Pergamon

Tetrahedron Vol. 50, No. 35, pp. 10477-10482, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00621-0

An Approach to 1-Alkyl-3-phenylpiperidine Derivatives Containing 2,5-Functionalized Groups: 1-Methyl-2-(4-chlorophenylthiomethyl)-5-(methoxycarbonyl)-piperidine.

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Abstract: Compound 6 was synthesized by regiospecific addition of 4-chlorothiophenol to diazoketone 5 in the presence of a rhodium (II) acetate catalyst. An annelation process presumably proceeded via initial attack of methylamine on the bromoacrylic ester to give the methyl α-(methylamino)methylacrylate. Reaction with ketone 6 then leads to intermediate acrylicenamine formation followed by cyclization to the unsaturated piperidine ring. Reduction of this cyclic enamine with sodiumcyanoborohydride in the presence of carboxylic acid produced the piperidine derivative 1-methyl-2-(4-chlorophenylthiomethyl)-5-methoxycarbonyl-piperidine.

The potency of the ergoline type dopamine agonists can be enhanced by certain substituents in the D-ring. It seems that this is the case with the pergolide 1 which carries the n-propyl and the (methylmercapto)methyl group in the 6 and 8 positions respectively.[1]

Indeed, pergolide, which is a conformationally constrained ligand,[2] is known to have strong affinity for both D_2 and 5-HT_{1A} receptors.

The 3-(3-hydroxyphenyl)-N-n-propylpiperidine 2, (±)-3-PPP, as can be seen, has an overlap with parts of the pergolide ring system. This compound is also a centrally acting dopamine receptor agonist with selectivity for dopamine autoreceptors.[3] It offers a potential alternative to the post-synaptic dopamine D_2antagonists, commonly used in the pharmacotherapy of schizophrenia.[4]

The enantiomer (-)-3-PPP is now undergoing clinical trials.

Whereas the pergolide is a conformationally rigid ligand, except for side-chain motions, the 3-PPP is a conformationally flexible molecule. Thus, it is possible to have low rotational barriers between the aromatic ring, and the piperidine ring, enabling it to adapt various rotameric forms of stable energy-minima for

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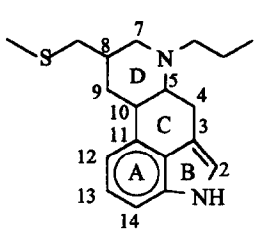
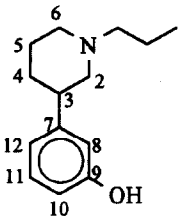
phenyl rotation. Due to the occurrence of these different conformers, there may be opposing pharmacological



1



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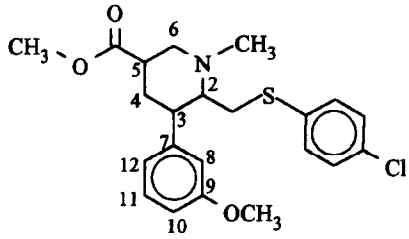


9(a,b,c)

Scheme 1

action within the same molecule.

In order that the pharmacological properties of rigid analogues of the various 3-PPP conformers can be addressed, a molecule possessing the structural features of compound 9 might be desirable.

Compound 9 presents the following characteristics.

(1) It possesses the ring system of 3-PPP.

(2) The two carbon atoms located between the N-atom and the aromatic ring, that is the C-2 and C-3, are both chiral centres, as are the corresponding C-5 and C-10 of pergolide, whereas in 3-PPP only one chiral center exists, and that is located on the carbon β to the nitrogen.

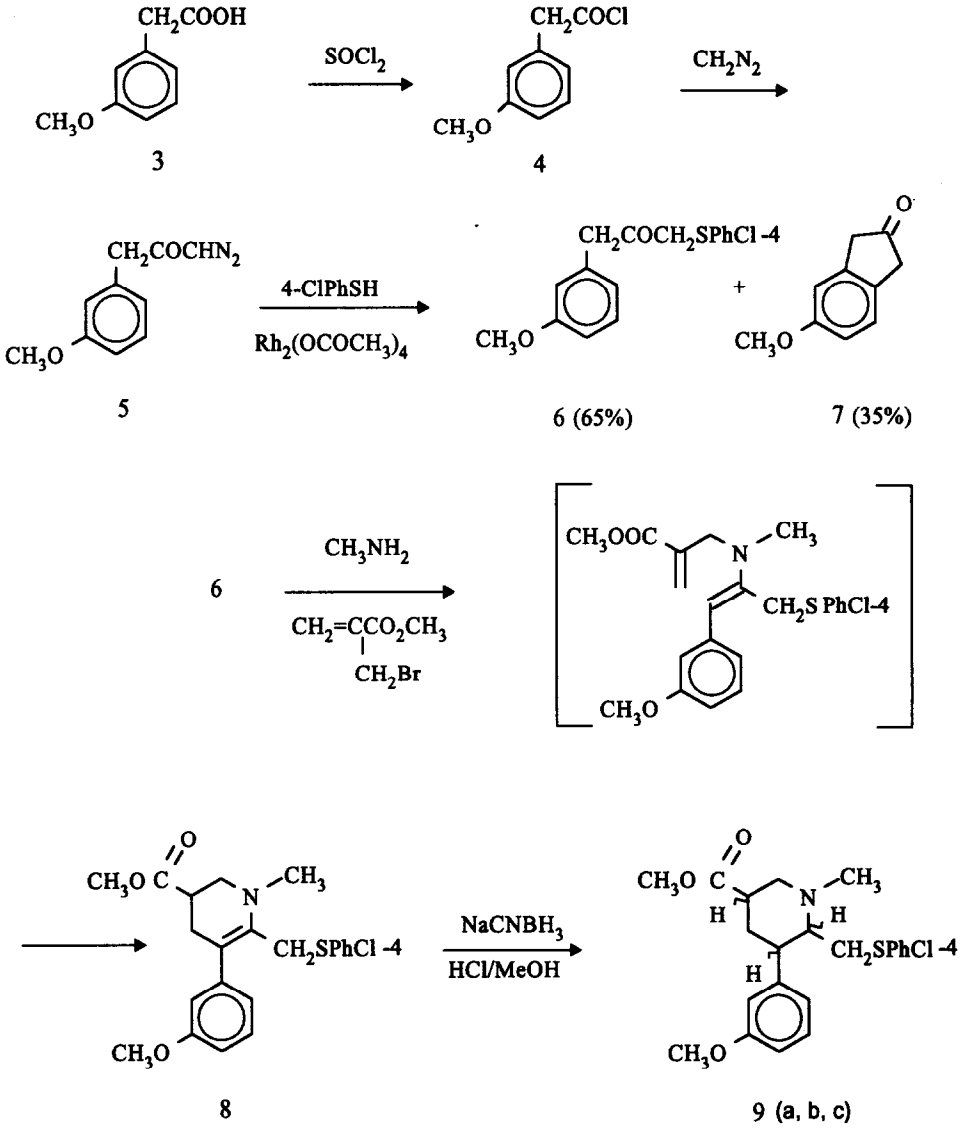
(3) The functional groups 4-Cl-$C_6H_4SCH_2$-and CH_3OOC- are located on the 2 and 5 carbons, respectively, of the piperidine ring of compound 9, and these carbon atoms are the corresponding 5 and 8 respectively of the D-ring of Pergolide. Both groups are exposed to chemical operations enabling desirable functionalities to be introduced regiospecifically, as it would be a CH_3SCH_2-group at position-5 of the piperidine ring of compound 9.

(4) It also carries the corresponding carbon-4 of the C-ring of Pergolide which further fulfils the requirements for an intriguing overlap with most parts of the structure of pergolide.

(5) The bulky group 4-Cl-$C_6H_4SCH_2$- at position-2 hinders rotation about the bond between the phenyl and piperidine rings. Thus different low energy conformers could be recognized and their pharmacological evaluation could be pursued.

For the synthesis of 2,3,5-trisubstituted N-alkylpiperidines the sequence of reactions shown in the scheme 2 was followed. The chloride 4 was prepared as a light pink liquid by a classical method, that is by treatment of the commercially available 3-methoxybenzeneacetic acid with thionyl chloride. Treatment of this chloride with a large excess of an ethereal solution of diazomethane yielded the diazoketone 5 as a yellow syrup, the structure of which was confirmed by its spectroscopic properties[5] (proton and carbon-13 NMR, IR). Addition of this diazoketone to a benzene solution of 4-chlorothiophenol in the presence of rhodium(II) acetate catalyst[6] at room temperature offered regiospecifically the ketone 6 as pale yellow syrup in 65% yield, along with the known 5-methoxy-2-indanone[5] 7 as a byproduct in 35% yield after separation by column chromatography. Ketone 6 was characterized by proton and carbon-13 nuclear magnetic resonance and infrared spectroscopy.

All other efforts to prepare the ketone 6, were unsuccessful as the following experiments indicate. Initially we investigated the reaction of the acyl chloride 4 with either [(4-chlorophenylthio)methyl]-trimethylsilane[7] or [chloro(4-chlorophenylthio)methyl]trimethylsilane[8] in the presence of fluoride ion as a



Scheme 2

catalyst (TBAF,CsF). Unfortunately, despite considerable efforts using a variety of reaction conditions we were unable to detect the formation of the desired product. Another attempt was made by reacting the N,N-diethyl-3-methoxyphenylacetamide [^{1}H-NMR ($CDCl_3$) δ=7.11(t, 1H), 6.73(d, 1H), 6.72(s, 1H), 6.67(d, 1H), 3.67(s, 3H, OCH_3), 3.56(s, 2H, $PhCH_2$-), 3.26(q, 2H), 3.18(q, 2H), 1.00(m,6H)], with the 4-chlorophenylsulfinyl carbanion lithium salt at -5 °C, but, in our hands, met with failure. We have not investigated this reaction further. Presumably the above failures may be attributed to the acidic character of the benzylic protons that make the resulting anion inert to further attack.

Having achieved the synthesis of ketone 6, we proceeded to the construction of the piperidine ring via enamine formation. An enamine function produced from this ketone can be stabilized by conjugation either with the adjacent 3- methoxyphenylgroup or with the 4-chlorophenylthio one. It seems, from the experimental results, that the predominant enamine is the one which is stabilized with the 3-methoxyphenyl substituent. Thus, dry methylamine was mixed with methyl α-(bromomethyl)acrylate in benzene solution, allowing enough time (three hours) to ensure complete formation of presumably the methyl-α-(N-methylamino)methyl]acrylate.[9] The subsequent addition of ketone 6 and refluxing the reaction mixture under Dean-Stark conditions led to intermediate enamine formation (scheme 2) which was followed by cyclisation to the piperidine ring. The piperidine derivative 8 (a cyclic enamine) thus formed, was purified by chromatography to give the product as a pale yellow oil in 56% yield. The proton and carbon-13 NMR spectra were consistent with the structure proposed. Reduction of enamine 8 in THF solution in the presence of acetic acid with sodium cyanoborohydride gave a mixture of three products. When reduction of enamines (via imonium ions) are carried out with alkali metal hydrides trans products are predominantly obtained. Consequently reduction of cyclic enamines are only reasonably stereoselective, with the preferred approach being from the less hindered side (equatorial attack) to give the axial product.[10] Assuming the above mixture to consist of diastereomers, separation was pursued by chromatography on silica gel with toluene/AcOEt (gradient) to give the three products in the ratio 1:2:3. In addition, high resolution mass spectrometry and carbon-13 and proton NMR spectra (relative ratios of hydrogens) indicated that these three compounds are isomers.[11]

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ on a Bruker AC-300 (300 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane, using chloroform as internal standard. IR spectra were recorded on a NICOLET DX320 and PERKIN-ELMER 551S spectrometers. High Resolution Mass Spectra were recorded on a ZAB2-SE-FPD spectrometer. Each reaction was monitored by TLC (silica gel 60F-254 plates). Column chromatography was performed using Merck Kieselgel 60 (70-230 mesh).

3-Methoxyphenylacetyl chloride 4.

To a solution of 3-methoxyphenylacetic acid (15.0 g, 90.3 mmol) in 400 ml of dry benzene, redistilled thionylchloride (21.0 g, 180.7 mmol) was added. The reaction was held at reflux for 4 hours and then the solvent was removed by distillation. The chloride was purified by vacuum distillation (80-85° C, 0.1 mmHg) to yield 9.9g (60%).

3-Methoxy benzyldiazomethylketone 5.

The purified chloride 4 dissolved in 50 ml of dry ether was added dropwise to an excess (> 3.5 equiv.) of distilled ethereal solution of diazomethane,[12] cooled in an ice bath, which was then allowed to stand overnight at room temperature. Excess diazomethane was removed by gentle heating on a steam bath, and the ether solution was dried (Na_2SO_4) by filtering through a pad of sodium sulphate. Removal of the solvent afforded the product as a yellow syrup (~7.9 g, 77%). ^{1}H-NMR ($CDCl_3$) δ= 7.22 (1H, t, J=7.8 Hz), 6.77 (3H, m), 5.12 (1H, s, CHCN), 3.77 (3H, s, OCH_3), 3.55 (2H, s,), ^{13}C-NMR ($CDCl_3$) δ= 192.74, 159.96, 136.03, 129.89, 121.73, 115.02, 112.79, 55.24 (OCH_3), 54.86 (CHN_2), 48.16. IR ($CDCl_3$, cm^{-1}) 3100 ($COCHN_2$), 2100, 1630.

3-Methoxy benzyl (4-chlorophenylthio)methylketone 6.

To a stirred solution of p-chlorothioanisole (8.61 g, 59.6 mmol) in dry benzene (250 ml) containing rhodium(II) acetate (25 mg) was added a solution of diazoketone 5 (7.6 g, 39.9 mmol) in dry benzene (50ml)

over twenty minutes, at room temperature. Nitrogen evolution was observed over the addition period. After an additional hour stirring , the reaction solution was washed with 5% aqueous sodium hydroxide, then with water,and dried (Na_2SO_4). Removal of solvent followed by chromatography on silica gel (hexane/ Toluene gradient) afforded the product 6 (7.95 g, 65%) as a light yellow oil and indanone 7 (4.2g, 35%). **6:** ^{1}H-NMR ($CDCl_3$) δ=7.21 (1H, t, J=7.9 Hz), 7.20 (4H, s), 6.80 (1H , dd, J= 8.2, 3.0 Hz), 6.77 (1H, d, J=7.5 Hz) 6.68 (1H, t, J=2.0 Hz), 3.81 (2H, s), 3.75 (3H, s, OCH_3), 3.65 (2H, s). ^{13}C-NMR ($CDCl_3$), δ=202.16, 159.80, 134.76, 134.0, 133.82, 131.03, 129.78, 129.22, 121.70, 115.00, 112.67, 55.02 (OCH_3), 47.65, 42.93. IR ($CDCl_3$, cm^{-1}) 1705, 1598 7: 1H-NMR ($CDCl_3$) δ=7.17 (1H, d), 6.82 (1H, s), 6.80 (1H, d), 3.78 (3H, s, OCH_3), 3.51 (2H, brs), 3.47 (2H, brs). ^{13}C-NMR ($CDCl_3$) δ= 215.22, 159.15, 138.94, 129.61, 125.75, 113.64, 110.22, 55.37 (OCH_3), 44.46, 43.38. IR ($CDCl_3$, cm^{-1}) 1738, 1600.

2-(4-Chlorophenylthiomethyl-3-(3-methoxyphenyl)-5-carbomethoxy-N-methyl 2,3 dehydropiperidine 8. Methyl α-(bromomethyl)acrylate (1.6 g, 8.9 mmol) prepared according to the described procedure[13] was dissolved in dry benzene (30 ml) under nitrogen and cooled to -5 °C using an ice salt bath. Excess dry methylamine was condensed into the solution (white precipitate). The mixture was stirred with cooling for an additional 20 min and then at room temperature for two hours. Into this reaction mixture was added (at 5-10 °C) dropwise a cold solution of the ketone 6 (2 g, 6.45 mmol) in 50 ml benzene. The mixture was refluxed (Dean-stark apparatus) for 45 hours, cooled to room temperature, evaporated, diluted with AcOEt and shaken with 2N HCl . The aqueous phase was made alkaline with saturated $NaHCO_3$ and reextracted with CH_2Cl_2, the combined organic phase dried over Na_2SO_4 and the solvent evaporated. The dark-red oil was purified by chromatography on silica gel (toluene/AcOEt, gradient) to give 8 as a light yellow oil (1.50 g, 3.58 mmol 56%). ^{1}H-NMR ($CDCl_3$) δ=7.25 (1H, s,), 6.80 (1H, brs), 6.77 (1H, brs), 6.75 (1H, brs), 7.22 and 7.12 (AA'BB'), 4.03 (2H, d, CH_2S), 3.81 (3H, s, OCH_3), 3.72 (3H, s, $COOCH_3$), 3.33 (2H, d, J=5.9 Hz, H-6), 2.99 (1H, m, H-5), 2.77 (3H, s, NCH_3), 2.68 (1H, dd, J=16.5, 8.6 Hz, H-4) and 2.55 (1H, dd, J=16.5, 5.9Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ=173.59 ($\underline{C}OOCH_3$), 159.84 (C-9), 150.94 (C-2), 140.11 (C-7), 137.62 , 130.26, 129.40 (C-11), 128.77 and 127.14 (AA'BB'), 120.22 (C-12), 113.68 (C-8), 111.26 (C-10), 92.95 (C-3), 55.11 (OCH_3), 52.40 (C-6), 51.82 ($COO\underline{C}H_3$), 40.04 (NCH_3), 39.12 (C-5), 36.10 ($\underline{C}H_2SPhCl$), 31.95 (C-4).

2-(4-Chlorophenylthiomethyl-3-(3-methoxyphenyl)-5-carbomethoxy- N-methylpiperidine, 9 (a,b,c). To a cooled (5-10 °C) solution of 8 (1.46 g, 4.8 mmol) in THF (30 ml) and glacial acetic acid (8 ml), sodium cyanoborohydride (462 mg, 7.3 mmol) was added. The mixture was stirred at room temperature for 3 hours, then water was added and the aqueous solution was basified with solid $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with water, dried over Na_2SO_4 and evaporated under vacuum. The residue (710 mg, 49%) was chromatographed on silica gel with toluene/AcOEt 20:1 and then with toluene/AcOEt 10:1. The isomer 9a is eluted first, followed by the isomer 9b and finally by the isomer 9c in a ratio 1:2:3. **9a** ^{1}H-NMR ($CDCl_3$) δ=7.21(1H ,t, J=7.8 Hz), 7.06 and 6.91(AA'BB'), J=8.5 Hz, 6.76 (1H ,dd, J=8.2, 2.4 Hz), 6.69(1H, d, J=7.5Hz), 6.62 (1H, t, J=1.9 Hz), 3.3 4 (1H, q, J=2.6 Hz), 3.78 (3H, s, OCH_3), 3.69 (3H, s, $COOCH_3$), 3.08 (1H, tt, J=11.9, 4.3 Hz), 3 .04 (1H, ddd, J=11.1, 3.6, 2.5Hz), 2.94 (1H, dd, J=13.5, 3.6Hz), 2.86 (1H, dd, J=11.5, 4.4 Hz), 2.66 (1H, t, J=11.5 Hz) , 2.64 (1H, dd, J=13.5, 10.7 Hz), 2.51 (3H, s, NCH_3), 2.14 (1H, ddd, J=14.2, 11.9, 4.2 Hz), 2.01 (1H, td, J=14.2, 3.4 Hz). ^{13}C-NMR ($CDCl_3$) δ=174.25, 159.85, 140.80, 134.65, 132.09, 131.22, 129.61, 128.91, 121.41, 114.88, 111.45, 65.12, 55.14, 51.76, 50.02, 44.75, 43.27, 37.76, 29.12, 26.45. IR(neat): 2950-2830w, 1733s. **9b** ^{1}H-NMR ($CDCl_3$) 7.18 (1H, t, J=7.9 Hz), 7.13 and 7.02(AA'BB', J=8.7 Hz), 6.83 (1H, d, J=7.6 Hz), 6.79 (1H, t, J=1.9 Hz), 6.74 (1H, dd, J=7.6 2.6 Hz), 3.68 (3H, s, OCH_3), 3.64 (3H, s, $COOCH_3$), 3.40 (1H, tt, J=11.9, 4.0Hz), 3.23 (1H, ddd, J=11.7, 4.2, 2.1 Hz), 3.17 (1H, dd, J=13.2, 5.0 Hz), 3.06 (1H, q, J=3.0 Hz), 2.91 (1H, dd, J=13.2, 10.9 Hz), 2.49 (1H, ddd, J=10.9, 5.0, 2.1Hz), 2.40 (3H, s, NCH_3),

2.27 (1H, t, J=11.7Hz), 2.04 (1H, brd, J=13.5 Hz), 1.60 (1H, dt, J=13.5, 3.2Hz). ^{13}C-NMR ($CDCl_3$) δ=174.36, 159.67, 139.86, 134.59, 132.11, 131.39, 129.40, 128.98, 121.88, 115.16, 112.00, 68.16, 59.19, 55.05, 51.76, 47.42, 43.34, 37.45, 36.84, 32.84. IR(neat): 2952-2770w, 1733s. **9c** ^{1}H-NMR ($CDCl_3$) δ=7.19 (4H, s), 7.18 (1H, t, J=8.1 Hz), 6.94 (1H, brs), 6.93 (1H, d), 6.74 (1H, dd, J=8.1, 2.8 Hz), 3.76 (3H, s, OCH_3), 3.61 (3H, s, $COOCH_3$), 3.37 (1H, dd, J=15.6, 3.1 Hz), 3.03 (1H, ddd, J=11.7, 3.6, 2.0 Hz), 2.97 (1H, dd, J=15.6, 5.6Hz), 2.93 (1H, ddd, J=11.6, 10.0, 4.2 Hz), 2.57 (1H, tt, J=11.6, 3.6 Hz), 2.39 (1H, ddd, J=10.1, 5.6, 2.2 Hz), 2.40 (3H, s, NCH_3), 2.34 (1H, t, J=11.7 Hz), 2.27 (1H, dtd, J=13.3, 4.1, 1.8 Hz), 1.67 (1H, q, J=13.3 Hz). ^{13}C-NMR ($CDCl_3$) δ=173.36, 159.43, 140.56, 133.82, 133.40, 132.46, 129.06, 129.01, 122.04, 115.58, 111.20, 66.68, 57.23, 55.06, 51.69, 47.52, 42.71, 40.63, 35.36, 34.71. IR(neat): 2960-2799w, 1733s. High resolution MS for all the three isomers (LSIMS method) Calcd for $C_{22}H_{27}ClO_3NS$ [MH^+]:420.966 (Average Mass), found 420.140 (Monoisotopic Mass).

Acknowledgments We wish to thank Dr. Joachim Raeber at Max-Planck Institut fuer Polymerforschung, Mainz, Germany for measurements of high resolution mass spectra.

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11. The stereochemical structures of these three isomers based on NMR-data were assigned as follows: Configurations: isomer 9a, axial-2-CH_2SPhCl-4, axial-3-$MeOC_6H_4$, equatorial-5-$COOCH_3$; isomer 9b, equatorial-2-CH_2SPhCl-4, axial-3-$MeOC_6H_4$, equatorial-5-$COOCH_3$ and isomer 9c, equatorial-2-CH_2SPhCl-4, equatorial-3-$MeOC_6H_4$, equatorial-5-$COOCH_3$. For the systematic NMR- analysis and details of their structure assignment see *Magnetic Resonance in Chemistry*, 1994, in press.
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(*Received in UK* 25 *January* 1994; *revised* 5 *July* 1994; *accepted* 15 *July* 1994)