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Serotonergic and Dopaminergic Activities of Rigidified (*R*)-Aporphine Derivatives

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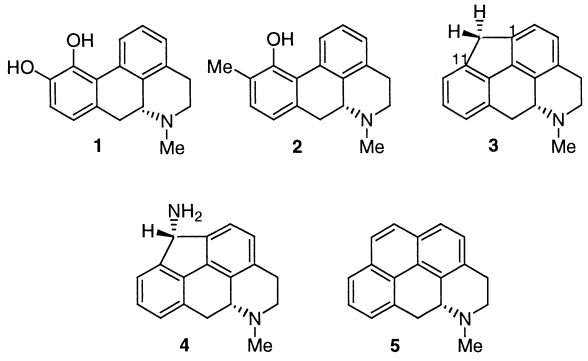
Abstract—Novel rigidified (*R*)-aporphine derivatives were synthesized from (*R*)-1,11-carbonylaporphine by ring expansion reactions. The structures of the novel analogues were assigned by NMR spectroscopy and X-ray crystallography. The compounds showed moderate affinities and selectivities at serotonin 5-HT_{1A} and 5-HT_7 and dopamine D_{2A} receptors.

Introduction

(*R*)-Apomorphine[1] (**1**) and modifications thereof have extensively been studied for their interaction with dopamine (DA) receptors in the central nervous system.[2] In addition, many natural aporphines have been isolated[3] and to a certain extent also been evaluated biologically at central DA receptors.[4]



In 1988, Cannon et al. published the 10-methyl substituted derivative of **1**, (*R*)-11-hydroxy-10-methylaporphine (**2**, HYMAP) in an effort to further study structure–activity relationships (SARs) of (*R*)-aporphines at DA receptors.[5] However, **2** was shown to be a selective serotonin 5-HT_{1A} receptor agonist.[6] This unexpected result made us then interested in the SARs of (*R*)-aporphines at serotonin receptors. We have previously reported on studies of **2** in which the 10- and/or 11-substituent has been modified.[7] Moreover, we recently reported on a novel and rigid (*R*)-aporphine structure, (*R*)-1,11-methyleneaporphine (**3**) which was functionalized in space below and above the plane of the ring structure. In this series of compounds a novel serotonin 5-HT_7 receptor antagonist, compound **4**, was discovered.[8]

In the present investigation we have expanded the medicinal chemistry around rigidified serotonergic analogues of (*R*)-aporphine. The synthesis, structure determination and pharmacological studies of the novel compounds based on ring structure **5** will be presented.

Chemistry

The novel ring structures[9] were synthesized as outlined in Scheme 1. Anhydrous trifluoroacetic acid peroxide,[10] generated in situ from urea hydrogen peroxide and trifluoroacetic acid anhydride,[11] was used as oxidizing agent in the Baeyer–Villiger reaction of 1,11-carbonylaporphine (**6**). Obtained *N*-oxides were conveniently reduced with $NaHSO_3$[12] to give the regioisomeric lactones **7** and **8** in a 55:45 ratio. The regioisomeric lactams **9** and **10** were obtained by a Beckmann rearrangement reaction of ketone **6**.[13] A one-pot method was used: ketone **6** was first treated with hydroxylamine hydrochloride in

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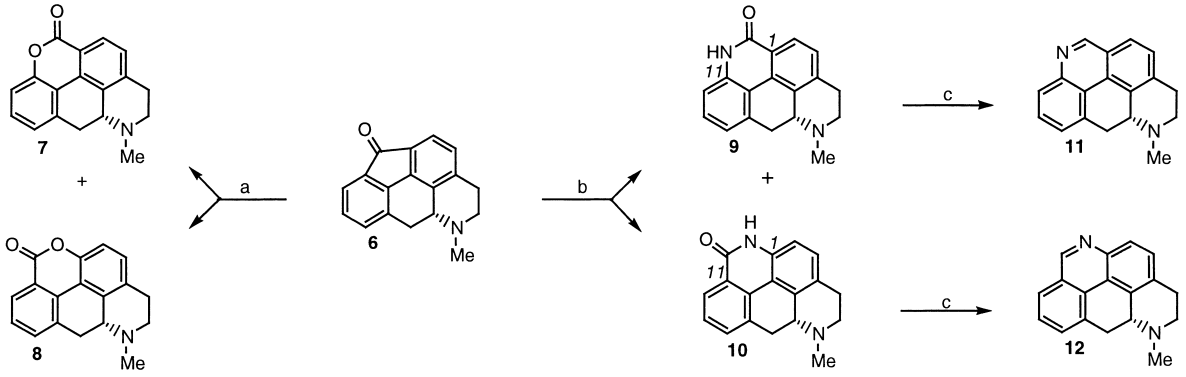


Scheme 1. (a) i. $(NH_2)_2CO{\cdot}H_2O_2$, $(CF_3CO)_2O$, Na_2HPO_4, CH_2Cl_2, rt, 22 h. ii. $NaHSO_3$, H_2O, rt, 4 h. iii. preparative HPLC (Dynamax 60-A column (8 μm SiO_2), hexanes:EtOH:Et_3N (90:10:0.3)), (**7**, 17% and **8**, 15%). (b) i. $NH_2OH{\cdot}HCl$, NaOAc, H_2O, 90 °C, 30 min. ii. polyphosphoric acid, 185 °C, 15 min. iii. column chromatography (SiO_2, $CHCl_3$:CH_2Cl_2:2-PrOH:MeOH (46:46:7:1)), (**9**, 40% and **10**, 23%). (c) i. $LiAlH_4$, dioxane, 100 °C, 15 min. ii. Pd/C, H_2O, 70 °C, 1 h, (**11**, 54% and **12**, 30%).

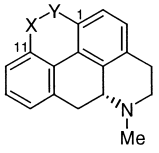
the presence of base to generate the oximes,[14] which were then treated with an excess of polyphosphoric acid. Efficient mechanical stirring and a reaction temperature of >160 °C in the second step of the reaction were crucial for a good yield.[15] The regioisomers **9** and **10** were obtained in a ratio of 60:40. The pyrido derivatives **11** and **12** were synthesized from lactams **9** and **10** by a two-step reaction sequence. First, the lactams were reduced with $LiAlH_4$ to the secondary amines, which were then oxidized to **11** and **12** with Pd/C. The intermediate amines were unstable and oxidation took place also during purification and storage. For example, the reduction product of **9** was completely oxidized to **11** after two weeks in D_2O at ambient temperature. Moreover, derivatizations of the secondary amines, for example to the corresponding acetamides or methylamines by reaction with acetyl chloride or iodomethane gave unstable compounds as indicated by NMR spectroscopy and TLC analysis.

Structure Determinations

The structure and the regiochemistry of the novel ring systems were established by a combination of X-ray crystallography, chemical correlation and NMR spectroscopy. The regiochemistry of **9** was unambiguously determined by X-ray crystallography. The assignment of **9** established indirectly also the regiochemistry of **10**, **11** and **12**. The regiochemistry of the novel derivatives could also be determined by ^{13}C NMR spectroscopy. The ^{13}C NMR chemical shifts of **7**–**12** were assigned by a combination of ^1H–^1H, ^1H–^{13}C and long-range ^1H–^{13}C (COLOC[16]) correlation experiments. A comparison of the ^{13}C NMR chemical shift of the aromatic carbon (C1 or C11) bonded to the regioisomeric heteroatom (N or O) indicated a consistent downfield shift for C11 in **9** and **11** compared to C1 in the corresponding isomers **10** and **12** (see Table 1). Therefore, the observed difference in chemical shift between **7** and **8** was used to assign their regiochemistry.

The solid-state conformation of **9** as determined by single crystal X-ray diffraction techniques is shown in Figure 1. It is as planar as the structure of the recently published 1,11-methyleneaporphines. The torsion angle between the two aromatic rings τ(C11,C11a,C11b,C1) in the crystal structure of **9** and **5** is −5° and −2°, respectively. For comparison, an average τ-value of −24° was previously found for the solid-state conformation of various (*R*)-aporphines.[8] Minimization (MM3) of the solid-state conformation of **9** resulted in the most stable conformation as identified in a Monte-Carlo search (MM3) using MacroModel.[17] Moreover,

Table 1. Selected ^{13}C NMR chemical shifts of importance for assignment of the regiochemistry of the novel derivatives



Compd	X–Y	δ (ppm) C11	δ (ppm) C1
7	–O–CO–	150.6	
8	–CO–O–		148.8
9	–NH–CO–	138.5	
10	–CO–NH–		133.3
11	–N=CH–	141.7	
12	–CH=N–		136.8

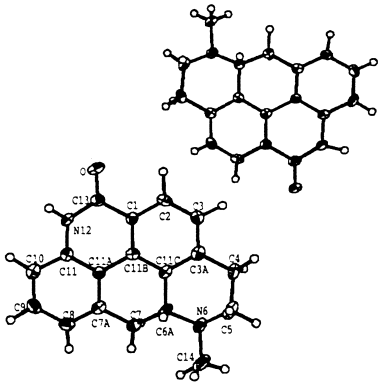


Figure 1. Perspective view (ORTEP) of the solid-state structure of **9** with crystallographic labelling of the atoms in one molecule. Displacement ellipsoids are represented at 50% probability level.

geometry optimization of the solid-state conformation of **9** by ab initio at the RHF/6-31G* level[18] confirmed the results obtained by MM3 (see Figure 2). Accordingly, the same preferred conformation of **9** is obtained both by experimental and computational methods.

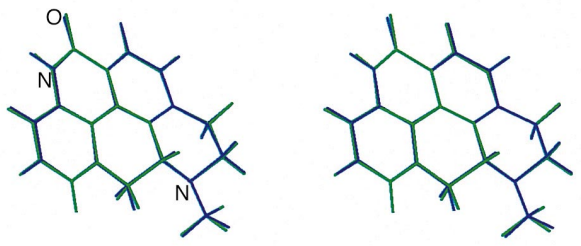


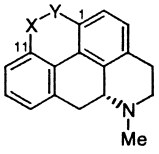
Figure 2. Stereoscopic representation of a best fit between the X-ray conformation of **9** (blue) and the corresponding ab initio geometry optimized conformation (green). All C, N and O atoms were fitted and the average distance between fitted atoms was 0.061 Å.

Pharmacological Evaluation and Discussion

The novel compounds were tested for their affinity to serotonin 5-HT_7 and 5-HT_{1A} receptors and to dopamine D_{2A} receptors in vitro as described previously.[8,19] The introduction of various two atom bridges between C1 and C11 in **3** gives regioisomeric compounds with variations in their pharmacological profiles. For example, the imino derivative **11** displays selectivity for 5-HT_7 receptors, whereas the regioisomer **12** and lactone **8** display selectivity for 5-HT_{1A} and D_{2A} receptors, respectively.

The C1-heteroatom binding regioisomers (**8**, **10**, **12**) show a similar trend as the C11-heteroatom binding regioisomers (**7**, **9**, **11**) at the serotonin receptor subtypes 5-HT_{1A} and 5-HT_7. In both groups the affinity decreases from the pyrido derivative to the lactam and the lactone.

Table 2. Binding affinities of the novel derivatives to 5-HT_7, 5-HT_{1A} and D_{2A} receptors



Compd	X–Y	K_i (nM)[a]		
		[^{3}H]5-HT (5-HT_7)	[^{3}H]8-OH-DPAT (5-HT_{1A})	[^{3}H]Raclopride (D_{2A})
7	–O–CO–	283 ± 128	1150 ± 270[b]	541 ± 17
8	–CO–O–	1480 ± 180	2030 ± 360[b]	265 ± 1
9	–NH–CO–	54.5 ± 8.8	178 ± 47	54.6 ± 27
10	–CO–NH–	341 ± 74	373 ± 9.5	6110 ± 3070
11	–N=CH–	27.2 ± 4.9	62.3 ± 14.2	1330 ± 350
12	–CH=N–	81.0 ± 12.0	33.9 ± 7.3	327 ± 35
3	$–CH_2–$	6.9 ± 0.3[c]	40.7 ± 12[c]	83.2 ± 9.9[c]
1		188 ± 17[c]	296 ± 15[d]	41.6 ± 4.7[d]

[a]The K_i values are means±standard errors of 2–3 experiments.
[b]Hippocampus.
[c]From ref 8.
[d]From ref 6b.

The most pronounced regioselectivity (112-fold) was displayed by lactams **9** and **10** at D_{2A} receptors. Otherwise a modest regioselectivity of only 2- to 6-fold at the three receptors was obtained.

A comparison of the affinities of the novel derivatives with those of the recently published analogues of **3** shows that a larger variation in the affinities is obtained within the latter group of compounds. This is most probably caused by the substituents being introduced below or above the plane of the ring system leading to larger structural and sterical differences in between those compounds. In the novel series of rigidified and regioisomeric (*R*)-aporphines the functional groups are introduced in the plane of the ring system and appear not to be different enough to produce a potent and highly selective receptor–ligand interaction (Table 2).

Acknowledgements

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9. The purity of all novel compounds was checked by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis (C,H,N). The CA names of the novel compounds are **7**: (6a*R*)-6a,7,8,9-tetrahydro-7-methylbenzo[1,8][2]benzopyrano[4,5,6-*hij*]isoquinolin-1(6*H*)-one; **8**: (6a*R*)-6a,7,8,9-tetrahydro-7-methyl-2*H*,6*H*-benzo-[4,5][2]benzopyrano[1,8,7-*hij*]isoquinolin-1(6*H*)-one; **9**: (6a*R*)-6a,7,8,9-tetrahydro-7-methyl-2*H*-pyrido[4,3,2-*jk*]thebenidin-1(6*H*)-one; **10**: (6a*R*)-6a,7,8,9-tetrahydro-7-methyl-2*H*-pyrido[2,3,4-*mn*]thebenidin-2-one; **11**: (6a*R*)-6a,7,8,9-tetrahydro-7-methyl-6*H*-pyrido[4,3,2-*jk*]thebenidine; **12**: (6a*R*)-6a, 7,8,9-tetrahydro-7-methyl-6*H*-pyrido[2,3,4-*mn*]thebenidine.
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