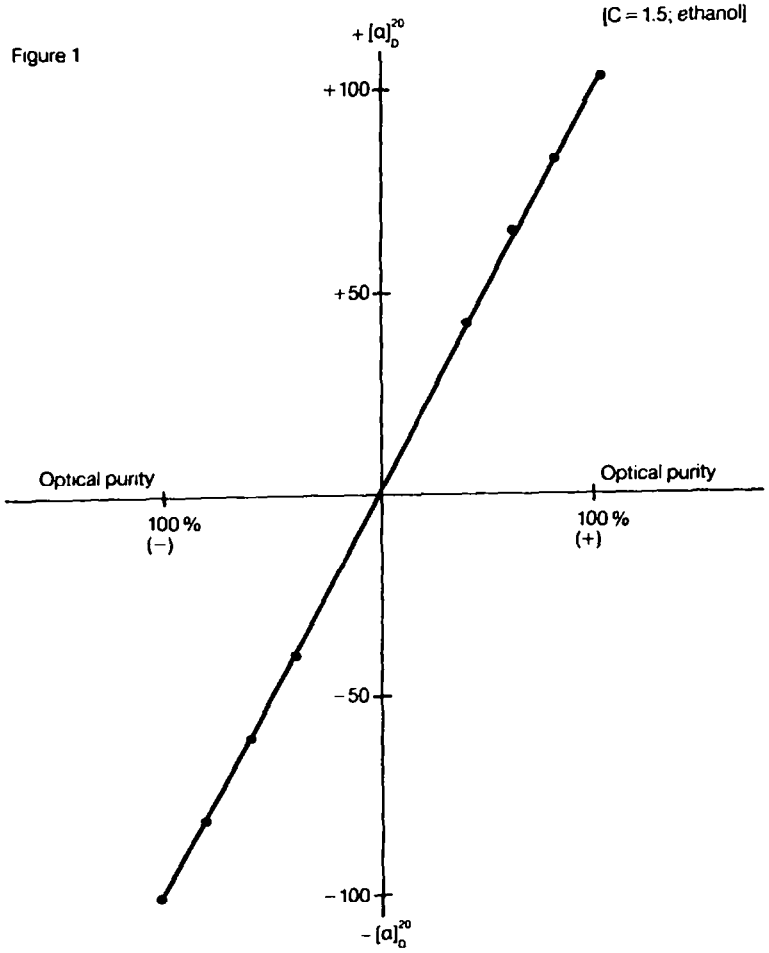
Scheme 3.



(−)Di-p-toluoyl-L-tartaric acid salt
$[\alpha]_D^{20}$: −100°

(+)Di-p-toluoyl-D-tartaric acid salt
$[\alpha]_D^{20}$: +102°

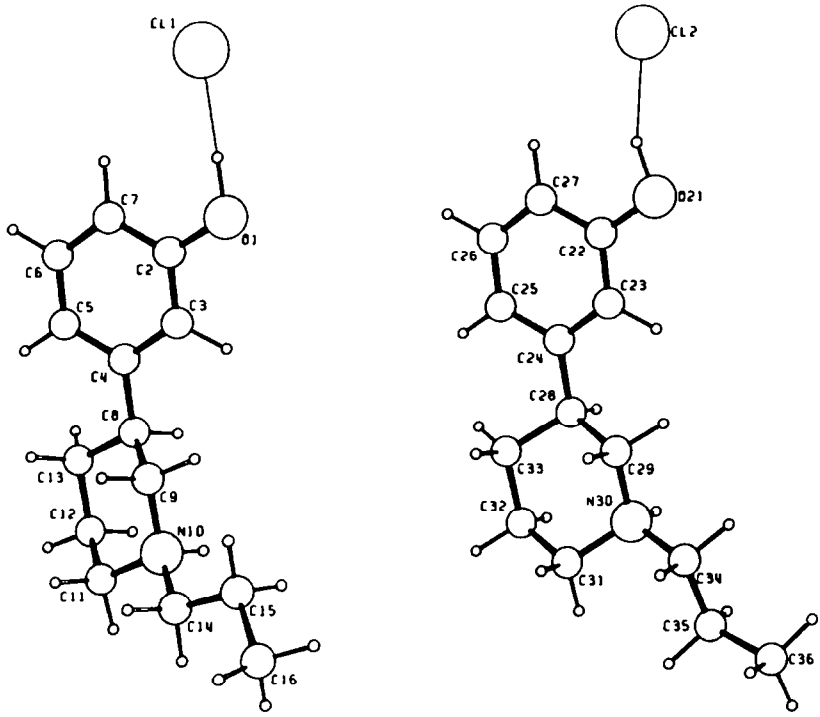
Figure 1



The optical rotation was plotted against known molar fractions (equal to known optical purity) of the two pure salts (12) and (13).

The X-ray crystallographic description of (-)-3-PPP.

The structure and the absolute configuration determinations were carried out as described in the experimental section, using the hydrochloride salt of (-)-3PPP. Two independent molecular conformations (A and B) were identified in the crystals as shown in Fig. 2. The determination of the absolute configuration was shown that (-)-3-PPP has the S configuration at the chiral carbon. All observed values of bond lengths and bond angles in the two conformations agree with each other within experimental error and generally also conform to the expected values with two exceptions. At the end of the propyl side chain of mol A, two neighbouring C - C bond distances refined to the values of 1.395(10) and 1.574(10) A, probably depending on the rather high thermal mobility in this region. The respective bond lengths in mol B have the values of 1.504(8) and 1.520(9) A.



A B

Figure 2

Views of the two crystallographically independent molecular conformations in the crystal structure of S(-)-3-(3-Hydroxyphenyl)-N-propylpiperidine hydrochloride(3), with atoms numbered as in the text.

The aromatic rings are flat to within 0.025 and 0.020 A in mol A and B, respectively. The piperidine rings have chair conformation in both molecules. the molecular conformations, however, are different. The big differences between special torsion angles in mol A and B (cf Table 3) suggest that the rotation around C(4) - C(8) and N(10) - C(14) bonds are relatively soft parameters which may be easily influenced by the crystal or by packing forces.

Table 3. Selected torsion angles with e.s.d.'s in parentheses, showing significant different values in the two crystallographically independent molecules.

Atoms involved	Torsion angles (°)	
	Mol. A	Mol. B
C(3) - C(4) - C(8) - C(9)	60.4(7)	32.8(7)
C(3) - C(4) - C(8) - C(13)	-175.3(8)	156.2(7)
C(5) - C(4) - C(8) - C(9)	-123.3(7)	-150.5(7)
C(5) - C(4) - C(8) - C(13)	0.9(8)	-27.1(7)
C(9) - N(10) - C(14) - C(15)	-60.5(8)	-171.9(6)
C(11) - N(10) - C(14) - C(15)	177.2(9)	64.2(6)

In the crystal structure of the present hydrochloride salt each chlorine anion is a proton acceptor in two H-bonds from two different molecules, one from the phenolic oxygen and one from the N atom. The O....Cl....N angles are 102.0(2)° in mol A and 105.9(2)° in mol B. The bond distances and angles in the hydrogen bonds are listed in Table 4.

Table 4. Hydrogen bond distances (Å) and angles (°).

The e.s.d.'s, where given, are in parentheses.

Atoms involved	X - H	H...Cl	X...Cl	X - H...Cl
O(1) - H(1).....Cl(1)	1.14	1.99	3.078(4)	158.4(2)
N(10) - H(10)....Cl(1)	1.00	2.13	3.125(6)	174.6(3)
O(21) - H(21)....Cl(2)	1.09	2.02	3.066(4)	158.6(2)
N(30) - H(30)....Cl(2)	1.03	2.07	3.097(5)	172.4(2)

EXPERIMENTAL

^{1}H-NMR spectra were recorded in $CDCl_3$ (TMS as internal standard $\delta = 0$) at 200 MHz using a Jeol FX 200 instrument. Chemical shift data are reported in ppm downfield from TMS where s, d, t, m designate singlet, doublet, triplet and multiplet respectively. Mass-spectrometry was performed on an LKB 9000 instrument at 70 eV. Optical rotations were measured on a polarimeter type AA 100 (Optical activity LTD). M.p:s were taken on a Mettler FP61 apparatus. All m.p:s are uncorrected.

The elemental analysis were performed by Analytische Laboratories Elbach, West Germany.

3-(3-Methoxyphenyl)pyridine

3-Methoxyphenylmagnesium bromide, prepared from 3-bromoanisole (50.5 kg, 270 mol) and Mg (9.7 kg, 399 mol) in dry THF (61 l) under N_2, was added to a solution of 3-bromopyridine (32.5 kg, 158 mol), dichlorobis(triphenylphosphine)nickel (II) (2.1 kg, 3.2 mol), in dry THF (100 l). The reaction vessel was immersed in an ice-water bath, and the addition rate was adjusted so that the temperature could be kept below 10°C. When the addition was complete, the reaction mixture was allowed to reach room temperature and then stirred under N_2 for 24 h. The resulting mixture was poured into ice cold dilute HCl and extracted with toluene. The aqueous layer was neutralized with a saturated K_2CO_3 solution and extracted with toluene. Drying (K_2CO_3) and evaporation of the toluene afforded the product as an oil. The product was identified by TLC and GC. Yield: 29 kg (76.5%) GC purity: >91%.

3-(3-Methoxyphenyl)-N-propylpiperidine (1)

3-(3-Methoxyphenyl)pyridine (29 kg, 156 mol) and 1-bromopropane (38 kg, 309 mol) were dissolved in dry acetone (45 l) and heated at 100°C in a high pressure steel vessel. After 20 h the reaction was interrupted and the solvent was evaporated. The residual quaternary 3-(3-methoxyphenyl)-1-propyl-pyridinium bromide was hydrogenated with 5% PtO_2 on carbon (3 kg) in methanol (400 l) at room-temperature and atmospheric pressure. The hydrogen uptake ceased after 24 h.

The catalyst was filtered off and the solvent was evaporated. The residual crude hydrobromide was dissolved in water, made alkaline and extracted with toluene. The organic-phase was dried and evaporated. The crude product is a light yellow oil. The product was identified by TLC and GC. Yield: 30 kg, 83%; GC purity:
93-94%.

(-)-3-(3-Methoxyphenyl)-N-propylpiperidine (2)

To a solution of the racemic base of 3-(3-methoxyphenyl)-1-propylpiperidine (1) (25 kg; 107 mol) in aqueous ethanol (300 l; 70%) at 50°, was added a solution of (-)-Di-p-toluoyl-L-tartaric acid 1 H_2O (42.5 kg; 105 mol) in aqueous ethanol (300 l; 70%). The warm solution was allowed to cool to room-temperature, then it was seeded and left at 8-10° overnight. The isolated salt was recrystallized twice from a 10% solution in aqueous ethanol (70%). The collected salt was treated with 1-M NaOH and extracted with ether. The ether-phase was dried and evaporated. The desired compound was obtained as a colourless oil. Yield: 6.3 kg (50% of the desired enantiomer)
M.p. (HCl) 199-201°C
$[\alpha]_D^{20}$ = -6.5° (c = 2.6; CH_3OH). (Lit.[2]: m.p. 200-202°C; $[\alpha]_D^{20}$ = -6.7°).

(-)-3-(3-Hydroxyphenyl)-1-propylpiperidine (3)

(-)-3-(3-Methoxyphenyl)-1-propylpiperidine (2) (6.3 kg; 27 mol) in 48% HBr (33 l) was heated at 120°C for 4 hours under nitrogen. The mixture was cooled and evaporated. The residue was made alkaline with a saturated solution of $NaHCO_3$ in water and was extracted four times with toluene. The organic phases were collected, dried and evaporated. The residual oil was converted into the hydrochloride salt and was recrystallized once from ethanol-ether giving colourless needle-shaped crystals. Yield: 5.2 kg (75%) M.p.: 185-187°C $[\alpha]_D^{20}$ = -6.8° (c = 2.1; MeOH. (Lit.[2]: m.p. 187-188°C; $[\alpha]_D^{20}$ = -7.1°).

S(-)-3-(3-methoxyphenyl)-1-propylpiperidine (2) and
S(-)-2-[(3-methoxy-phenyl)-methyl]-1-propyl-pyrrolidine (6) ((Scheme 2)

A Grignard-reagent was prepared from 3-bromoanisole (6.33 g; 0.039 mol) and magnesium (0.79 g; 0.0328 mol) in tetrahydrofuran (25 ml). The reagent was divided in two equal parts. One part was added dropwise to a suspension of S(-)-2-chloromethyl-1-propyl-pyrrolidine hydrochloride (4) (3.2 g; 0.0162 mol) in tetrahydrofuran (16 ml) at -10°C. Cuprous iodide (0.3 g; 0.0016 mol) was added to the other part and stirring was continued at room temperature for one hour. The two parts were combined and stirring continued at room temperature for further 2 hours. The mixture was poured on ice - hydrochloric acid and washed with ether. The aqueous phase was made alkaline and extracted with ether. After drying (Na_2SO_4) and removal of the solvent in vacuo, a colourless oil was obtained. Yield: 3.1 g (82%). GC-analysis (10 m, SE-54: 175°C) indicated two products in a ratio of 82 to 18. The compounds were separated by preparative HPCL chromatography [Waters prep-PAK-500/silica; CH_2Cl_2:NH_3 4M in ethanol (100-3)]. The amines were transferred to their corresponding hydrochloride salts and characterized by NMR, MS, $[\alpha]_D^{20}$, melting points and elementary analysis.

Compound 2 (18%): NMR ($CDCl_3$) δ 0.89 (t, 3H); δ 1.50 (m, 3H); δ 1.73 (m, 2H); δ 1.95 (m, 3H); δ 2.80 (m, 1H); δ 3.0 (m, 2H); δ 3.79 (s, 3H); δ 6.77 (m, 3H); δ 7.26 (m, 1H) ppm. MS (70 eV) m/z 233 (6.2%), 204 (100%), 121 (9.1%), 70 (8%) M.p.: 200-201°C $[\alpha]_D^{25}$: -6.5°C (c = 2.1; MeOH)

Compound 6 (82%): NMR ($CDCl_3$) δ 0.93 (t, 3H); δ 1.68 (m, 6H); δ 2.12 (m, 2H); δ 2.39 (m, 2H); δ 2.81 (m, 1H); δ 3.03 (d, 1H); δ 3.20 (t, 1H); δ 3.79 (s, 3H); δ 6.75 (m, 3H); δ 7.19 (m, 1H)ppm. MS (70 eV) m/z 233 (0.14%), 204 (1%), 121 (3%), 112 (100%) 70 (22%)
M.p.: 111-111.5°C $[\alpha]_D^{25}$: -16.25° (c = 2.3; MeOH)

Elementary analysis:	C	H	N	O	Cl
Calculated	66.7	8.9	5.1	5.9	13.1
Found	66.7	8.8	5.1	6.0	13.0

(+)-3-(3-methoxyphenyl)-1-(-)-O-methyl-mandeloylpiperidine amide (9) (Scheme 3).

(+)-3-(3-methoxyphenyl)piperidine hydrochloride (7) (2 mg) was mixed with water (2 ml). CH_2Cl_2 (2 ml) and 5% NaOH (0.5 ml) under vigourious stirring. R(-)-O-Methyl-mandeloyl chloride (10 μl) (prepared from corresponding acid and thionyl chloride at 0°) was added and analysis was performed on the CH_2Cl_2-phase after 15 min. GC (50 m SE-54 cross lenked fused silica 270°. FI-detector) indicated a purity of 99.2% for compound 7 and 99.4% for compound 8.

(-)-3-(3-methoxyphenyl)-N-propylpiperidine, (-)-Di-p-toluoyl-L-tartaric acid salt (12) and (+)-3-(3-methoxyphenyl)-N-propylpiperidine, (+)-di-p-toluyl-D-tartaric acid salt (13).

The two enantiomers (7) and (8) were propylated and precipitated as salts from 70% aqueous ethanol as described earlier for compound (2). Compound (12): $[\alpha]_D^{25}$ = -100°, compound (13): $[\alpha]_D^{25}$ = +102°. (c = 1.5, ethanol).

Experimental for structure determination of (3)

Colourless, needle-shaped crystals of 3 were obtained as described above. A single crystal with approximate dimensions 0.14 x 0.10 x 0.75 mm was selected for data collection. The intensities of 2875 reflections with $\theta<65°$ were measured on a Philips PW 1100 computer-controlled diffractometer at room temperature, with graphite-monochromatized CuK_α radiation and ω-2θ scan technique. The net intensities were corrected for Lorentz and polarization effects but not for absorption ($\mu_{x\text{-ray, calc.}}$ = 21.8 cm^{-1}).

The unit cell is orthorhombic, $P2_12_12_1$ with a = 20.464(10), b = 18.367(8), c = 7.442(3) A and two molecules per asymmetric unit. The cell dimensions were refined by least-squares fitting of the preliminary cell parameters measured on the diffractometer to powder data from a Guinier photograph, taken with strictly monochromatized CuK_α radiation (λ = 1.5406 A) and using Si (a = 5.4309 A at 298 K) as an internal standard.

The structure was solved by direct method using the MULTAN 80[11] program system and refined by full matrix least-squares procedure of the SHELX[12] system. The positions of the non-hydrogen atoms were refined together with their anisotropic temperature factors. The hydrogen positions were calculated geometrically after each cycle of the refinement, except for two H atoms in each molecule (H(1) in the phenol -OH group and H(10) attached to N(10)) which were located from difference Fourier maps and kept fixed during the subsequent calculations. The refinement of the structural model against 1949 reflections, all with F = 6 σ (F) and unit weights, converged to a final R value of 0.0465. The fractional atomic parameters are listed in Table 1.

Determination of the absolute configuration of 3

The absolute configuration of (-)-3-(3-hydroxyphenyl)-N-propyl-piperidine (3) was determined by the Bijvoet method[13]. The Bijvoet ratio $X_h = 2(I_h - I_{-h})/(I_h + I_{-h})$ was calculated from observed atomic positions for each Friedel pair with $\Theta < 35°$. Fifteen Friedel pars exhibiting large Bijvoet differences and Bijvoet rations were selected for measurement. For each unique hkl, the intensities of eight symmetry related reflections were measured and the average net intensities of the four equivalent reflections for I_h and I_{-h} respectively, were used. The good agreement between calculated and observed Bijvoet ratios (cf. Table 2) confirms that the studied molecules have the absolute configuration shown in Fig. 2. The anomalous scattering factors were taken from International Tables for X-ray Crystallography[14].

Table 2. Calculated (X_c) and observed (X_o) Bijvoet ratios.

Cu K_α radiation was used.

H	K	L	X_c	X_o	Θ (°)	F_{obs} (x10)
2	1	1	8.97	9.75	7.75	893
2	1	2	-5.55	-5.25	12.97	1277
6	1	1	-7.84	-8.30	14.60	548
4	2	2	-14.28	-16.43	15.64	357
6	6	1	14.20	13.61	20.73	520
2	8	1	-20.77	-22.17	21.06	300
8	1	2	-49.38	-40.29	21.60	206
6	3	3	10.24	11.29	23.85	592
3	8	2	14.64	13.88	24.23	502
2	1	4	-19.13	-26.27	25.04	277
7	8	1	11.15	10.13	26.06	583
4	2	4	20.45	30.83	26.67	181
8	1	4	-26.42	-23.72	30.94	206
3	8	4	-19.64	-17.35	33.04	257
8	8	3	21.47	24.92	33.22	267

Table 1. Fractional atomic parameters ($x10^4$) and equivalent isotropic temperature factors ($x10^3$) for the non-hydrogen atoms and fractional atomic parameters ($x10^3$) and isotropic temperature factors ($x10^3$) for the hydrogen atoms involving in the H-bonds. (E.s.d.'s, where given, are in parentheses).

Atom	X	Y	Z	U_{eq} ($Å^2$)
Cl(1)	8451(1)	12451(1)	5107(2)	
O(1)	7701(2)	11015(2)	6146(6)	
C(2)	8021(3)	10380(3)	5692(8)	
C(3)	7712(3)	9730(3)	6113(8)	
C(4)	7988(3)	9063(3)	5653(8)	
C(5)	8594(2)	9066(3)	4774(9)	
C(6)	8904(2)	9718(3)	4409(8)	
C(7)	8628(2)	10397(3)	4867(8)	
C(8)	7657(3)	8354(3)	6196(8)	
C(9)	6974(3)	8321(3)	5350(10)	
N(10)	6621(3)	7638(3)	5914(8)	
C(11)	7004(3)	6969(3)	5380(12)	
C(12)	7669(4)	6988(3)	6215(12)	
C(13)	8043(3)	7674(3)	5731(11)	
C(14)	5949(3)	7568(4)	5075(13)	
C(15)	5528(3)	8137(4)	5525(16)	
C(16)	4811(3)	7999(5)	4839(13)	
Cl(2)	5778(1)	5556(1)	6773(2)	
O(21)	5216(2)	4097(2)	5537(9)	
C(22)	5626(3)	3533(3)	5563(9)	
C(23)	5380(3)	2839(3)	5347(9)	
C(24)	5781(3)	2229(3)	5426(7)	
C(25)	6449(3)	2343(3)	5676(9)	
C(26)	6692(3)	3036(4)	5889(10)	
C(27)	6295(3)	3639(3)	5851(9)	
C(28)	5493(2)	1464(3)	5342(8)	
C(29)	4881(3)	1436(3)	4162(8)	
N(30)	4579(2)	698(2)	4198(6)	
C(31)	5041(3)	141(3)	3470(9)	
C(32)	5666(3)	138(3)	4532(9)	
C(33)	5986(3)	892(3)	4673(9)	
C(34)	3937(3)	716(3)	3209(9)	
C(35)	3543(3)	28(3)	3376(10)	
C(36)	2079(3)	127(4)	2498(12)	
H(1)	807	1148	601	140(32)
H10	658	765	725	62(2)
H(21)	552	455	588	181(40)
H(30)	445	60	552	105(26)

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