

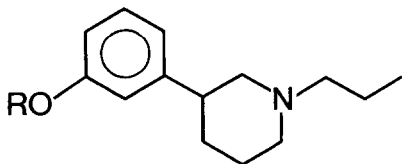
AN EFFICIENT RESOLUTION OF 3-PPP AND ASSIGNMENT OF THE ABSOLUTE CONFIGURATION.

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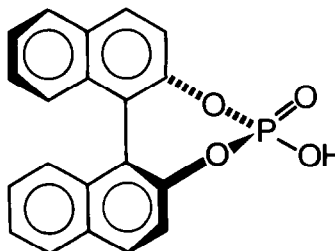
Abstract: (+)-3-PPP has been resolved by means of (+)- and (-)-2,2'-(1,1'-binaphthyl)phosphoric acid (BNPPA) in high optical purity; (+)-3-PPP has been assigned the R configuration on the basis of a single crystal X-ray analysis.

3-(3-Hydroxyphenyl)-N-n-propylpiperidine (+)-3-PPP has been claimed to be the first apparently selective dopaminergic autoreceptor agonist reported (1). In order to understand the mechanism of action of 3-PPP at the molecular level, the resolution of the racemic compound seems essential. Since the only resolution method so far reported appears to be rather laborious (2), we investigated a direct separation of the enantiomers of 3-PPP.



R=H :3-PPP

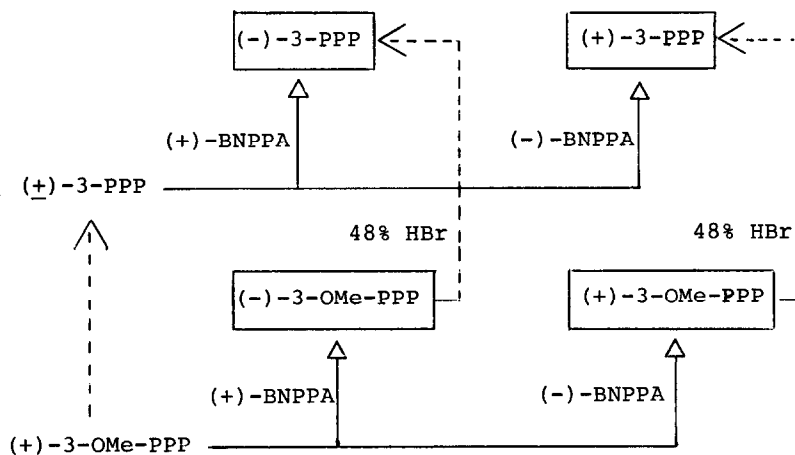
R=Me:3-OMe-PPP



(+)-(S)-BNPPA

This goal has been achieved efficiently by the use of both atropisomeric 2,2'-(1,1'-binaphthyl)-phosphoric acids BNPPA (3) as the resolving agents (see scheme - upper half). Thus, by means of (+)-BNPPA the separation of (-)-3-PPP was effected first, while subsequently (+)-3-PPP was separated from the mother liquor by (-)-BNPPA or vice versa.

Scheme



Resolution of 3-PPP

a) **(-)-3-PPP**: A solution of 1.0 equivalent of (+)-3-PPP (4) in methanol (1.0 molar) was treated with 0.7 equivalents of (+)-BNPPA ($[\alpha]_D^{20} = +607^\circ$, $c=1$ in MeOH) in methanol/methylene chloride = 9:1 (0.1 molar). On evaporating the mixture to half of its volume, a white crystallizate precipitated which, after standing overnight at 4°C , was filtered and washed with two portions of cold methanol/ethyl acetate = 1:1. The collected crystals were recrystallized from hot methanol and after standing overnight at 4°C filtered and washed. From this salt, the base of (-)-3-PPP was extracted into the organic phase on partitioning between ethyl acetate and aqueous ammonia. The ethyl acetate extract, after drying and evaporating, was dissolved in ethyl acetate and filtered over a short column of silica gel (0.063-0.2 mm); 72.5% of (-)-3-PPP were obtained as a light yellow oil, which was crystallized as the hydrochloride from ethanol/diethyl ether; (-)-3-PPP·HCl, white crystals, m.p. $185-186^\circ\text{C}$, $[\alpha]_D^{20} = -7.4^\circ$ ($c=2.2$ in MeOH).

b) **(+)-3-PPP**: The mother liquor from the above described separation of (-)-3-PPP was partitioned between ethyl acetate and aqueous ammonia and the organic phase dried over magnesium sulfate and evaporated. This residue was treated with (-)-BNPPA ($[\alpha]_D^{20} = -608^\circ$, $c=1$ in MeOH) to yield after recrystallization, recovery of the base and filtration on silica gel 75% of (+)-3-PPP which was crystallized as the hydrochloride; (+)-3-PPP·HCl, white crystals, m.p. $184-185^\circ\text{C}$, $[\alpha]_D^{20} = +7.4^\circ$ ($c=2.2$ in MeOH).

In order to estimate the optical purity of the enantiomers, the following 270 MHz- ^1H -NMR studies were performed: 0.06 and 0.09 molar solutions of (-)-3-PPP and (+)-3-PPP in CDCl_3 each displayed identical spectra with a sharp triplet ($J=7.4$ Hz) at 0.870 and 0.869 ppm which is assigned to the terminal (N-propyl)Me. Interestingly, in the spectrum of a 0.1 molar solution in CDCl_3 of a mixture

of (-)-3-PPP and (+)-3-PPP in the ratio of 2:1, two sets of triplets ($J=7.4$ Hz) for these Me protons were observed in the ratio of 2:1 at 0.850 and 0.836 ppm. Evidently, the environment of the molecules of one enantiomer is of a diastereomeric nature with respect to the molecules of the other enantiomer. Such an effect has already been reported, see e.g. (5), as an exception to the rule that normally the $^1\text{H-NMR}$ spectra of the enantiomers and mixtures thereof are identical when performed in an achiral solvent under the same operating conditions.

As a direct application of this observation, the approximate determination of the optical purity of the enantiomers was possible. Since a 98:2 mixture of (-)-3-PPP and (+)-3-PPP again displayed two sets of signals in the ratio of 98:2 for the terminal (N-propyl)Me, the enantiomeric excess of the above obtained (+)- and (-)-3-PPP was estimated to exceed 96% ee.

In addition to the above described resolution of (+)-3-PPP, also the synthetic precursor (+)-3-OMe-PPP (see scheme - lower half) was successfully separated into its enantiomers. Thus, (-)-3-OMe-PPP was obtained from the salt formation with (+)-BNPPA and (+)-3-OMe-PPP with (-)-BNPPA. Both OMe-enantiomers were individually cleaved by 48% HBr to yield (-)-3-PPP and (+)-3-PPP, respectively (identified as the hydrochloride: m.p. 185-186°C, $[\alpha]_D^{20} = -7.4^\circ$ and $+7.4^\circ$ ($c=1$ in MeOH)).

The hydrobromide salt of (+)-3-OMe-PPP m.p. 189-191°C, $[\alpha]_D^{20} = +5.6^\circ$ ($c=1$ in MeOH), proved most suitable for an X-ray analysis. The white crystals have the space group $P2_1$ with $a=7.331(2)$, $b=8.442(2)$, $c=13.068(3)$, $A=101.80(2)$, $Z=2$. Intensities with $\theta < 28^\circ$ were measured at 183°K by the ω -scan technique on a Nicolet R3m diffractometer using Mo-K radiation from a graphite monochromator and were corrected for absorption ($\mu=2560 \text{ m}^{-1}$) by an improved Busing-Levy (6) method. The structure was solved by direct and heavy atom methods and 1579 data with $I > 2.50 \sigma(I)$ were used to refine the non-hydrogen atoms anisotropically by least squares to convergence at $R(\sum|\Delta|/\sum|F_o|)$ values of 0.0334 and 0.0395 for R(+) and S(-) isomers. The corresponding R^G ($\sqrt{(\sum w\Delta^2/\sum w|F_o|^2)}$) figures are 0.0447 and 0.0526; application of the Hamilton test (7) leads to the assignment of the R-configuration to the (+)-3-OMe-PPP isomer. This is illustrated in an Ortep drawing in the Figure. Hydrogen atom positions were calculated at the start of each new least-squares run and all computations were done with the SHELXTL program system (8).

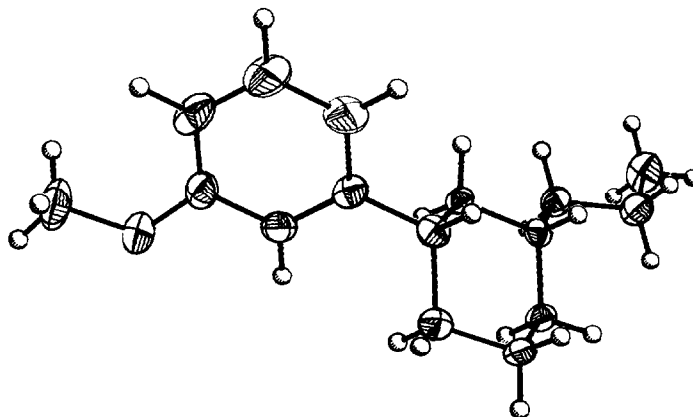


Figure: ORTEP drawing of (+)-3-OMe-PPP.HBr

References and Footnotes

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