Synthesis of beta-carbolines as potential serotonin receptor ligands
Burm, B.E.A.

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Chapter 7

Spiro-fused Oxindoles as Conformationally Restricted Serotonin and Muscarine Analogues

Abstract

Oxidation of tryptamine derived cyclic amines described in the previous chapter, followed by a condensation similar to the Pictet-Spengler reaction resulted in a class of compounds with a structure totally different from the bridged β-carbolines obtained in chapter 6. The oxygen atom blocked the indole 2-position so that condensation with aldehydes now afforded spiro-fused oxindoles. Structural similarity between those new bicyclic systems and known muscarine M₁ agonists and 5-HT₃ antagonists is proposed.
7.1 Introduction

7.1.1 Muscarinic receptors

Acetylcholine is the endogenous neurotransmitter at cholinergic synapses and neuroeffector junctions in the central and peripheral nervous systems. The actions of acetylcholine are mediated through nicotinic and muscarinic cholinergic receptors, which transduce signals via distinct mechanisms. Classification of the two main groups of cholinergic receptors is based upon the classical agonists, muscarine and nicotine. The structure of nicotine is very different from that of acetylcholine and the molecular basis for binding to the nicotinic cholinergic receptors is unclear. The structure of muscarine, on the other hand, reflects to some extent the structure of acetylcholine. It is known that the quaternary ammonium group is essential for interaction with the muscarinic receptors and also the ether function appears to be strongly involved in receptor binding.

Figure 7.1

Within cholinergic receptors heterogeneity exists: several subtypes of both the nicotinic and muscarinic receptor have been described. The mapping of potential subtypes within the nicotinic class however, is in an early stage as compared to the muscarinic receptors. Molecular cloning studies have revealed five subtypes of muscarinic cholinergic receptor, designated M₁ through M₅ based on pharmacological specificity. All known subtypes of muscarinic receptors are coupled to second messenger systems and thus interact with members of G proteins that regulate a variety of effector proteins within cells. Homology within the M₁, M₄ and M₅ subtypes and the M₂ and M₃ subtypes was found. The first group eventually has its effect in various Ca²⁺-mediated events, whereas the latter group regulates specific ion-channels.

In general, agonists, that stimulate the muscarinic receptors, manifest little selectivity for the various subtypes. The clinical uses of muscarinic agonists are primarily found in gastrointestinal diseases and in ocular pharmacology. Agonists that show functional selectivity for M₁ over M₂ receptors are interesting because of their potential use in treating the intellectual
impairment associated with Alzheimer's disease.

Muscarinic antagonists are usually highly selective for muscarinic over nicotinic receptors. In addition, a growing number of antagonists show selectivity for particular muscarinic subtypes, thus holding promise for the blocking of certain actions of acetylcholine and minimising side effects. The therapeutic uses of muscarinic antagonists include gastrointestinal disorders, motion sickness, parkinsonian symptoms, which includes Parkinson's and Alzheimer's disease and also in ocular pharmology.

7.1.2 Muscarine M₁ agonists compared to 5-HT₃ antagonists

As a starting point in search for selective muscarine receptor ligands, modification of the naturally occurring muscarine agonist arecoline led to the development of several analogous compounds (Figure 7.2). Molecular orbital calculations towards charge distributions of the protonated forms of piperidines and quinuclidines revealed that the latter resembled the quaternary ammonium entity in acetylcholine more closely and resulted in the development of agonist 5. Further analogues feature the modification of the metabolically labile ester functionality and resulted in a series of quinuclidine-based derivatives such as 6, possessing a heteroaromatic substituent. Also quinuclidin-2-ones substituted with various mono- and bicyclic aromatic rings such as 7, and spiro-cycloquinuclidines 8 were found to exhibit muscarine ligand binding activity.

![Figure 7.2](image)

Figure 7.2

The synthesis and biochemical evaluation of a series of indole oxazolines spirofused to an azacyclic ring have been described (Figure 7.3). Analogy can be seen with the structure of the muscarine agonists depicted in figure 7.2. The azacycle was varied from mono- to bicyclic systems, including piperidines and 1-aza-bicyclo alkanes (e.g. 9, 10 and 11). As a result of the conformational restriction caused by the spiro-centre, the relative positions of the key pharmacophoric elements are precisely defined. These include an aromatic lipophilic binding region, an electrostatic interaction with a charged nitrogen and linkage of those two characteristics by a heterocyclic function containing at least one hydrogen-bond acceptor. All compounds
synthesised behaved as 5-HT$_3$ antagonists, while tertiary amines exhibited high affinity, suggesting that lipophilic interactions also play a significant role in the binding of the electrostatic pharmacophoric element.

![Figure 7.3](image)

Molecular studies performed on twelve known muscarinic M$_1$ agonists have shown some striking similarities between the muscarinic M$_1$ agonist and 5-HT$_3$ antagonist pharmacophore models (Figure 7.4). Muscarinic ligand acetylcholine 1 and 5-HT$_3$ antagonist quipazine 12 share these characteristics, which for both models include a protonable basic or quaternary nitrogen atom, which is elevated by about 0.5 Å above a plane containing an electric dipole. The nitrogen acting as the positively charged side of the dipole preferably is surrounded by lipophilic environment as in for instance diethylamine, piperidine and quinuclidine. The intercharge distance of the dipole between the cationic nitrogen atom and the electronegative end, usually an ester-functionality or a biostere thereof, is about 5 Å.

![Figure 7.4](image)

The most obvious difference between muscarine M$_1$ agonists and 5-HT$_3$ antagonists is the additional aromatic system in many 5-HT$_3$ antagonists not present in the muscarinic M$_1$ agonists. Usually 5-HT$_3$ antagonists also possess a tertiary and preferably rigid N-heterocyclic side chain. A certain degree of relationship between muscarinic M$_1$ agonist and 5-HT$_3$ antagonist pharmacophores was shown by the modification of 3-aminopyridazine 13, a compound known to have a selective M$_1$ receptor affinity (Figure 7.5). Development of analogues of 13, for instance
piperazines 14 or 15, resulted in the observation of IC$_{50}$ values for the 5-HT$_3$ receptor binding of respectively 10 and 36 nM, whereas the affinity for the muscarinic receptors was found above 10,000 nM.

![Chemical structures](image)

**Figure 7.5**

### 7.1.3 Spiro-fused oxindoles as muscarine and serotonin receptor ligands

Taken into account the pharmacological requirements, described in the previous paragraph, derivatives 19 were expected to act as either muscarine or serotonin receptor ligands: they possess an aromatic plane connected by an acyl function to a basic nitrogen atom that is part of a bicyclic system. Also the interatomic distance between the nitrogen atom and the oxygen, that is part of the acyl function, meets the requirement of four to five bonds (5 Å).

![Chemical structures](image)

**Figure 7.6**

In connection to the work described in chapter 6, we already had cyclic tryptamines 16, 17 and 18 to our disposal (Figure 7.6). The analogy in the condensation reaction of 2-oxytryptamines with an aldehyde and the Pictet-Spengler reaction, prompted us to expand the methodology described in chapter 6 to condensations with the 2-oxo-derivatives of cyclic amines 16, 17 and 18. As a result of the unavailability of the indole 2-position, compounds possessing general structure 19 were expected to be formed in the condensation with aldehydes. Because of the well defined positions of the pharmacophoric elements, important for muscarine and 5-HT$_3$ binding,
spiro-fused oxindoles 19 are postulated as conformationally restricted receptor ligands.

### 7.2 Sporo-fused Oxindoles

#### 7.2.1 Synthesis of precursors

Oxindoles are abundant structures in nature, especially in the botanical kingdom. They form not only the basis for many alkaloids, but also play an important role in the biosynthesis of indole alkaloids. Biological conversion of the indoloquinolizidine alkaloid geissoschizine 20 to the pyrrolo[2,3-c]-carbazole akuammicine 21 involves a rearrangement via a spiro-fused oxindole (Figure 7.7). The 1,2-alkylshifts described in § 6.5.1 were based on the reverse reaction: rearrangement of spiro-indolenines derived from oxindoles to tetrahydro-β-carbolines.

![Figure 7.7](image)

The synthesis of various spiro-fused oxindoles 24, including formosanine 22, has been achieved using a cyclisation reaction between the imine derived from 2-oxytryptamine 23 and an aldehyde (Figure 7.8). This strategy has also found application in the biomimetic synthesis of aspidosperma and strychnos alkaloids, which share the pyrrolo[2,3-c]-carbazole skeleton also present in 21.

![Figure 7.8](image)
The cyclic secondary amines 16, 17 and 18 were synthesised straightforwardly using the procedures described in chapter 6. A simple and generally applicable method for the oxidation of indoles to oxindoles has been described: a variety of tryptamines was converted to the corresponding oxindoles employing a dimethyl sulfoxide mediated oxidation.

\[ \text{DMSO} \xrightarrow{\text{HCl, H}_2\text{O}} \]

\[ 16 \rightarrow 25 \quad 17 \rightarrow 26 \quad 18 \rightarrow 27 \]

Scheme 7.1

Oxidation of the piperidines 16 and 17 easily afforded the respective oxindoles 25 and 26 as stable compounds. Oxidation of 3-(3-indolyl)pyrrolidine 18 using the method depicted in scheme 7.1 was complicated by the instability of the product, oxindole 27. Therefore the reaction was performed using an excess of dimethyl sulfoxide and 27 was immediately used in the next reaction. Complete decomposition of this oxindole was observed by storing it during one night.

7.2.2 1-Azabicyclo[3.2.1]octanes

Condensations of oxindole 25 with representative aldehydes was investigated using a variety of both acid and base catalysed conditions. Pure acetic acid at 90 °C (method A) or sodium acetate in methanol (method B) proved to be suitable for most of the aldehydes. The parent spiroazabicyclooctane ring system 28 (R = H), obtained by reaction with one equivalent of formaldehyde, was formed as a mixture of the two possible diastereomers in a ratio of approximately 3 : 1. The diastereomers were separated using flash chromatography, and fully characterised using 2D NMR spectroscopy (see § 7.2.5). Hexanal was chosen as an example for aliphatic aldehydes. Longer reaction times and excess aldehyde were required to give acceptable yields. Surprisingly only two diastereomers out of four were obtained. Obviously for steric reasons, in both isomers a and b, the R-substituent adopts an exo-orientation in relation with the bicyclic ring system as was deduced from model studies. Benzaldehyde was completely unreactive even after using large excess reagent and prolonged reaction times. Slow decomposition of the starting material was the only process observed.
Scheme 7.2

Table 7.1: Condensation of oxindole 25 with selected aldehydes.

<table>
<thead>
<tr>
<th>product</th>
<th>R</th>
<th>ratio a : b</th>
<th>conditions</th>
<th>yield (%)</th>
<th>time (h)</th>
<th>temp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>H</td>
<td>76 : 24</td>
<td>A</td>
<td>81</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>29</td>
<td>(CH2)4CH3</td>
<td>63 : 37</td>
<td>A</td>
<td>57</td>
<td>5</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55 : 45</td>
<td>B</td>
<td>57</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>30</td>
<td>C2H5</td>
<td></td>
<td>A</td>
<td>0</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B</td>
<td>0</td>
<td>48</td>
<td>65</td>
</tr>
</tbody>
</table>

(a) The ratio according to the 1H NMR spectrum of the crude reaction mixture.
(b) A = HOAc; B = NaOAc, MeOH.
(c) Isolated yields over 2 steps.

During NMR-analysis in CDCl3, it turned out that both pentyl-substituted diastereomers 29 were configurationally unstable. After one night at room temperature partial isomerisation took place, which could be completed by heating at 50 °C during six hours. Both pure isomers equilibrated to the same 63 : 37 isomer ratio, exactly the same as was obtained from their synthesis in acetic acid. No such observation was made with the formaldehyde derived products 28. To confirm their stability, both pure isomers 28a and 28b were heated in acetic acid at 90 °C (method A). No isomerisation was observed and it took several hours at 100 - 110 °C before some isomerisation had occurred.

7.2.3 1-Azabicyclo[2.2.2]octanes

The same reaction conditions as described for the synthesis of azabicyclo[3.2.1]octanes, § 7.2.2, were used to prepare 1-azabicyclo[2.2.2]octane derivatives. Formaldehyde, which is in general very reactive, gave no product at all under these conditions. Only unidentified polymeric material was detected. Hexanal was again successful and after separation, the desired quinuclidines were obtained in reasonable yield (two steps from 17).

Due to the symmetry in the piperidine-part of oxindole 26 only two diastereomers are possible from the condensation with aldehydes. Preference for diastereomer b, in which less
sterical hinderance between the R-substituent and the aromatic ring exists, was observed. In contrast to the 1-azabicyclo[3.2.1]octanes (§ 7.2.2), these isomers showed no interconversion. With benzaldehyde, a moderate yield of the two isomers was obtained. Structural analysis with this inseparable mixture was performed by comparison of its $^1$H NMR and NOESY spectra with those of the pentyl derivatives.

![Scheme 7.3](image)

**Table 7.2:** Condensation of oxindole 26 with selected aldehydes.

<table>
<thead>
<tr>
<th>product</th>
<th>R</th>
<th>ratio a : b</th>
<th>conditions</th>
<th>yield (%)</th>
<th>time (h)</th>
<th>temp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>H</td>
<td>21 : 79</td>
<td>A</td>
<td>0</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>32</td>
<td>(CH$_3$)$_2$CH$_3$</td>
<td>21 : 79</td>
<td>A</td>
<td>47</td>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>33</td>
<td>C$_6$H$_5$</td>
<td>36 : 64</td>
<td>B</td>
<td>61</td>
<td>10</td>
<td>65</td>
</tr>
</tbody>
</table>

(a) The ratio according to the $^1$H NMR spectrum of the crude reaction mixture.
(b) A = HOAc; B = NaOAc, MeOH.
(c) Isolated yields over 2 steps.
(d) Inseparable mixture of isomers.
(e) The reaction did not go to completion.

7.2.4 1-Azabicyclo[2.2.1]heptanes

The third cyclic tryptamine, 3-(3-indolyl)pyrrolidine 18, turned out to be more problematic. Instability of the oxindole 27 is probably responsible for low yields in the condensation reaction (Table 7.3). In principle four diasteromers can be formed, except in the case of formaldehyde where only two are possible. In the reaction with formaldehyde however only one diastereomer was observed, whereas hexanal afforded three diastereomers with general structure 35. Separation by flash chromatography afforded the pure isomer a and an inseparable mixture of isomer b and c. During analysis isomer a was found unstable: under slightly acidic conditions (silica or CDCl$_3$) and heating, it equilibrated to isomer c. In the case of benzaldehyde
only two inseparable diastereomers were detected. By comparison of the $^1$H NMR chemical shifts, the two diastereomers were tentatively assigned structures $36b$ and $36c$ in relation to the isomers $35a$, $35b$ and $35c$ obtained from the condensation of 27 with hexanal.

![Scheme 7.4](image)

Table 7.3: Condensation of oxindole 27 with selected aldehydes.

<table>
<thead>
<tr>
<th>product</th>
<th>R</th>
<th>ratio a : b : c$^b$</th>
<th>conditions$^b$</th>
<th>yield (%)$^c$</th>
<th>time (h)</th>
<th>temp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>H</td>
<td>1 isomer</td>
<td>A</td>
<td>6</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>35</td>
<td>(CH$_2$)$_2$CH$_3$</td>
<td>50 : 5 : 45</td>
<td>B</td>
<td>8</td>
<td>12</td>
<td>rt</td>
</tr>
<tr>
<td>36</td>
<td>C$_6$H$_5$</td>
<td>0 : 69 : 31$^d$</td>
<td>B</td>
<td>6</td>
<td>12</td>
<td>55</td>
</tr>
</tbody>
</table>

(a) The ratio according to the $^1$H NMR spectrum of the crude reaction mixture.
(b) A = HOAc; B = NaOAc, MeOH.
(c) Isolated yields over 2 steps.
(d) Inseparable mixture of isomers.

7.2.5 nOe studies of the azabicyclooctanes

In order to gain insight in the three-dimensional structure of the synthesised spiro-fused oxindoles, NOESY spectra of the pentyl-azabicyclooctanes were recorded. First, all protons were assigned using $^1$H-$^1$H and $^1$H-$^1$C correlation spectroscopy. Especially nOe correlations between protons of the bicyclic system and the aromatic hydrogens at C-8 (in 29) and C-7 (in 32) were very informative, as can be seen from tables 7.4 and 7.5.

The nOe in azabicyclo[3.2.1]octane 29, between H-8 and H-4$_ax$, revealed the piperidine ring in diastereomer b to adopt the chair-conformation. Some overlap in the $^1$H NMR spectra of isomer a prevented unambiguous assignment of the piperidine conformation. However, the downfield shift of H-4, caused by deshielding of the carbonyl function indicates also a chair-conformation for the piperidine ring in isomer a. Irrespective of its conformation, it can be concluded that isomer a has an extended structure whereas isomer b is more compact. These differences might be important for the lipophilic interactions with the receptor.
Due to the symmetry in the quinuclidine ring system, as mentioned before, only two chiral centres are present in the azabicyclo[2.2.2]octanes. The only difference between the diastereomers 32a and 32b therefore exists in the orientation of the pentyl-substituent. This distinction can clearly be seen by the presence of the nOe's between H-1 and H-7 in diastereomer a and between H-7 and H-15 in diastereomer b. Sterical reasons offer an explanation for the favoured formation of the latter diastereomer.
Table 7.6: NOESY spectrum of 32a

<table>
<thead>
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<th>selected through space interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
</tr>
<tr>
<td>H-3</td>
</tr>
<tr>
<td>H-3ₜ</td>
</tr>
<tr>
<td>H-4ₜ</td>
</tr>
<tr>
<td>H-7</td>
</tr>
</tbody>
</table>

Table 7.7: NOESY spectrum of 32b

<table>
<thead>
<tr>
<th>selected through space interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
</tr>
<tr>
<td>H-3</td>
</tr>
<tr>
<td>H-3ₜ</td>
</tr>
<tr>
<td>H-4ₜ</td>
</tr>
<tr>
<td>H-5</td>
</tr>
<tr>
<td>H-7</td>
</tr>
<tr>
<td>H-1₄</td>
</tr>
</tbody>
</table>

7.3 Concluding Remarks

Tryptamine derived cyclic amines undergo Pictet-Spengler condensation with aldehydes affording bridged tetrahydro-β-carbolines as was shown in the previous chapter. In this chapter the same amines were employed, but via oxidation the indole 2-position was made unavailable. Use of essentially a similar strategy, condensation with an aldehyde, resulted in a class of totally different compounds, spiro-fused azabicycloalkanes. The formation of azabicyclooctanes from the condensation of indolylpiperidines and some selected aldehydes gave the best results. Synthesis of azabicycloheptanes was less successful due to the instability of the pyrrolidine derived oxindole which is the starting material in the condensation.

Taken into account the pharmacological requirements reported for the muscarine M₁ and 5-HT₃ receptors, all these compounds can be looked upon as potential serotonine and muscarine receptor ligands. The size and nature of the lipophilic pocket that accommodates the nitrogen bicycle can be further investigated by variation of the R-substituent, easily accomplished by using different aldehydes in the condensation reaction. In principle, substitution or extension of the aromatic plane is also a possibility, thus making this class of compounds a subject worth-while for further investigation.
7.4 Acknowledgements

Martin Wanner is gratefully acknowledged for performing part of the syntheses described in this chapter.

7.5 Experimental

General methods. For experimental details see section 3.6 on page 50. For the NMR assignments of the products in this chapter the numbering as shown for structures 25, 27, 29, 32 and 35 has been used.

3-(2-Oxindol-3-yl)piperidine (25). To a mixture of 3-(3-indolyl)piperidine 16 (400 mg, 2.0 mmol) in dimethylsulfoxide (1.5 mL, 20.0 mmol) hydrochloric acid (3.0 mL, 36.4 mmol, 37%) was added dropwise. The mixture was stirred during 30 min at rt, then water and an aqueous sodiumbisulfite solution (3 mL) were added. The mixture was stirred during several min, saturated with K₂CO₃ and EtOAc/5% EtOH (5 mL) was added. The layers were separated and the water layer was extracted with EtOAc/5% EtOH (3x). The combined organic layers were dried (Na₂SO₄) and evaporated affording 25 (585 mg, 1.57 mmol, 79%, corrected for 2 eq. DMSO), as two isomers according to the ¹³C NMR spectrum: Rₖ (CH₂Cl₂/MeOH/concd NH₄OH 80/15/5) 0.23; ¹H NMR δ 7.21 - 7.14 (m, 2H, H-6 or H-7), 6.96 (t, J = 7.5 Hz, 1H, H-5), 6.84 (d, J = 7.5 Hz, 1H, H-4), 3.31 (br s, 1H, H-3), 3.03 (br d, J = 11.8 Hz, 1H, H-9 or H-11), 2.97 (br d, J = 12.2 Hz, 1H, H-9 or H-11), 2.77 - 2.68 (m, 1H, H-9 or H-11), 2.60 (s, (CH₃)₂SO), 2.51 - 2.43 (m, 1H), 2.27 - 2.18 (m, 1H), 1.70 - 1.58 (m, 2H), 1.51 - 1.39 (m, 1H); ¹³C NMR δ 149.5 (C-2), 142.5 (C-7), 142.5 (C-7), 128.1 (C-3), 128.0 (C-3), 127.6, 127.6, 124.5, 124.1, 121.6, 121.5, 109.5, 109.4, 49.9 (C-3), 49.7 (C-3), 49.5, 48.6, 46.3, 46.2, 40.7 (CH₃)SO, 40.2 (C-8), 40.1 (C-8), 26.9 (C-13), 26.7 (C-13); IR ν 3436, 1706; HRMS (FAB) obs. mass 217.1360, calcd for C₁₃H₁₇NO₂ (M + 1) 217.1341.

4-(2-Oxindol-3-yl)piperidine (26). To a mixture of 4-(3-indolyl)piperidine 17 (2.07 g, 10.4 mmol) in dimethylsulfoxide (1.4 mL, 20.0 mmol) hydrochloric acid (5.0 mL, 0.61 mol, 37%) was added dropwise. The mixture was stirred during 45 min at rt, EtOAc (20 mL), EtOH (1 mL) and a saturated Na₂CO₃ solution (25 mL) were added at 0 °C. The water layer was further basified with K₂CO₃, the layers were separated and the water layer extracted with EtOAc/5% EtOH (3x). The combined organic layers were dried (Na₂SO₄) and evaporated. The yellow oil thus obtained still contained dimethyl sulfoxide, but was used for the condensations. An analytical sample was prepared by flash chromatography (CH₂Cl₂/MeOH/concd NH₄OH 80/15/5) followed by crystallisation from EtOAc yielding 26 (1.29 g, 5.94 mmol, 57%) as a crystalline yellow compound: Rₖ (CH₂Cl₂/MeOH/concd NH₄OH 80/15/5) 0.45; mp 149 - 151 °C; ¹H NMR δ 7.22 (d, J = 7.5 Hz, 1H, H-4 or H-7), 7.18 (t, J = 7.7 Hz, 1H, H-5 or H-6), 6.98 (t, J = 7.5 Hz, 1H, H-5 or H-6), 6.82 (t, J = 7.7 Hz, 1H, H-4 or H-7), 3.34 (d, J = 3.5 Hz, 1H, slow
exchange with D, H-3), 3.08 (br d, J = 12.5 Hz, 1H, H-10_eq or H-12_eq), 3.01 (br d, J = 12.4 Hz, 1H, H-10_eq or H-12_eq), 2.58 (ddd, J = 12.4 Hz, J = 12.4 Hz, J = 3.0 Hz, 1H, H-10_eq or H-12_eq), 2.25 - 2.18 (m, 2H, H-8, H-10_eq or H-12_eq), 1.59 (ddd, J = 12.4 Hz, J = 12.4 Hz, J = 12.4 Hz, J = 4.2 Hz, 1H, H-9_eq or H-13_eq), 1.38 (ddd, J = 12.4 Hz, J = 12.4 Hz, J = 12.4 Hz, J = 4.2 Hz, 1H, H-9_eq or H-13_eq). IR v 3436, 1708; HRMS (EI) obs. mass 216.1263, calcd for C_10H_15O_N: 216.1263.

3-(2-Oxindol-3-yl)pyrrolidine (27).

To a solution of 3-(3-indolyl)pyrrolidine 18 (106 mg, 0.57 mmol) in dimethyl sulfoxide (1.5 mL, 21.1 mmol) hydrochloric acid (3.0 mL, 0.37 mol, 37%) was added dropwise. The mixture was stirred during 45 min at rt. EtOAc (20 mL), EtOH (1 mL) and a saturated Na_2CO_3 solution (25 mL) were added at 0 °C. The water layer was further basified with K_2CO_3, the layers were separated and the water layer extracted with EtOAc/5% EtOH (3x). When a third, yellow layer was being formed more water and K_2CO_3 were added. The combined organic layers were dried (Na_2SO_4) and evaporated giving oxindole 27 together with dimethyl sulfoxide. Due to the instability of the product it was used as such for further reaction: R, (CH_2Cl_2/MeOH/concd NH_4OH 80/15/5) 0.51; 'H NMR (CDCl_3/5% CD_3OD) 5 8.59 (br s, 1H, H-1), 7.23 (d, J = 7.8 Hz, 1H, H-4 or H-7), 7.16 (t, J = 7.9 Hz, 1H, H-5 or H-6), 6.99 (t, J = 7.8 Hz, 1H, H-5 or H-6), 6.84 (d, J = 7.8 Hz, 1H, H-4 or H-7), 3.55 - 3.50 (m, 1H), 3.24 - 3.07 (m, 1H), 3.03 - 2.81 (m, 3H), 2.72 - 2.57 (m, 1H), 1.72 - 1.58 (m, 1H).

Condensation reactions

General procedure A: The oxindole was prepared prior to use from the corresponding amine (1 eq.) according to the procedure described above. A solution of this freshly prepared oxindole and aldehyde (1-5 eq.) in acetic acid was stirred during the time and temperature indicated. The reaction mixture was concentrated in vacuo, an aqueous saturated solution of K_2CO_3 and EtOAc were added. The layers were separated and the water layer was extracted with EtOAc/5% EtOH (3x). When a third, yellow layer was being formed more water and K_2CO_3 were added. The combined organic layers were dried (Na_2SO_4) and evaporated giving oxindole 27 together with dimethyl sulfoxide. Due to the instability of the product it was used as such for further reaction: R, (CH_2Cl_2/MeOH/concd NH_4OH 80/15/5) 0.51; 'H NMR (CDCl_3/5% CD_3OD) 5 8.59 (br s, 1H, H-1), 7.23 (d, J = 7.8 Hz, 1H, H-4 or H-7), 7.16 (t, J = 7.9 Hz, 1H, H-5 or H-6), 6.99 (t, J = 7.8 Hz, 1H, H-5 or H-6), 6.84 (d, J = 7.8 Hz, 1H, H-4 or H-7), 3.55 - 3.50 (m, 1H), 3.24 - 3.07 (m, 1H), 3.03 - 2.81 (m, 3H), 2.72 - 2.57 (m, 1H), 1.72 - 1.58 (m, 1H).

Condensation of 25 with formaldehyde (28).

General procedure A was followed using 25 prepared from 16 (67 mg, 0.36 mmol) and paraformaldehyde (11 mg, 0.37 mmol). After 2 h at 90 °C the conversion was complete. According to the 'H NMR spectrum of the crude reaction mixture two diastereomers in a ratio of 76 : 24 had been formed. Flash chromatography (EtOAc/EtOH/NEt, 75/15/10) gave 28b (21 mg, 0.07 mmol, 19%) as a glass. The other diastereomer 28a (50 mg, 0.22 mmol, 62%) was crystallised from acetonitrile.

28a: mp 177 - 179 °C; 'H NMR δ 9.65 (br s, 1H, H-12), 7.32 (d, J = 7.5 Hz, 1H, H-10), 6.95 (t, J = 7.5 Hz, 1H, H-9), 6.83 (d, J = 7.5 Hz, 1H, H-11), 3.56 (br d, J = 13.1 Hz, 2H, H-14; H-16), 3.38 (d, J = 13.1 Hz, 1H, H-14), 3.29 - 2.98 (m, 4H, H-3, H-4, H-14, H-16), 2.17 (br s, 1H, H-5), 2.06 - 1.97 (m, 1H, H-5), 1.84 - 1.75 (m, 1H, H-5), 1.38 - 1.33 (m, 1H, H-4_eq); 13C NMR δ 181.1 (C-13), 139.8 (C-11a), 136.6 (C-7a), 127.6 (C-10), 122.6 (C-8), 122.0 (C-9), 109.1 (C-11), 61.2 (C-1), 60.8 (C-7), 58.5 (C-3 or C-14), 56.0 (C-3 or C-14), 48.1 (C-6), 27.9 (C-5), 17.4 (C-4); IR ν 3437, 1708; HRMS (EI) obs. mass 228.1259, calcd for C_{14}H_{16}O: 228.1263.

28b: 'H NMR δ 9.16 (br s, 1H, H-12), 7.60 (d, J = 7.5 Hz, 1H, H-8), 7.20 (t, J = 7.5 Hz, 1H, H-10), 7.00 (t, J = 7.5 Hz, 1H, H-9), 6.90 (d, J = 7.5 Hz, 1H, H-11), 4.09 (br d, J = 11.4 Hz, 2H, H-14_eq), 3.56 (d, J = 13.0 Hz, 1H, 160
Condensation of 25 with hexanal (29). General procedure A was followed using 25 prepared from 16 (20 mg, 0.1 mmol) and hexanal (60 μL, 0.5 mmol). After stirring during 5 h at 90 °C, a mixture of two diastereomers in a ratio of 29a : 29b = 63 : 37 was formed according to 1H NMR spectroscopy of the crude reaction mixture (see text). Alternatively the reaction could be performed following general procedure B, reacting 25 (55 mg, 0.15 mmol), sodium acetate (20 mg, 0.25 mmol) and hexanal (60 μL, 0.5 mmol) during 6 h at 55 °C. According to 1H NMR spectroscopy of the crude reaction mixture two diastereomers in a ratio of 29a : 29b = 55 : 45 had been formed. Flash chromatography (EtOAc/PE/NET3, 65/30/5) gave 29a (14 mg, 0.05 mmol, 31%) and 29b (12 mg, 0.04 mmol, 26%) both as a glass.

29a: 1H NMR δ 7.86 (br s, 1H, H-12), 7.36 (d, J = 7.6 Hz, 1H, H-8), 7.19 (t, J = 7.6 Hz, 1H, H-10), 6.97 (t, J = 7.6 Hz, 1H, H-9), 6.85 (d, J = 7.6 Hz, 1H, H-11), 3.67 - 3.62 (m, 2H, H-1, H-14eq), 3.20 - 3.09 (m, 2H, H-3), 3.04 - 2.93 (m, 2H, H-4a, H-4b), 2.21 (br d, J = 2.9 Hz, 1H, H-6), 2.06 - 2.01 (m, 1H, H-5), 1.86 - 1.77 (m, 1H, H-5), 1.52 - 1.44 (m, 1H, H-15), 1.43 - 1.36 (m, 1H, H-14eq), 1.34 - 1.23 (m, 2H, H-17), 1.18 - 0.99 (m, 4H, H-16, H-18), 0.98 - 0.86 (m, 1H, H-15), 0.76 (t, J = 6.7 Hz, 3H, H-19); 13C NMR δ 180.1 (C-13), 139.5 (C-11a), 132.5 (C-7a), 127.5 (C-10), 124.3 (C-8), 121.8 (C-9), 109.1 (C-11), 71.1 (C-1), 62.6 (C-7), 60.7 (C-14), 56.9 (C-3), 49.0 (C-6), 34.5 (C-15), 31.6 (C-16), 27.4 (C-5), 27.4 (C-17), 22.3 (C-18), 17.8 (C-4), 13.8 (C-19); IR ν 3437, 1708; HRMS (EI) obs. mass 229.1345, calcd for C13H11NO2 (M + 1) 229.1341.

Condensation of 26 with hexanal (32). General procedure B was followed using 26 prepared from 17 (400 mg, 2.0 mmol), sodium acetate (492 mg, 6.0 mmol) and hexanal (1.25 mL, 10.0 mmol). Stirring the reaction mixture during 10 h at 65 °C resulted in complete conversion. According to the 1H NMR spectrum of the crude mixture the diastereomers had been formed in a ratio of 32a : 32b = 36 : 64. Flash chromatography (EtOAc/PE/NET3, 60/40/10) yielded both diastereomers 32a (131 mg, 0.44 mmol, 22%) and 32b (232 mg, 0.78 mmol, 39%) as a glass. Alternatively the reaction could be performed following general procedure A. Using 26 (20 mg, 0.1 mmol) and hexanal (25 μL, 0.2 mmol), after stirring during 8 h at 90 °C the diastereomers 32a : 32b (14 mg, 0.05 mmol, 47%) were formed in a ratio of 21 : 79 according to the 1H NMR spectrum of the crude reaction mixture.

32a: R2, (PE/EOx/AC/NET3, 60/30/10) 0.18; 1H NMR δ 8.30 (br s, 1H, H-11); 7.37 (d, J = 7.4 Hz, 1H, H-7), 7.19 (t, J = 7.4 Hz, 1H, H-9), 7.03 (t, J = 7.4 Hz, 1H, H-8), 6.86 (d, J = 7.4 Hz, 1H, H-10), 3.45 - 3.37 (m, 1H, H-13eq), 3.21 - 3.16 (m, 1H, H-3eq), 3.15 - 3.05 (m, 3H, H-1, H-3), 2.81 (dd, J = 11.0 Hz, 1H, H-13), 2.49 - 2.41 (m, 1H, H-14eq), 2.18 - 2.10 (m, 1H, H-4a), 1.85 - 1.77 (m, 1H, H-15), 1.71 (br s, 1H, H-5), 1.52 - 1.44 (m, 2H, H-4, H-15), 1.35 - 1.27 (m, 1H, H-14), 1.19 - 1.01 (m, 5H, H-16, H-17, H-18), 0.98 - 0.88 (m, 1H, H-16), 0.72 (t, J = 6.8 Hz, 3H, H-19); 13C NMR δ 179.7 (C-12), 140.3 (C-10a), 134.9 (C-6a), 127.4 (C-7), 124.2 (C-8), 121.6 (C-9), 109.2 (C-10), 64.4 (C-1), 52.6 (C-6), 49.7 (C-3), 41.4 (C-13), 31.5 (C-16), 31.4 (C-5), 29.7 (C-
Condensation of 26 with benzaldehyde (33). General procedure B was followed using 26 freshly prepared from 17 (200 mg, 1.0 mmol), sodium acetate (246 mg, 3.0 mmol) and benzaldehyde (0.51 mL, 5.0 mmol). The reaction did not go to completion (44 h, 60–65 °C). According to the $^1$H NMR spectrum of the crude mixture two diastereomers had been formed in a ratio of 33a : 33b = 36 : 64. Flash chromatography (EtOAc/PE/NET 40/55/5) gave a single isomer of 33a as a glass: $^1$H NMR δ 7.4 (br s, 1H, H-11), 7.55 (d, J = 7.4 Hz, 1H, H-7), 7.29 - 6.77 (m, 15H, Ar, H-10, H-14, H-13), 2.55 - 2.35 (m, 2H, H-13, H-14), 1.52 - 1.40 (m, 15H, Ar, H-10, H-14, H-13), 1.09 - 0.82 (m, 4H, H-15, H-16, H-17, H-18), 0.72 - 0.65 (m, 4H, H-16, H-19); $^1$C NMR δ 131.8 (C-12), 140.6 (C-10a), 129.6 (C-6a), 127.6 (C-8 or C-9), 126.6 (C-7 or C-10), 121.3 (C-7 or C-10), 109.9 (C-8 or C-9), 61.9 (C-1), 53.3 (C-6), 49.2 (C-3 or C-13), 41.6 (C-18), 27.2 (C-18), 22.6 (C-18), 22.1 (C-17), 20.4 (C-4 or C-14), 13.7 (C-19); IR v 3435, 1704; HRMS (EI) obs. mass 298.2059, calcd for C$_{16}$H$_{18}$O$_{3}$N, M + 1 299.2117.

Condensation of 27 with formaldehyde (34). General procedure A was followed with 27 freshly prepared from 18 (100 mg, 0.54 mmol) sodium acetate (246 mg, 3.0 mmol) and paraformaldehyde (16 mg, 0.54 mmol) in acetic acid (2 mL). The reaction mixture was stirred during 2 h at 70 °C. Flash chromatography (CH$_2$Cl$_2$/MeOH/coned. NH$_4$OH 80/20/2) afforded 34a as a glass: $^1$H NMR δ 8.04 (br s, 1H, H-11), 7.53 (d, J = 6.8 Hz, 1H, H-7), 7.30 (d, J = 7.6 Hz, 1H, H-8 or H-9), 7.15 - 7.08 (m, 1H, H-8, H-9), 4.49 (d, J = 16.6 Hz, 1H, H-1), 3.77 (d, J = 16.6 Hz, 1H, H-1), 3.40 - 3.32 (m, 2H, H-3, H-5), 3.09 (d, J = 10.8 Hz, 1H, H-13), 2.93 (d, J = 10.8 Hz, J = 2.8 Hz, 1H, H-13), 2.88 - 2.81 (m, 1H, H-3 or H-4a), 2.14 - 2.01 (m, 2H, H-3 or H-4a, H-4); IR v 3435, 1705.

Condensation of 27 with hexanal (35). General procedure B was followed using 27 freshly prepared from 18 (400 mg, 1.98 mmol) and hexanal (16 mg, 0.19 mmol) in acetic acid (2 mL). The mixture was stirred at rt during one night. In the crude reaction mixture 3 isomers could be discerned in a ratio of 35a : 35b : 35c = 50 : 5 : 45. Flash chromatography (EtOAc/PE/NET 60/40/10) gave 35a as a glass: $^1$H NMR δ 8.13 (C-12), 180.1 (C-12), 140.7, 140.6, 140.5, 139.2, 135.2, 130.3, 129.4, 129.1, 128.0, 127.9, 127.8, 127.4, 127.0, 126.6, 126.3, 126.2, 125.8, 125.3, 123.8, 121.8, 121.1, 115.5, 110.2, 110.0, 65.2 (C-1), 63.6 (C-1), 55.1 (C-6), 55.0 (C-6), 49.5, 49.3, 43.1 (2C), 31.9 (C-5), 31.6 (C-5), 22.8, 22.7, 22.3, 20.7; IR v 3435, 1705; HRMS (FAB) obs. mass 305.1667, calcd for C$_{16}$H$_{18}$ON$_{2}$ (M + 1) 305.1654.

The mixture was stirred at rt during one night. In the crude reaction mixture 3 isomers could be discerned in a ratio of 35a : 35b : 35c = 50 : 5 : 45. Flash chromatography (EtOAc/PE/NET 60/40/10) gave 35a as a glass: $^1$H NMR δ 8.13 (C-12), 180.1 (C-12), 140.7, 140.6, 140.5, 139.2, 135.2, 130.3, 129.4, 129.1, 128.0, 127.9, 127.8, 127.4, 127.0, 126.6, 126.3, 126.2, 125.8, 125.3, 123.8, 121.8, 121.1, 115.5, 110.2, 110.0, 65.2 (C-1), 63.6 (C-1), 55.1 (C-6), 55.0 (C-6), 49.5, 49.3, 43.1 (2C), 31.9 (C-5), 31.6 (C-5), 22.8, 22.7, 22.3, 20.7; IR v 3435, 1705; HRMS (FAB) obs. mass 305.1667, calcd for C$_{16}$H$_{18}$ON$_{2}$ (M + 1) 305.1654.
35b: $^1$H NMR (from the mixture) $\delta$ 9.10 (br s, 1H, H-11), 7.22 - 7.15 (m, 2H, H-7, H-8 or H-9), 6.99 (t, $J = 7.6$ Hz, 1H, H-8 or H-9), 6.92 (d, $J = 7.6$ Hz, 1H, H-10), 3.79 (br d, $J = 9.4$ Hz, 1H, H-13), 3.42 - 3.38 (m, 1H, H-1), 3.10 - 3.03 (m, 1H), 2.89 - 2.82 (m, 1H), 2.67 - 2.66 (m, 1H, H-5), 2.62 - 2.53 (m, 2H, H-13), 1.65 - 1.60 (m, 1H), 1.49 - 1.41 (m, 1H), 1.30 - 1.00 (m, 6H), 0.91 - 0.87 (m, 1H), 0.70 (t, $J = 6.9$ Hz, 3H, H-18); $^1$C NMR $\delta$ 182.9 (C-12), 141.8 (C-11a), 128.2 (C-7a), 127.5, 126.9, 120.9, 109.9 (C-11), 71.0 (C-1), 59.9, 56.1, 54.9, 50.8 (C-5), 43.9, 31.4, 26.8, 25.4, 22.1, 13.7 (C-18); IR $\nu$ 3436, 1703.

35c: $^1$H NMR (from the mixture) $\delta$ 8.02 (br s, 1H, H-11), 7.35 (d, $J = 7.6$ Hz, 1H, H-7), 7.21 (d, $J = 7.6$ Hz, 1H, H-8 or H-9), 7.00 (t, $J = 7.6$ Hz, 1H, H-10), 3.37 (br d, $J = 9.8$ Hz, 1H, H-13), 3.08 - 2.96 (m, 3H, H-1, H-3, H-13), 2.58 - 2.56 (m, 2H, H-3, H-5), 2.47 - 2.41 (m, 1H), 1.63 - 0.98 (m, 7H), 0.94 - 0.75 (m, 2H), 0.73 (t, $J = 7.0$ Hz, H-18); IR $\nu$ 3436, 1703.

Condensation of 27 with benzaldehyde (36). General procedure B was followed using 27 freshly prepared from 18 (149 mg, 0.80 mmol) and benzaldehyde (120 µL, 1.20 mmol). The mixture was stirred during one night at 55 °C. The diastereomers were formed in a ratio of 36b : 36c = 69 : 31 according to $^1$H NMR spectroscopy. Flash chromatography (PE/ EtOAc 50/50 then PE/EtOAc/NEt, 60/25/15) gave an inseparable mixture of two isomers 36b and 36c (14 mg, 0.05 mmol, 6%).

36b: $^1$H NMR (from the mixture) $\delta$ 7.95 (br s, 1H, H-11), 7.47 - 6.93 (m, 8H, H-7, H-8, H-9, Ar-H), 6.83 (d, $J = 7.5$ Hz, 1H, H-10), 4.23 (br s, 1H, H-11), 4.19 (br d, $J = 9.8$ Hz, 1H, H-13), 3.31 (ddd, $J = 12.1$ Hz, $J = 12.1$ Hz, $J = 6.9$ Hz, 1H, H-3), 3.04 - 2.99 (m, 1H, H-3), 2.80 (d, $J = 4.1$ Hz, 1H, H-5), 2.74 - 2.68 (m, 1H, H-13), 2.19 - 2.12 (m, 1H, H-4, Ar-H), 1.74 - 1.65 (m, 1H, H-4),$^1$C NMR (from the mixture) $\delta$ 178.9 (C-12), 141 - 109 (24 C's), 77.7 (C-1), 61.1 (C-3), 60.9 (C-6), 54.7 (C-3), 51.7 (C-5), 23.6 (C-4); IR $\nu$ 3437, 1705.

36c: $^1$H NMR (from the mixture) $\delta$ 8.12 (br s, 1H, H-11), 7.47 - 6.93 (m, 5H, H-7, H-8 or H-9, Ar-H), 6.56 (t, $J = 7.6$ Hz, 1H, H-8 or H-9), 6.39 (d, $J = 7.6$ Hz, 1H, H-10), 4.45 (br s, 1H, H-11), 3.49 (br d, $J = 9.9$ Hz, 1H, H-13), 3.17 (ddd, $J = 11.3$ Hz, $J = 11.3$ Hz, $J = 4.4$ Hz, 1H, H-3a), 3.06 - 3.04 (m, 1H, H-3), 2.74 - 2.68 (m, 2H, H-5, H-13), 2.59 - 2.53 (m, 1H, H-4), 1.49 - 1.46 (m, 1H, H-4); $^1$C NMR (from the mixture) $\delta$ 178.9 (C-12), 141 - 109 (24 C's), 79.4 (C-1), 61.0 (C-3), 60.2 (C-6), 55.3 (C-3), 50.9 (C-5), 25.0 (C-4); IR $\nu$ 3437, 1705.

7.6 References and Notes


2. Two classification systems for muscarinic cholinergic receptors are used in literature. The first is based on the pharmacological response to the available agonists and antagonists (M, through M4), the other is derived from molecular cloning methods using different tissues (M1 through M5). So far the correlation between these subtypes is not entirely clear, although M1-M5 are generally accepted to have pharmacological characteristics identical to M1-M5, respectively.


13. 7-alkyl-spiro[1-azabicyclo[3.2.1]octane-6,3'-[3'H]indole]-2'(1'H)-one.

14. No attempts were made to remove traces of acid from the CDCl.

15. 2-alkyl-spiro[1-azabicyclo[2.2.2]octane-3,3'-[3'H]indole]-2'(1'H)-one.


17. See chapter 6, § 6.2 and § 6.8, for the synthesis of the tryptamine derived cyclic amines.