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AN EFFICIENT AND INEXPENSIVE RESOLUTION OF THE POTENT DOPAMINERGIC SUBSTANCE 3-(3-HYDROXY PHENYL)-N-(1-PROPYL)-PIPERIDINE (±)-3-PPP

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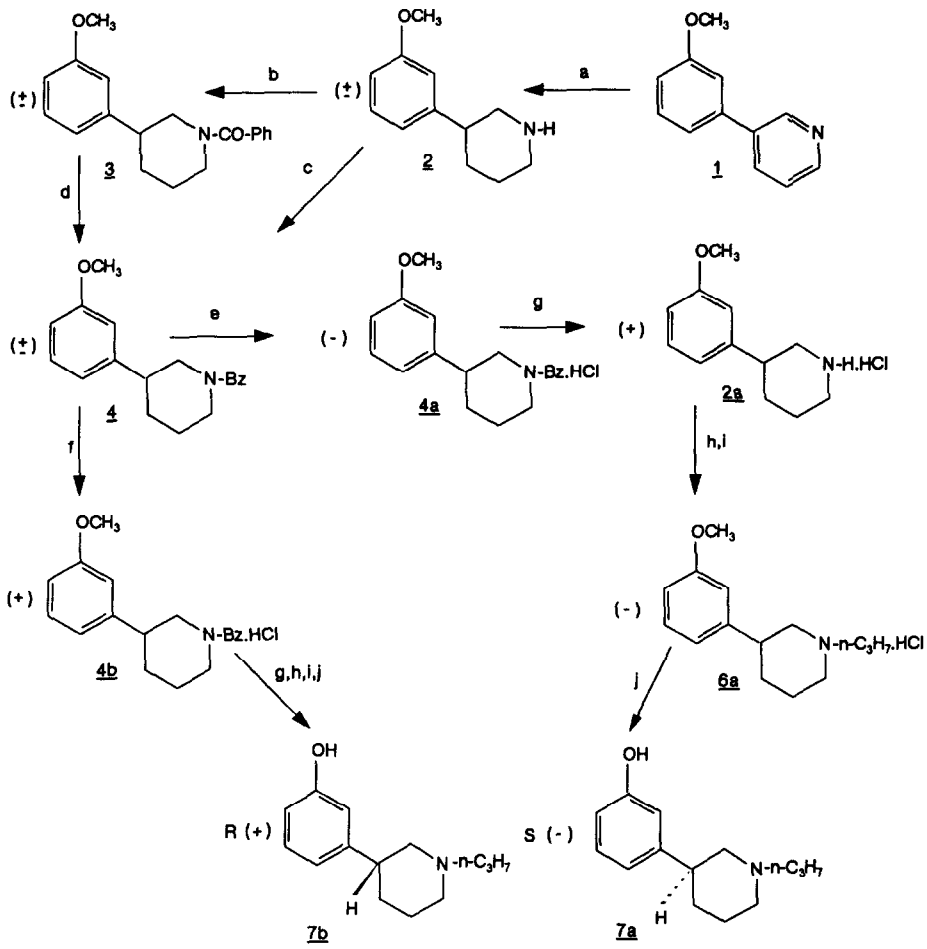
Abstract : A new convenient and inexpensive resolution of the dopaminergic agonist (±)-3-PPP is described.

3-(3-Hydroxyphenyl)-N-(1-propyl)-piperidine, (±)-3-PPP, was initially described as a potent and selective dopaminergic autoreceptor agonist [1]. Recent studies revealed that (+)-3-PPP binds also with high selectivity to sigma receptors [2], and that (-)-3-PPP in constrast to (+)-3-PPP acts as an antagonist at postsynaptic dopaminergic receptors [3]. To date three methods have been described for the preparation of the (+)-and (-)-isomers of 3-PPP.

The first calls for a tedious sequence of 8 steps (scheme I), involving the resolution of an N-benzyl derivative intermediate 4 with (+)- and (-) -dibenzoyltartaric acid [4,5]. Subsequently 4 was obtained by $LiAlH_4$ reduction of the corresponding amide 3.

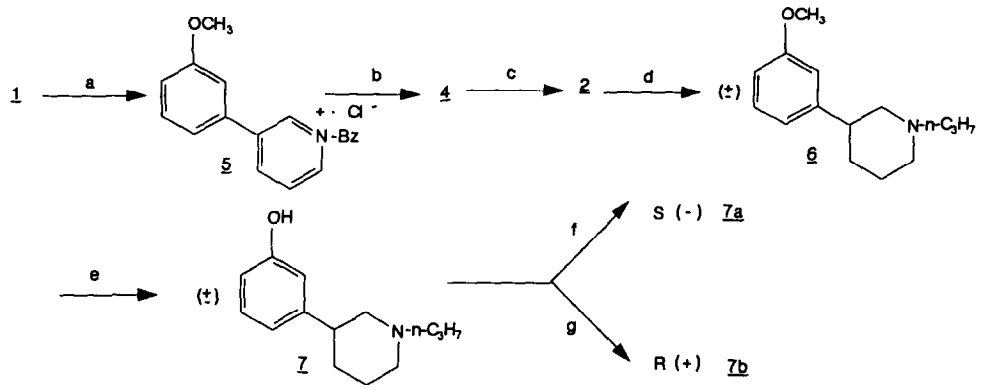
A related method published by the same group utilizes the non commercialy available (+)- and (-)-O-methylmandeloyl chloride [5] as the resolving agent, followed by a column chromatographic separation [6]. In 1983 an efficient resolution of 3-PPP using the very expensive binaphtyl phosphoric acid (BNPPA) was described [7].

Owing to the lack of a really satisfactory method amenable to large-scale preparations we investigated new routes directed toward the synthesis of (+)- and (-)-3-PPP. The results are indicated below.



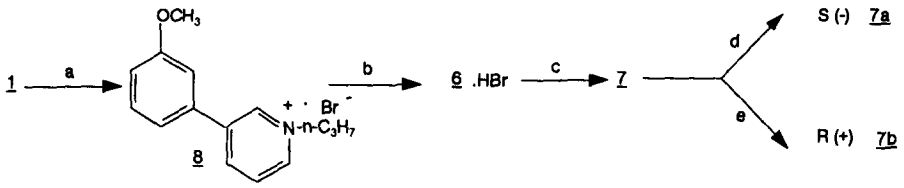
Scheme I -Reagents : (a) H_2,10% PtO_2,50 Psi,MeOH; (b) PhCOCl; (c) benzyl chloride; (d) $LiAlH_4$; (f) (+)-dibenzoyl-D-tartaric acid,MeOH; (f) (-)-dibenzoyl-L-tartaric acid,MeOH; (g) H_2,Pd(C); (h) CH_3CH_2COCl; (i) $LiAlH_4$; (i) 48% aq HBr.

Our first attempts utilized a careful catalytic reduction of the N-benzyl salt 5 (scheme II) with 5 % PtO_2 (RT, 1 atm.) and afforded in 90 % yield the N-benzyl derivative. It is notheworthy that under the same experimental conditions when 10 % Pd/C was used as the catalyst the starting material was obtained in a nearly quantitative yield [8]. This reduction of an ammonium salt proved to be superior to the $LiAlH_4$ reduction of the N-benzoyl amide 3 as described in ref. 4 and avoids some sluggishness encountered during the reductions of the pyridine nucleus [9]. The N-benzyl derivative 4 was deprotected (10 % of Pd/C, 1 atm.) and the resulting amine 2 was alkylated (75 %) with propionic acid/$NaBH_4$ [10]. Attempted resolutions of 6 using various agents were all unsuccessful. However the demethylation of 6 (48 % HBr, reflux), gave the less soluble derivative 7 which was resolved using (+)- and (-)-dibenzoyltartaric acid.



Scheme II -Reagents : (a) benzyl choride,dry $CH_3COC_2H_5$,reflux; (b)H_2,5% PtO_2,1 atm,MeOH; (c) H_2,Pd/C,EtOH; (d) C_2H_5COOH,$NaBH_4$,dry toluene; (e) 48% aqueous HBr,reflux; (f) (-)-dibenzoyl-L-tartaric acid monohydrate, EtOH 95%; (g) (+)-dibenzoyl-D-tartaric acid,EtOH 95%.

In order to shorten further the preparation of (+)- and (-)-3-PPP we then envisaged to carry out the separation on the N-propyl derivative 6 (scheme III) which was easily obtained by catalytic reduction of 8 with PtO_2. Alternatively 6 can be prepared by $NaBH_4$ reduction of 8 followed by catalytic reduction using the less expensive Pd/C. The resolution was indeed achieved by heating an alcoholic solution of the final racemic 7 with (-)-dibenzoyltartaric acid. From the mother liquors the (+)-isomer was obtained by treatment with (+)-dibenzoyltartaric acid.



Scheme III -Reagents : (a) C_3H_7Br,dry acetone,reflux; (b) H_2,5% PtO_2,1 atm,MeOH; (c) 48% aqueous HBr,reflux; (d) (-)-dibenzoyl-L-tartaric acid monohydrate,EtOH 95%; (e) (+)-dibenzoyl-D-tartaric acid, EtOH 95%

In conclusion, we have been able to prepare in good yields (37 % overall yield from 1) and high optical purity (ee > 99%) the (+)- and (-)-enantiomers of 3-PPP. The method is new, rapid (four steps) and inexpensive. Furthermore because $LiAlH_4$ reduction of the benzamide derivative precursor (step d, scheme 1) can be avoided quantities up to 100 g of each enantiomer can be prepared routinely in one batch.

Resolution of : 3-PPP

a) (-)-3PPP : A solution of (-)-dibenzoyl-L-tartaric acid monohydrate (17.18g, 0.045 mol) in hot 95% ethanol (60 ml) was added to a stirred solution of 3-PPP (10 g, 0.045 mol) in hot 95% ethanol (30 ml). After stirring at ambient temperature, the resulting salt was separated by filtration and recrystallized from absolute ethanol. The collected salt was treated with 10% Na_2CO_3 and the free amine was extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4) and the solvent was evaporated.The residual amine was then passed through a short column of silica gel 60 (70-230 Mesh ASTM) with EtOAc as eluent.4.1g of (-) -3-PPP was obtained and then converted to the hydrochloride. One recrystallization from ethanol-ether afforded (-) -3-PPP, HCl as white crystals, mp = 187-188°C, $[\alpha]_D^{20}$ = -7.4 (C = 2.2, MeOH) lit[5].mp = 187-188°C $[\alpha]_D^{22}$ = -7.1 (C = 2.2, MeOH).

b) (+) -3-PPP : The mother liquor from the above separation of (-) -3-PPP was treated with 10 % Na_2CO_3 and EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. The residue was treated with (+)-dibenzoyl -D-tartaric acid in hot 95 % ethanol. After recrystallization from ethanol, recovery of the base and filtration on silica gel, 4 g of (+) -3-PPP was obtained. 3-PPP, HCl was crystallized hydrochloride to give white crystals, mp = 187-188°C $[\alpha]_D^{20}$ = +7.4 C = 2.2, MeOH) lit[5] mp = 187-188°C, $[\alpha]_D^{22}$ = +7.1 (C = 2.1, MeOH).

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