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SYNTHESIS OF RIGID DOPAMINE CONGENERS: CIS AND TRANS 2-(p-METHOXYPHENYL)-3-METHYLMORPHOLINE

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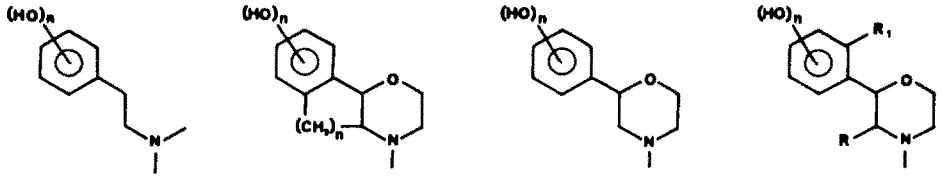
ABSTRACT - A synthetic pathway is reported for the preparation of cis and trans forms of 2-(p-methoxyphenyl)-3-methyl-morpholine from the same key-compound, the p-methoxy- -(N,N'-dibenzylamino)-propiophenone, through stereospecific reduction processes.

It is known that since dopamine (A) can assume different conformations, it can also interact with different specific receptors.

In these last few years it has become a matter of great interest to study dopamine analogs where the fundamental skeleton is incorporated in a much more complex structure, in order to more (- less limit conformational freedom[1].



(A) (B) (C) (D)

For this purpose particularly rigid molecules such as tricyclic compounds of type (B)[2-4] or structures having more conformational freedom such as 2-phenylmorpholine (C)[5,6] have been considered. In the latter case both the conformational variations of the morpholine ring and the free rotation of the benzene ring enables the molecule to assume different three-dimensional forms having comparable energies. Together with other authors, we have been interested previously in the derivatives of 2-phenylmorpholine and we have reported the synthesis of tricyclic analogs of dopamine such as indeno- and naphtho-oxazine derivatives[3].

Pharmacological studies carried out[2] on some derivatives of naphthoxazine have shown that these compounds are highly active as D_2 agonists and also remarkably stereoselective towards this receptor.

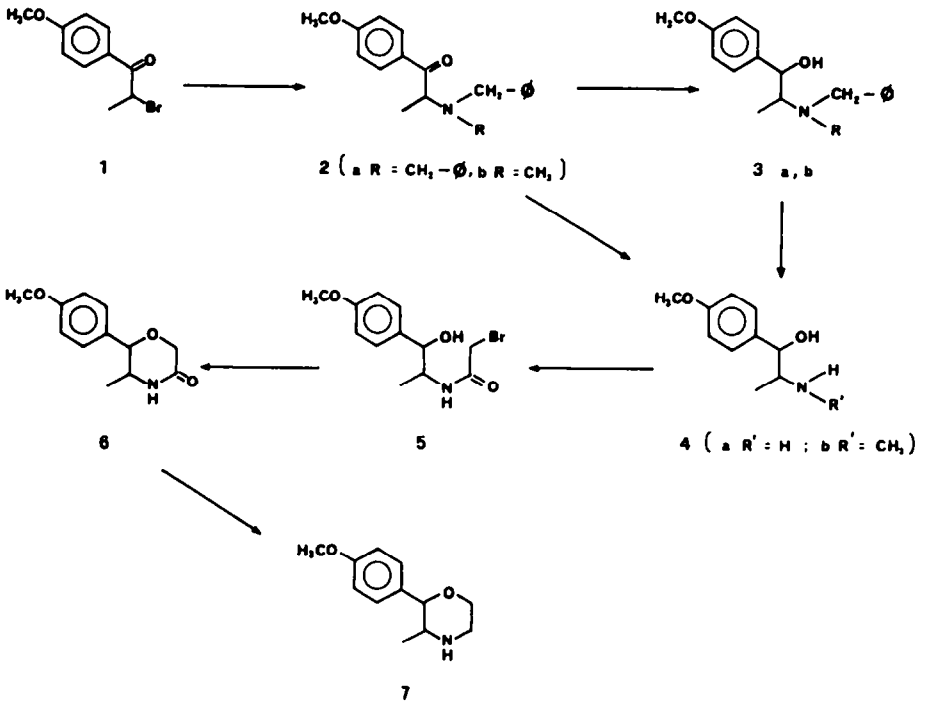
An intermediate rigidity between the tricyclic derivatives (B) and phenylmorpholine (C) can be realized by introducing suitable substituents on the benzene and/or morpholine rings in order to obtain different conformers according to the steric hindrance and the electrostatic interactions that the substituent generates. Furthermore the presence of the R substituent in position 3 of the morpholine nucleus gives cis-trans geometrical isomers in which the R group itself can assume an axial or equatorial position.

Studies of the structure-activity relationships of these derivatives allow us to investigate the role played by the interactions that the molecule may establish in regions adjacent to the dopamine receptor.

In this present paper a synthetic method is reported that allows us to obtain both the cis and trans derivatives of 2-phenyl-3-methylmorpholine in good yields, using the same intermediate

product as starting material. In this particular case the p-methoxy- -(N,N-dibenzylamino)propiophenone 2a has been used as the key-compound and the synthesis of the cis and trans derivatives of 2-(p-methoxyphenyl)-3-methylmorpholine has been achieved.

The reduction of N,N-disubstituted -amino-propiophenones can give both of the stereoisomeric alcohols according to the nature of the substituent on the nitrogen, the technique and the reducing agent in a stereospecific way.[7,8]



So, starting from the above-mentioned intermediate, which had been obtained by reacting N,N-dibenzylamine with -bromoketone (1), we have obtained both erythro and threo 1-(p-methoxyphenyl)-2-amino-1-propanol 4a. The catalytic hydrogenation on palladium caused the simultaneous reduction of the keto group and the elimination of the two benzylic groups with the formation of the erythro aminoalcohol in almost quantitative yields and without the threo isomer. The latter has been obtained, always with good yields, through two successive reductions. The first, carried out with lithium aluminium hydride, gave the N,N-dibenzylamino alcohol 3 and the second, by means of catalytic hydrogenation, removed the two benzylic groups.

A similar stereospecificity has been observed for reduction of the p-methoxy- -(N-methyl-N-benzylamino)-propiophenone 2b which was prepared by reacting 1 with N-methylbenzylamine. In this case we have obtained, always in very high yields, the two threo and erythro forms of the 1-(p-methoxyphenyl)-2-(N-methylamino)-1-propanol 4b. The stereochemistry of the aminoalcohols which have been synthesized, has been evidenced by ^{1}H NMR analysis and the experimental data obtained were in agreement with the data reported in literature for similar compounds.[7,9]

In fact, on going from the threo to the erythro isomer, we have noted, for the proton on the carbon atom bearing the alcoholic function, a chemical shift of 0.5-0.6 p.p.m. to lower fields

and that the coupling constant too decreases from 9 to 3 c.p.s. .

The threo and the erythro aminoalcohols were then cyclized by a known method[10] through the N-(-bromoacetyl)-derivatives into morpholones which, by reduction with $LiAlH_4$, gave the trans and cis morpholines respectively. The cis and trans isomerism of these cyclic compounds is confirmed by the NMR data since they show the same variation of the chemical shift and coupling constant as the corresponding open-chain compounds. This means that the configuration of chiral centers does not vary during cyclization.

On the basis of this synthetic pathway, the preparation of other analogous rigid congeners of dopamine is in progress.

EXPERIMENTAL

All melting points were determined in open capillaries using a Büchi-Tottoli apparatus and are uncorrected. Microanalyses were performed with a Hewlett-Packard 185 CHN analyzer and are within 0.4 % of the calculated values. The ^{1}H-NMR spectra were recorded with Varian EM 390 and XL 200 instruments at 90 and 200 MHz respectively, using TMS as internal standard (chemical shifts are expressed in).

p-Methoxy- -(N,N-dibenzylamino)-propiophenone (2a)

p-Methoxy- -bromopropiophenone 1, prepared according to the reported method[11] (0.04 moles) was reacted with dibenzylamine (0.08 moles) and KI (0.0018 moles) in acetone (500 ml) under stirring at room temperature for 3 days. After filtration the solvent was evaporated under vacuum. The residue was purified by crystallization from MeOH and the compound with m.p. 77-8° in 70 % yield was obtained; NMR ($CDCl_3$):7.23(s,10H,N-CH_2-C_6H_5), 6.7-7.7(double d,4H,aromatic H), 4.3(q,1H,CH), 3.8(s, 3H,OCH_3), 3.6(q,4H,N-CH_2), 1.3(d,3H,CH_3).

p-Methoxy- -(N-methyl benzylamino)-propiophenone (2b)

It was obtained as described before, using methyl-benzylamine; m.p. 62-3°.
NMR($CDCl_3$):8.1-6.8(double d,4H,aromatic), 7.25(s,5H,N-CH_2-C_6H_5), 4.2(q,1H,CH), 3.83(s,3H,OCH_3), 3.80(s,2H,CH_2), 2.2(s,3H,N-CH_3), 1.25(d,3H,CH_3).

Erythro 1-(p-methoxyphenyl)-2-amino-1-propanol HCl (**erythro** 4a)

Compound 2a (0.07 moles) dissolved in EtOH(600 ml) containing HCl conc.(4.9 ml) was hydrogenated at 1 Atm pressure using 10 % Pd/C (4.9g). After filtration through celite and evaporation of the solvent, the compound was obtained in 96 % yield: m.p. 221-2°(crystals from EtOH-Et_2O).
NMR($DMSO-d_6$):7.4-6.8(double d,4H,aromatic), 4.95(d,J=3cps,1H,CH-OH), 3.75(s,3H,OCH_3), 3.5-3.2(m, 1H,CH-NH_2), 0.95(d,3H,CH_3).

Erythro 1-(p-methoxyphenyl)-2-(N-methylamino)-1-propanol HCl (**erythro** 4b)

In the same manner compound 2b was hydrogenated to obtain erythro 4b: m.p. 219-220°(crystals from EtOH).
NMR(DMSO-d_6):7.4-6.8(double d,4H,aromatic), 5.15(d,J=3cps,1H,CH-OH), 3.75(s,3H,OCH_3), 3.4-3.1(m, 1H,CH-NH), 2.6(s,3H,CH_3-N), 0.95 (d,3H,CH_3).

Threo 1-(p-methoxyphenyl)-2-(N,N-dibenzylamino)-1-propanol (**threo** 3a)

Compound 2a (0.041 moles) in dry ether(150 ml) was added to $LiAlH_4$(3g) suspended in dry ether(400 ml) and the mixture was refluxed for 1h. After the usual working-up threo 3a was obtained in 94 % yield: m.p. 142-6°.
NMR($CDCl_3$):7.3(s,10H,N-CH_2-C_6H_5), 7.1-6.7(double d,4H,aromatic), 4.3(d,J=9cps,1H,CH-OH), 3.7(s, 3H,OCH_3), 4.0-3.2(double d,4H,CH_2), 2.9-2.6(m,1H,CH-N), 0.8(d,3H,CH_3).

Threo 1-(p-methoxyphenyl)-2-(N-methylbenzylamino)-1-propanol (**threo** 3b)

In the same manner compound 2b gave threo 3b: m.p. 96-7°.
NMR($CDCl_3$):7.3(s,5H,N-CH_2-C_6H_5), 7.3-6.7(double d,4H,aromatic), 4.25(d,J=9cps,1H,CH-OH), 3.75(s, 3H,OCH_3), 3.8-3.3(double d,2H,CH_2), 2.9-2.5(m,1H,CH-N), 0.8(d,3H,CH_3).

Threo 1-(p-methoxyphenyl)-2-amino-1-propanol HCl (**threo** 4a)

Compound threo 3a (0.038 moles) in EtOH(360 ml)-HCl conc. (2.6 ml) was hydrogenated at 1 Atm pressure using 10 % Pd/C (2.6 g). After filtration and evaporation of the solvent threo 4a was obtained in 93 % yield: m.p. 234-6°.

NMR(DMSO-d_6):7.4-6.8(double d,4H,aromatic),4.45(d,J=9cps,1H,CH-OH), 3.75(s,3H,OCH_3),3.4-3.0(m, 1H,CH-NH_2), 0.95(d,3H,CH_3).

Threo 1-(p-methoxyphenyl)-2-(N-methylamino)-1-propanol (**threo** 4b)

In the same manner compound threo 3b was transformed in compound threo 4b HCl. The salt was then dissolved in NaOH dil. and the free base extracted with CH_2Cl_2. After crystallization from CH_2Cl_2-petr.ether threo 4b was obtained: m.p. 111-5°.
NMR on the HCl salt(DMSO-d_6): 7.5-6.8(double d,4H,aromatic), 4.55(d,J=9cps,1H,CH-OH), 3.75(s,3H, OCH_3), 3.6-3.1(m,1H,CH-N), 2.55(s,3H,CH_3-N); 0.95(d,3H,CH_3).

Cis 2-(p-methoxyphenyl)-3-methyl-5-morpholinone (**cis** 6)

Compound erythro 4a (0.108 moles) in CH_2Cl_2(820 ml) was added to NaOH(0.258 moles) dissolved in the smallest quantity of water. To this mixture bromoacetyl chloride(0.141 moles) in a little CH_2Cl_2 was added slowly under stirring at 0°C and the stirring was continued for 4 h. After separation of the layers, the organic solution was washed with dilute HCl and H_2O. Evaporation of the solvent gave the intermediate erythro 5 which was used without purification. KOH(7.3 g) in EtOH (300 ml) was added dropwise to this compound dissolved in EtOH (950 ml). After 24h of stirring, the mixture was poored into water, extracted with CH_2Cl_2 and washed with H_2O. Evaporation of the solvent gave cis 6 in 55 % yield: m.p. 139-40°(crystals from CH_2Cl_2 -petr.ether).
NMR($CDCl_3$):7.85(broad,1H,NH), 7.4-6.8(double d,4H,aromatic), 4.85(d,J=3cps,1H,CH-OH), 4.35(s,2H, CH_2), 3.80(s,3H,OCH_3), 3.9-3.5(m,1H,CH-N), 0.95(d,3H,CH_3).

Trans 2-(p-methoxyphenyl)-3-methyl-5-morpholinone (**trans** 6)

As described above, starting from threo 4a(0.085 moles), trans 6 was obtained (51 %): m.p. 176-7°(crystals from CH_2Cl_2-petr.ether).
NMR($CDCl_3$): 7.45(broad,1H,NH), 7.4-6.8(double d,4H,aromatic), 4.3(d,2H,CH_2), 4.10(d,J=9cps,1H, CH-OH), 3.8(s,3H,OCH_3), 3.8-3.5(m,1H, CH-N), 1.0(d,3H,CH_3).

Cis 2-(p-methoxyphenyl)-3-methylmorpholine HCl (**cis** 7)

Cis 6(0.06 moles) in dry THF(200 ml) was added dropwise to a suspension of $LiAlH_4$(2.3 g) in dry THF(150 ml). The mixture was refluxed overnight and then worked-up in the usual way. The obtained residue was dissolved in dry ether and treated with dry HCl. The precipitate salt was purified by crystallization from MeOH-Et_2O: m.p. 81-4°.
NMR on the free base($CDCl_3$): 7.30-6.75(double d,4H,aromatic), 4.62(d,J=3cps,1H,CH-O), 3.80(s,3H, OCH_3), 0.95(d,3H,CH_3).

Trans 2-(p-methoxyphenyl)-3-methylmorpholine HCl (**trans** 7)

Trans 6 was treated as described for the cis isomer. Trans 7 HCl was obtained:m.p.190-3°C.
NMR on the free base($CDCl_3$): 7.40-6.70(double d,4H,aromatic), 3.85 (d,J=9cps,1H,CHO), 3.75(s,3H, OCH_3), 2.85(m,4H,CH_2), 0.80(d,3H,CH_3).

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