# 10,11- EPOXY- 3-METHYL- 1,2,3,4- TETRAHYDRO-4a,10b-PROPANO-BENZO[f]ISOQUINOLIN-12-ONES: A NOVEL TYPE OF OPIOID ANALGESICS – SYNTHETIC APPROACH AND STRUCTURE ELUCIDATION

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<u>Abstract</u> - The title compounds were obtained by nucleophilic cyclopropane ring opening and intramolecular Hofmann reactions, starting from 7,14-cyclo-dihydro-codeinone (1). An X-ray analysis of 10,11-epoxy-9-methoxy-3-methyl-1,2,3,4-tetrahydro-4a,10b-propanobenzo[*f*]isoquinolin-12-one dimethyl acetal (3) was performed as basis of molecular modeling studies.

### INTRODUCTION

There has been a resurgence of interest in the development of opioid analgesics since the existence of different binding receptors has become evident.<sup>1-3</sup> In the meantime, the theory of multiple opioid receptors is well established, stimulating investigations on development of selective agonists and antagonists with different profile of action.

Although analgesia is mediated by  $\mu$ ,  $\kappa$  and  $\delta$  receptors, most of the opioids act via the  $\mu$  receptor. This is associated with unwanted side effects such as physical dependence, constipation and respiratory depression. In recent years, attention has focused on the development of  $\kappa$  agonists providing analgesics without these undesired  $\mu$  specific properties.

Starting from 1, a simple reaction sequence affords a novel type of analgesics, which is characterized by a great similarity to the natural opioids, but a new orientation of the binding sites.



#### **RESULTS AND DISCUSSION**

As reported in a previous paper, we found that under selected reaction conditions (SOCl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH) the cyclopropane moiety of **1** is functionalized to the  $\beta$ -halomethyl acetal.<sup>4</sup> Whereas **2** is unreactive towards nucleophiles as neopentyl halide in presence of a base the intramolecular attack of the nitrogen is favoured yielding the Hofmann product (**3**).<sup>4</sup> The synthesis of **3** can be simplified by a one-pot procedure affording the acetal respectively the ketone (**4**) in a yield of more than 90 %. A hydrogenation step provides **5** or **6**.

The acetal (3) enables an approach to a novel ring system, which still incorporates the essential structure elements of opioids. In this manner, the ketones (4) and (6) can be regarded as leading substances of a novel structure class, which, excluding the cyclopentanone ring, solely differs from natural opioids in the transposed annelated piperidine ring. Recently, a series of constrained *N*-methylaminoethylbenzamides has been synthesized to clarify how the orientation of the aromatic ring relative to the basic nitrogen influences the binding profile of the molecules.<sup>5</sup> Accordingly, an X-ray analysis of **3** was performed, additionally to pharmacological investigations, to get parameters for molecular modeling studies (Figure 1). The atom coordinates and thermal factors are summarized in Tables 1 and 2.

	x	У	z	U <sub>11</sub>	<sup>U</sup> 22	U <sub>33</sub>	U <sub>23</sub>	<sup>U</sup> 13	<sup>U</sup> 12
C1	0.1308(3)	0.0088(4)	0.1337(6)	0.037(3)	0.043(3)	0.047(3)	~0.009(3)	0.006(3)	0.006(3)
C2	0.2205(3)	-0.0237(4)	0.0703(7)	0.031(3)	0.050(4)	0.058(4)	~0.002(3)	0.010(3)	0.005(3)
C4	0.1571(3)	-0.1706(4)	-0.0528(6)	0.039(3)	0.038(3)	0.051(3)	~0.003(3)	0.010(3)	-0.006(3)
C4a	0.0639(3)	-0.1446(4)	-0.0044(5)	0.037(3)	0.033(3)	0.041(3)	0.001(3)	0.005(3)	0.001(2)
C5	0.0347(4)	-0.2121(4)	0.1258(6)	0.047(3)	0.041(3)	0.043(3)	0.010(3)	0.015(3)	0.012(3)
C6	-0.0261(3)	-0.1845(4)	0.2211(6)	0.048(3)	0.053(4)	0.039(3)	0.016(3)	0.003(3)	0.015(3)
C6a	-0.0709(3)	-0.0853(4)	0.2073(5)	0.039(3)	0.061(4)	0.034(3)	0.005(3)	0.001(3)	0.009(3)
Ç7	-0.1531(4)	-0.0562(5)	0.2610(6)	0.051(3)	0.066(4)	0.042(3)	0.007(3)	+0.009(3)	0.013(3)
C8	-0.1930(3)	0.0334(5)	0.2143(6)	0.043(3)	0.075(4)	0.046(3)	~0.009(4)	-0.012(3)	0.004(3)
C9	-0.1571(3)	0.0971(4)	0.1046(6)	0.039(3)	0.047(3)	0.049(3)	~0.010(3)	0.001(3)	-0.003(3)
C10	-0.0751(3)	0.0673(4)	0.0526(5)	0.035(3)	0.037(3)	0.044(3)	~0.006(3)	-0.008(3)	0.005(3)
C10a	-0.0329(3)	-0.0162(4)	0.1107(5)	0.029(3)	0.039(3)	0.038(3)	~0.007(3)	-0.003(3)	0.006(3)
C10b	0.0548(3)	-0.0300(4)	0.0366(5)	0.032(3)	0.034(3)	0.040(3)	~0.005(3)	-0.001(3)	0.005(3)
C11	0.0370(3)	0.0324(3)	-0.1016(5)	0.031(3)	0.028(3)	0.039(3)	~0.002(3)	-0.004(2)	0.003(2)
C12	0.0055(3)	-0.0478(4)	-0.2145(5)	0.028(3)	0.035(3)	0.041(3)	0.007(3)	0.001(3)	0.003(2)
C13	-0.0001(3)	-0.1535(3)	-0.1355(5)	0.032(3)	0.034(3)	0.040(3)	0.002(3)	0.005(3)	0.005(2)
C14	0.3104(3)	-0.1710(5)	0.0084(7)	0.039(3)	0.070(4)	0.079(4)	0.008(4)	-0.002(3)	-0.014(3)
C15	-0.2711(4)	0.2237(4)	0.1097(7)	0.052(4)	0.063(4)	0.095(5)	~0.017(4)	-0.011(4)	-0.015(3)
C16	-0.0871(4)	0.0607(4)	-0.3635(7)	0.067(4)	0.048(4)	0.086(4)	0.029(4)	0.032(4)	0.007(3)
C17	0.0622(4)	-0.1190(5)	-0.4411(6)	0.071(4)	0.081(5)	0.046(3)	~0.021(4)	-0.008(4)	0.012(4)
N1	0.2226(3)	-0.1376(3)	0.0555(5)	0.032(2)	0.047(3)	0.056(3)	~0.001(3)	0.010(2)	-0.003(2)
01	-0.0297(2)	0.1098(2)	-0.0637(4)	0.039(2)	0.031(2)	0.052(2)	0.005(2)	-0.012(2)	-0.004(2)
02	-0.1954(2)	0.1805(3)	0.0414(4)	0.047(2)	0.056(3)	0.071(3)	~0.005(2)	-0.013(2)	-0.012(2)
03	-0.0794(2)	-0.0294(3)	-0.2747(4)	0.030(2)	0.042(2)	0.059(2)	0.012(2)	0.013(2)	0.005(2)
04	0.0707(2)	-0.0449(3)	-0.3246(3)	0.039(2)	0.049(2)	0.035(2)	~0.004(2)	-0.005(2)	0,009(2)

Table 1. Atomic coordinates and thermal parameters of  $3 [pm^2 \times 10^{-4}]$  with standard deviations ()

Table 2. Calculated atomic coordinates of hydrogen atoms of 3

	x	У	z		x	Y	z
H11	0.1281	0.0921	0,1401	H141	0.3583	-0.1466	0.0882
H12	0.1237	-0.0236	0.2417	H142	0.3119	-0.2541	-0.0014
H21	0.2296	0.0117	-0.0353	H143	0.3257	-0.1365	-0.0958
H2 2	0.2722	0.0010	0.1429	H151	-0.2939	0.2891	0.0471
H41	0.1623	-0.2531	-0.0680	H152	-0.3222	0.1661	0.1151
H42	0.1703	-0.1319	-0.1549	H153	-0.2545	0.2487	0.2187
H51	0.0660	-0.2862	0.1400	H161	-0.1536	0.0671	-0.4035
H61	~0.0428	-0.2358	0.3098	H162	-0.0712	0.1282	-0.2996
H71	~0.1857	-0.1044	0.3405	H163	-0.0425	0.0550	-0.4547
H81	~0.2547	0.0557	0.2630	H171	0.1155	-0.1090	-0.5174
н111	0.0927	0.0735	-0.1459	H172	0.0642	-0.1962	-0.3967
н131	0.0199	-0.2153	-0.2074	H173	0.0005	-0.1072	-0.4965
H132	~0.0662	-0.1677	-0.0978				

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Figure 1. Perspective view and atom labelling of the X-ray structure of 3<sup>7</sup>

Figure 2. Molecule fitting of the crystal structures of 3 (-) and morphine (---). The substituents are omitted in consideration of better visibility, excluding the *N*-methyl group.

Molecule fitting of **3** with morphine as reference molecule exposes the remarkable structure modification in the area of the piperidine molety.<sup>6</sup> Although the binding sites retain in their relative positions, the distance between the nitrogen atoms of the overlapped crystal structures is more than 2 Å (Figure 2).

The modified annelation results in a higher flexibility of the piperidine ring which also allows the boat conformation, according to force field calculations.<sup>8</sup> However, the coupling constants of the piperidine protons (400 MHz) affirm the chair conformation in solution which is in agreement to the conformation in crystal state. The correct assignment of the piperidine protons could be ascertained by formation of methiodide (7), followed by Hofmann degradation yielding **8** as reference substance.



#### EXPERIMENTAL

Melting points were taken on a Kofier hot stage apparatus and are uncorrected. Solvents and common reagents were obtained commercially and used as received or purified as follows: dichloromethane was distilled under nitrogen from phosphorus pentoxide, methanol was refluxed under nitrogen over magnesium and distilled. Elemental analyses were performed by Dr. J. Zak and Mag. J. Theiner, Institut für Physikalische Chemie der Universität Wien. Preparative thin layer chromatography was carried out on 2 mm aluminum oxide 60 HF254 plates (MERCK). Ir spectra were recorded as thin films on salt discs on a Perkin Elmer model 298 spectrophotometer. Nmr spectra were determined by using the spectrometers Varian EM 390, Bruker AC 80, WM 250, and AM 400 WB.<sup>9</sup> All substances were measured in CDCl<sub>3</sub> as solvent with (CH<sub>3</sub>)<sub>4</sub>Si as the internal reference. Mass spectra were obtained by using a Varian MAT 111A spectrometer.

(4aR, 10bS, 11R)-10,11-Epoxy-1,2,3,4-tetrahydro-9-methoxy-3-methyl-4a,10b-propanobenzo[/]isoquinolin-12-one Dimethyl Acetal (3) and (4aR, 10bS, 11R)-10,11-Epoxy-1,2,3,4 -tetrahydro-9-methoxy-3-methyl-4a,10b-propanobenzo[/]isoquinolin-12-one (4)

300 mg (1 mmol) of 1 were dissolved in dry dichloromethane (20 ml) and dry methanol (5 ml). The solution was cooled to -20  $^{\circ}$ C and thionyl chloride (1 ml, 14 mmol) was added dropwise. After stirring for 5 h at room temperature, the reaction mixture was recooled to -20  $^{\circ}$ C and a solution of 5 g of K<sub>2</sub>CO<sub>3</sub> in 20 ml of methanol was added. Then, this mixture was refluxed over a period of 8 h.

A (providing 3): The solution was diluted with water, the volatile solvents were removed under reduced pressure, and the resulting aqueous solution was extracted with dichloromethane (3x20 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness. The oily residue was treated with ethanol, giving the crystalline acetal (3) (340 mg, 98 %). mp 163  $^{\circ}$ C (methanol); <sup>1</sup>H-nmr (400 MHz):  $\delta$  (ppm) 6.67, 6.59 (2H, AB-system, J = 8.0 Hz, 7-H, 8-H), 6 .45 (1H, d, J = 9.0 Hz, 6-H), 5.65 (1H, d, J = 9.0 Hz, 5-H), 4.78 (1H, s, 11-H), 3.88 (3H, s, arom. OCH<sub>3</sub>), 3.25, 3.21 (each 3H, each s, acetal-OCH<sub>3</sub>), 2.76 (1H, d, J = 11.5 Hz, 2a-H), 2.70 (1H, d, J = 11.0 Hz, 4a-H), 2.31 (3H, s, N-CH<sub>3</sub>), 2.26

(1H, d, J = 11.0 Hz, 4b-H), 1.97 (1H, dt, J = 3.6 Hz, J = 11.5 Hz, 2b-H), 1.90 - 1.75 (2H, m, 1a-H, 2a-H), 1.84 (1H, d, J = 14.0 Hz, 13a-H), 1.38 (1H, d, J = 14.0 Hz, 13b-H); ir and ms correspond to ref. 4.

B (providing 4): After acidifying the solution with 6N HCl, the reaction mixture was stirred for 20 min at room temperature. Then, the solution was concentrated in vacuo, basified with 2N NaOH to pH 8 and extracted with dichloromethane (3x20 ml). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent afforded 275 mg (92 %) of 4. mp 157  $^{\circ}$ C (methanol); <sup>1</sup>H-nmr (90 MHz):  $_{\delta}$  (ppm) 6.72 (2H, s, 7-H, 8-H), 6.56 (1H, d, J = 9.0 Hz, 6-H), 5.83 (1H, d, J = 9.0 Hz, 5-H), 4.73 (1H, s, 11-H), 3.87 (3H, s, OCH<sub>3</sub>), 2.30 (3H, s, NCH<sub>3</sub>); ir: 1750 (C = O); ms (m/z): 297 (M<sup>+</sup>). Anal. Calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>3</sub>: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.70; H, 6.37; N, 4.83.

# (4aR,10bS,11R)-10,11-Epoxy-1,2,3,4,5,6-hexahydro-9-methoxy-3-methyl-4a,10b-propanobenzo[f]isoquinolin-12-one Dimethyl Acetal (5)

300 mg (0.87 mmol) of **3** were dissolved in acetic acid (10 ml) and hydrogenated at 80  $^{\circ}$ C for 6 h (5 % Pd/C, 30 mg). The reaction mixture was filtered and evaporated to dryness. The oily residue was dissolved in water, basified with solid Na<sub>2</sub>CO<sub>3</sub> and extracted with dichloromethane (3x20 ml). After drying over Na<sub>2</sub>SO<sub>4</sub> the drying agent was removed by filtration, and the solvent was removed to yield 280 mg (93 %) of 5. mp 144 - 145  $^{\circ}$ C (methanol); <sup>1</sup>H-nmr (90 MHz):  $_{\delta}$  (ppm) 6.66, 6.56 (2H, AB-system, J = 8.0 Hz, 7-H, 8-H), 4.70 (1H, s, 11-H), 3.84 (3H, s, arom. OCH<sub>3</sub>), 3.22, 3.16 (each 3H, each s, acetal-OCH<sub>3</sub>), 2.28 (3H, s, NCH<sub>3</sub>); ms (m/z) 345 (M<sup>+</sup>). Anal. Calcd for C<sub>20</sub>H<sub>27</sub>NO<sub>4</sub>: C, 72.21; H, 7.07; N, 4.67. Found: C, 71.93; H, 7.03; N, 4.42.

### (4aR,10bS,11R)-10,11-Epoxy-1,2,3,4,5,6-hexahydro-9-methoxy-3-methyl-4a,10b-propanobenzo[f]isoquinolin-12-one (6)

A (Starting from 5): 300 mg (0.87 mmol) of 5 were dissolved in 2N HCl (20 ml) and warmed on a water bath (60  $^{\circ}$ C) for 20 min. The solution was then basified with 2N NaOH (pH 8) and extracted with dichloromethane. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to yield 235 mg (91 %) of **6** as a spontaneously crystallizing oil.

B (Starting from 3): 300 mg (0.87 mmol) of 3 were dissolved in 2N HCl (50 ml) and hydrogenated at 60  $^{o}$ C for 8 h (5% Pd/C, 30 mg). After filtration, the solution was evaporated, the oily residue was diluted with water and basified with solid Na<sub>2</sub>CO<sub>3</sub> (pH 8). Then, the aqueous solution was extracted with dichloromethane (3x20 ml). The combined dichloromethane extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated, leaving 230 mg (90 %) of 6. mp 136 - 137  $^{o}$ C (methanol); <sup>1</sup>H-nmr (90 MHz):  $\delta$  (ppm) 6.64 (2H, s, 7-H, 8-H), 4.63 (1H, s, 11-H), 3.80 (3H, s, OCH<sub>3</sub>), 2.26 (3H, s, NCH<sub>3</sub>); <sup>13</sup>C-nmr (20.1 MHz):  $\delta$  (ppm) 214.7 (12-C), 146.2 (10-C), 142.3 (9-C), 130.8 (10a-C), 127.2 (6a-C), 121.8 (7-C), 114.3 (8-C), 88.6

(11-C), 65.6, 52.5, 51.0 (2-C, 4-C, 5-C), 56.6 (OCH<sub>3</sub>), 46.4 (NGH<sub>3</sub>), 49.7, 37.9, 29.2, 28.5 (1-C, 4a-C, 10b-C, 13-C), 23.7 (6-C); ir: 1745 (C=O); ms (m/z): 299 (M<sup>+</sup>). Anal. Calcd for  $C_{18}H_{21}NO_3$ : C, 72.21; H, 7.07; N, 4.67. Found: C, 72.16; H, 7.07; N, 4.58.

### (4aR,10bS,11R)-10,11-Epoxy-1,2,3,4-tetrahydro-9,12,12-trimethoxy-3,3-dimethyl-4a,10bpropanobenzo[/]isoquinolinium lodide (7)

300 mg (0.87 mmol) of **3** were dissolved in methanol (10 ml), methyl iodide (5 ml, 80 mmol) was added, and the solution was refluxed for 20 min. Evaporation and crystallization from water gave 350 mg (83 %) of **7** as yellow crystals. mp 192-193 <sup>o</sup>C (water/methanol); <sup>1</sup>H-nmr (80 MHz):  $\delta$  (ppm) 6.68 (2H, AB-peak, 7-H, 8-H), 6.50 (1H, d, J = 9.6 Hz, 6-H), 5.91 (1H, d, J = 9.6 Hz, 5-H), 4.82 (1H, s, 11-H), 3.87 (3H, s, arom. OCH<sub>3</sub>), 3.67, 3.61 (each 3H, each br s, N<sup>+</sup>(CH<sub>3</sub>)<sub>2</sub>), 3.25, 3.21 (each 3H, each s, acetal-OCH<sub>3</sub>).

## (4aR,10bS,11R)-10,11-Epoxy-3,4-dihydro-9-methoxy-3,3-dimethyl-2,3-seco-4a,10b-propanobenzo[/]isoquinolin-12-one Dimethyl Acetal (8)

A solution of 100 mg (0.21 mmol) of 7 in a mixture of water and methanol (20 ml, 10:1) was transferred to a column packed with an anion exchange resin (Amberlite IRA-400), which was previously treated with 2N NaOH and washed with water. The elution afforded a solution of the quaternary ammonium base, which was concentrated under reduced pressure, redissolved in methanol, and heated for 1 h at 170  $^{\circ}$ C in vacuo (10 mm Hg). Then, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with water (3x10 ml), and dried over Na<sub>2</sub>SO<sub>4</sub>. The drying agent was removed by filtration and the solvent was evaporated in vacuo affording a brownish oil. Preparative tlc (eluent: 2-propanol) yielded 45 mg (61 %) of 8 as a colorless oil. <sup>1</sup>H-Nmr (250 MHz) :  $_{\delta}$  (ppm) 6.68, 6.61 (2H, AB-system, J = 8.0 Hz, 7-H, 8-H), 6.42, 5.90 (2H, AB-system, J = 10.0 Hz, 5-H, 6-H), 5.98, 5.13, 5.07 (each 1H, ABX-system, J = 6.9 Hz, J = 9.6 Hz, J = 17.0 Hz, 1-H, 2a-H, 2b-H), 4.91 (1H, s, 11-H), 3.88 (3H, s, arom. OCH<sub>3</sub>), 3.31, 3.28 (each 3H, each s, acetal-OCH<sub>3</sub>), 2.61, 2.55 (2H, AB-system, J = 14.0 Hz, 4a-H, 4b-H), 2.39 (6H, s, N(CH<sub>3</sub>)<sub>2</sub>), 2.33 (1H, d, J = 14.0 Hz, 13β-H), 1.35 (1H, d, J = 14.0 Hz, 13α-H); ms (m/z): 357 (M<sup>+</sup>).

#### Crystallography

Crystal data:  $C_{20}H_{25}NO_4$ ,  $M_r = 343.47$ , crystal dimensions 0.68 x 0.23 x 0.15 mm, orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, a = 1522.1(2), b = 1294.2(1), c = 917.07(5) pm, V = 1806.54 x 10<sup>6</sup> pm<sup>3</sup>, Z = 4, D<sub>c</sub> = 1.263 g/cm<sup>3</sup>.

Intensity data were collected at room temperature with a Philips PW1100 four-circle diffractometer by using monochromatized Mo-K<sub> $\alpha$ </sub> radiation (graphit monochromator). Throughout data collection 1649 independent reflections [1286 with I > 2<sub> $\sigma$ </sub>(i)] were obtained in the range of  $\Theta$  = 26<sup> $\circ$ </sup>, 1648 reflections

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were used for structure solution and refinement. The structure was solved by direct method (MULTAN 78<sup>10</sup>), and refined by blocked cascade least-squares procedures (SHELX 76<sup>11</sup>). All nonhydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were calculated under the presupposition of ideal geometry, the refinement was done in combination with their carrier atoms. The refinement results in the final atom coordinates and thermal parameters, listed in Tables 1-2, and the R-values R = 0.075 and R<sub>w</sub> = 0.067 [w =  $1/(\sigma^2 + 0.0002 \times F^2)$ ].<sup>12</sup>

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