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DESIGN AND SYNTHESIS OF NEW POTENTIAL LIGANDS OF μ- AND δ-OPIATE RECEPTORS IN THE SERIES OF DECAHYDRO-4*a*-HYDROXY-6-ISOQUINOLONE

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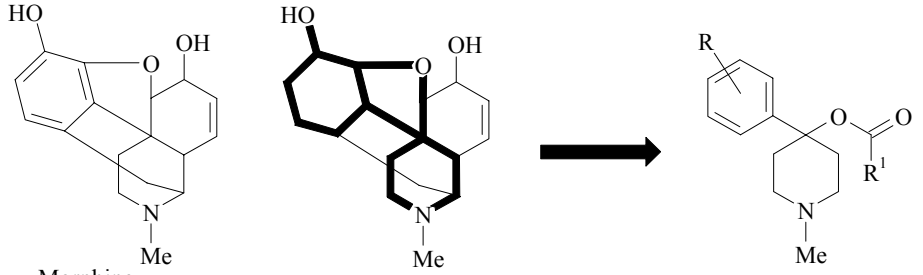
A new approach has been proposed for simplification of the morphine molecule in order to obtain new potential μ- and δ-opiate receptor ligands. The reaction of 1,2,5-trimethyl-4-piperidone and 2,2-dimethyl-4-tetrahydropyrone with substituted benzalacetones under Robinson ring fusion conditions gave decahydroisoquinoline and decahydroisochromene derivatives. A thorough conformational analysis of these products was carried out. The effect of the products on the functional activity of opiate receptors on the mouse vas deferens isolated organ (MVD) model was studied. Prior screening showed that 8-(p-dimethylaminophenyl)-4a-hydroxy-2,3,8a-trimethyldecahydro-6-isoquinolone displays opiate activity and has agonist properties.

Keywords: 4*a*-hydroxydecahydroisoquinolines, 4*a*-hydroxy-2,3,8*a*-trimethyl-8-phenyldecahydro-6-isoquinolone, morphine, 1,2,5-trimethyl-4-piperidone, agonists, Robinson ring fusion, MVD model, opiate activity.

A series of newly synthesized, highly efficient analgesic compounds has recently been obtained [1]. Most of these compounds were obtained by simplifying the morphine molecule while retaining its structural elements [2].



Morphine — Analgesic compounds

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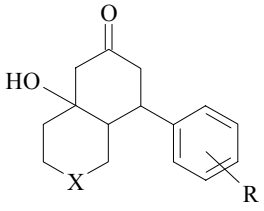
This approach has yielded compounds differing in strength and duration of analgesic activity, rate and extent of addiction, and other side effects [3].

At present, an important problem is the search for new opioid receptor blockers, namely, antagonists of narcotic analgesics, which are commonly used in the treatment of acute poisoning caused by morphine-group compounds.

In the present work, we designed and synthesized potential ligands for μ- and δ-opiate receptors, differing in their structural criteria, from existing linear and polycondensed systems.

Our modification pathway presupposes a rigid decahydroisoquinoline system within the morphine molecule, which differs from 4-phenylpiperidine derivatives by the lack of conformational changes and the possibility of further study of the relationship between structure and the pharmacologic action; the 4-phenylpiperidine system lacks such possibility.

The existence of a hydroxyl group at C-4*a* in the decahydroisoquinoline system, as in the case of 4-phenylpiperidine derivatives [2], provides for hydrophilic properties of the system. The structural alterations carried out on the morphine molecule permit a systematic search for agonists and antagonists of narcotic analgesics in the series of decahydroisoquinoline systems.

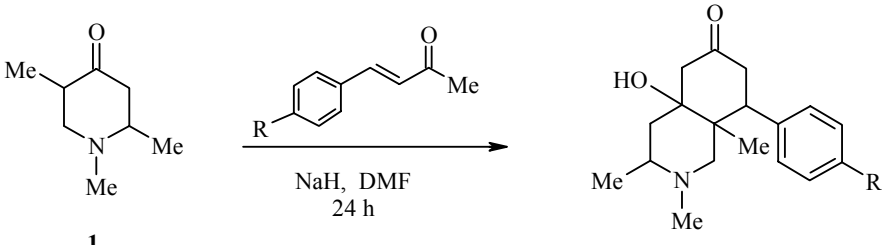


X = O, NMe

Methods have been reported for the preparation of decahydro-6-isoquinolone derivatives [4], which are initial building blocks for obtaining manzamine alkaloids, which display antibacterial and antimalarial activity, and for the synthesis of antagonists of NMDA and iGluR5 receptors [5, 6]. A new class of analgesic compounds has been developed on the basis of tricyclic polycondensed systems containing a decahydroisoquinoline fragment [7].

The Mannich reaction with subsequent Robinson ring closure is a pathway, which we have chosen for the modification of piperidine derivatives in order to obtain bicyclic condensed systems [8].

N-Substituted 4-piperidones and 2,2-dimethyl-4-tetrahydropyrone were selected as model compounds. Defined conditions were selected for each individual reaction. We have shown that the reaction of 1,2,5-trimethyl-4-piperidone with substituted benzalacetones in the presence of NaH under Mannich reaction conditions at room temperature leads to the formation of 4*a*-hydroxy-2,3,8*a*-trimethyl-8-phenyldecahydro-6-isoquinolone (**2**) and 8-(*p*-dimethylaminophenyl)-4*a*-hydroxy-2,3,8*a*-trimethyldecahydro-6-isoquinolone (**3**).



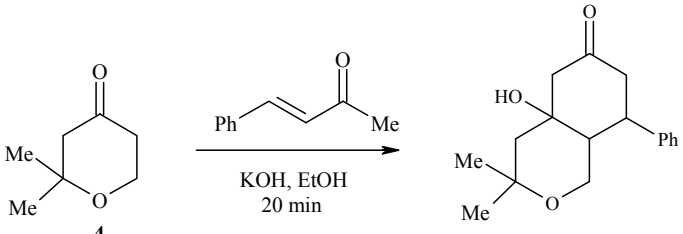
1 **2, 3**

2 R = H (34%); **3** R = NMe_2 (39%)

The ^{1}H NMR spectra of the products confirmed the formation of polycondensed systems **2** and **3** as indicated by the singlets for the 8*a*-CH_3 protons at 0.92 (compound **2** in DMSO-d_6) and 0.89 ppm (compound **3** in $CDCl_3$) and the doublets for H-5 in the decahydroisoquinoline system at 2.18 and 3.00 ppm (for **2** in DMSO-d_6) and 1.73 and 2.92 ppm (for **3** in $CDCl_3$).

The reaction of N-methyl-4-piperidone, 3-tropone, and N-benzyl-4-piperidone with benzalacetone at room temperature and different solvents such as ethanol and DMF using strong bases such as KOH and NaH did not lead to the formation of decahydro-4*a*-isoquinoline systems. Instead, polymerization predominates. Polymerization is reduced to a side process in the reaction of N-benzyl-4-piperidone with benzalacetone in DMF at -20°C. Thin-layer chromatographic analysis indicated formation of a mixture of two compounds, which could not be separated by recrystallization. The elemental analysis data for this mixture of potential stereoisomers and mass spectrometric analysis were in accord with formation of the decahydroisoquinoline system. Complete identification of the mixture obtained was not possible due to the complex NMR spectra of the mixture of potential stereoisomers.

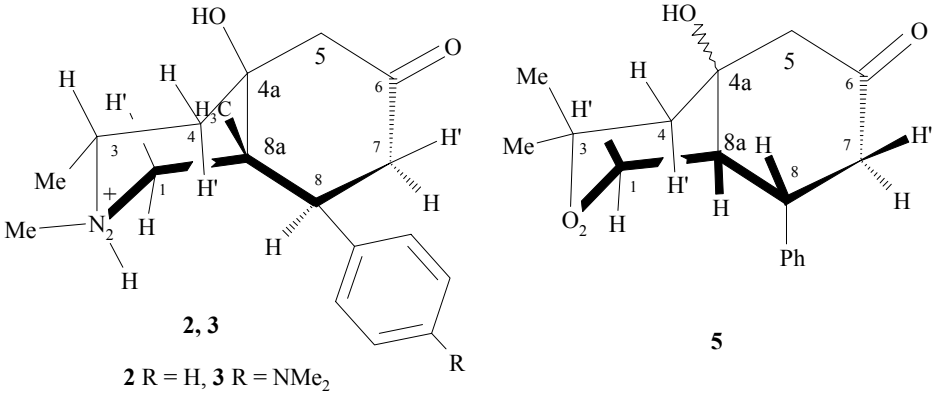
The reaction of 2,2-dimethyl-4-tetrahydropyrone (**4**) with benzalacetone proceeded in the presence of a milder base, KOH, at room temperature.



4 **5** (27%)

The IR spectra of compounds **2**, **3**, and **5** showed stretching bands for the aliphatic C=O group at 1700-1710 cm^{-1} and for the hydroxyl group at 3380-3440 cm^{-1}.

The stereochemistry of decahydroisoquinolines **2** and **3** and 4*a*-hydroxy-3,3-dimethyl-8-phenyldecahydroisochromen-6-one (**5**) was studied by ^{1}H NMR spectroscopy. The assignment of the signals of the protons in the ^{1}H NMR spectra of compounds **2**, **3**, and **5** was carried out by double resonance experiments. The coupling constants were used to establish that in keto alcohol **2**, the H-3 and H-4' protons (J = 13.2) and the H-3 and H-4 protons (J ~ 0 Hz) are in *a,a* and *a,e* positions, respectively, while H-8 and H-7' (J = 13.6) and H-8 and H-7 (J = 4.0 Hz) occupy *a,a* and *a,e* positions. The 3-CH_3 methyl group occupies an equatorial position, while the methyl group at the nitrogen atom is also in an equatorial position. The presence the *trans* constants for N(2)H^+ and H-1' (J = 12.7 Hz) confirms this. The aromatic substituent at C-8 is in an equatorial position.



2, 3 **5**

2 R = H, **3** R = NMe_2

TABLE 1. Some Coupling Constants for **2, 3**, and **5**

Compound	SSCC, J, Hz*								
	$J_{1a,1e}$	$J_{1a,2a(NH+)}$	$J_{3a,4a}$	$J_{3a,4e}$	$J_{4a,4e}$	$J_{5a,5e}$	$J_{7a,7e}$	$J_{8a,7a}$	$J_{8a,7e}$
2	13.10	12.70	13.2	~0	13.4	13.4	13.4	13.6	4.0
3	12.2	—	11.5	2.9	14.4	12.0	14.8	14.8	3.9
5*[2]	13.0	—	—	—	13.5	13.5	11.7	—	4.1

* *a* – axial, *e* – equatorial position.

*[2] $J_{1a(8a)a}$ = 12.5; $J_{1e(8a)a}$ = 4.1; $J_{8a(8a)a}$ = 13.7 Гц.

The arrangement of 8*a*-CH_3 and 4*a*-OH compound on the ring and the conformation of the decahydroisoquinoline groups system have already been studied in detail by X-ray diffraction structural analysis for compound **2** [9].

The coupling constants for compound **3** are similar to those for compound **2** (Table 1).

We employed two-dimensional COSY spectroscopy to check the assignment of the signals for the protons of some fragments in compounds **3** and **5** (Figs. 1 and 2).

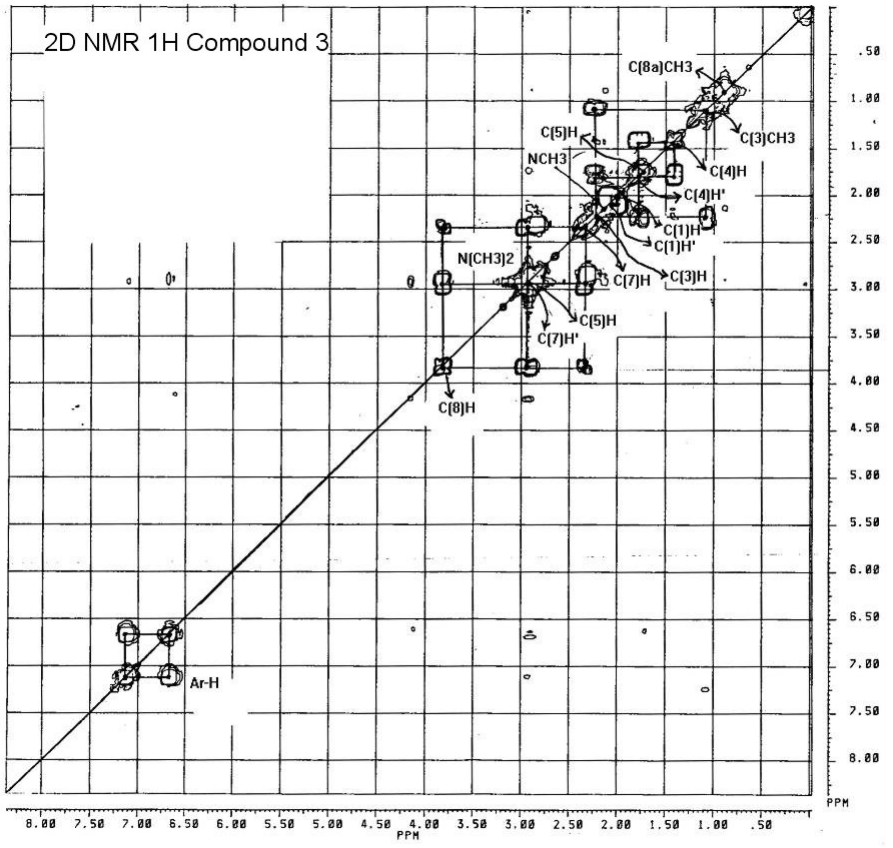


Fig. 1. Two-dimensional COSY spectrum for compound **3**.

The coupling constants obtained were used to establish that, in compound **5**, the decahydroisochromene fragment protons H-1' and H-8*a* ($J_{1a8(a),a}$ = 12.5) and H-8*a* and H-8 ($J_{8a(a),8a}$ = 13.7 Hz) are found in *a,a* and *a,a* positions, respectively, which presupposes the existence of a bicyclic system in a cisoid conformation.

We also studied the effect of products **2**, **3**, and **5** on the functional activity of the opiate receptors in an isolated organ model. For the pharmacological experiments, the mouse vas deferens (MVD) model selected permitted us to show that only compound **3** at concentration $6.65 \cdot 10^{-5}$ mole/liter displays an analgesic effect and is an agonist for μ- and δ-opiate receptors. In this case, we find a change in the MVD smooth muscle cells and, thus, drop in the e.j.p.s. (excitatory junction potential) [10]. A solution of $1 \cdot 10^{-5}$ mole/liter morphine was used as the control.

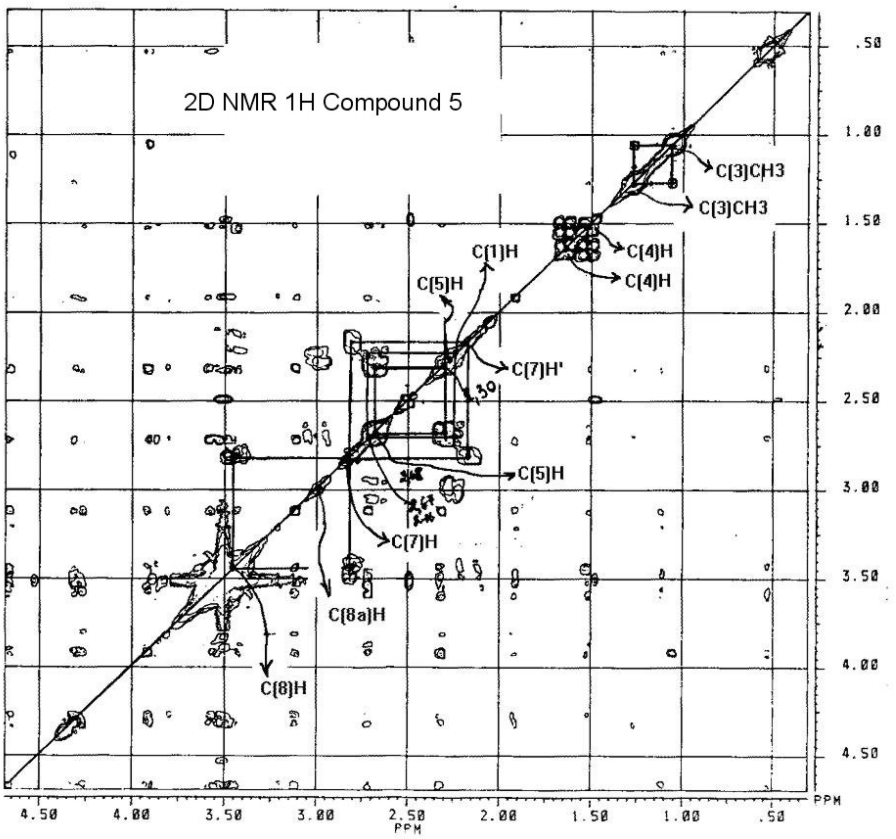


Fig. 2. Two-dimensional COSY spectrum of compound **5**.

EXPERIMENTAL

The reaction course and purity of the compounds were monitored using thin-layer chromatography on Silufol UV-254 plates and gas-liquid chromatography on a Tsvet-152 chromatograph equipped with a 0.7-m column (ø3 mm) packed with 5% SE-30 on Chromaton N-AW 0.16-0.20 mm. The gas carrier was nitrogen. The temperature programming was 75-325°C at 22°C/min. The ^{1}H NMR spectra were taken on a Bruker A-250 spectrometer at 250 MHz with HMDS as the internal standard. The IR spectra were taken on a Perkin-Elmer spectrometer for KBr pellets. The mass spectra were taken on an HP-5972 mass spectrometer with 70 eV ionizing electron energy. The melting points were determined on a Kofler block Boetius .

All the solvents were purified in accord with standard procedures.

4*a*-Hydroxy-2,3,8*a*-trimethyl-8-phenyldecahydro-6-isoquinolone (2). 60% NaH 0.42 g was added portion by portion with continuous stirring durring 1 h to a solution of 1,2,5-trimethyl-4-piperidone (1.5 g, 10 mmol) in DMF (30 ml). Then, a solution of benzalacetone (1.16 g, 8 mmol) in DMF (10 ml) was added

dropwise to the enolate solution obtained. The reaction mixture was stirred and left for three days. The solution obtained was poured into water, left overnight, and extracted with benzene. The extract was washed thrice with water and dried over $CaCl_2$. The solvent was distilled off. The residue was recrystallized from cyclohexane to give 0.79 g (34%) compound **2**; mp (base) 166-168°C, mp (hydrochloride) 245-247°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (coupling constants given in Table 1): 0.92 (3H, s, 8*a*-CH_3);1.42 (3H, d, 3-CH_3); 1.68 (1H, d, H*e*-4); 1.93 (1H, dd, H*a*-4); 2.09 (1H, dd, H*e*-7); 2.18 (1H, d, H*e*-5); 2.62 (1H, d, H*e*-1); 2.76 (3H, d, N–CH_3); 2.95 (1H, dd, H*a*-1); 3.09 (1H, d, H*a*-5), 3.42 (1H, dd, H*a*-7); 3.55 (1H, dq, H*a*-3); 3.82 (1H, dd, H*a*-8); 5.69 (1H, s, 4*a*-OH); 7.20-7.75 (5H, m, Ar-H); 10.02 (1H, dq, NH^+a). Found, %: C 67.10; H 8.12; Cl 10.79; N 4.33. $C_8H_{25}NO_2$·HCl. Calculated, %: C 66.76; H 8.03; Cl 10.97; N 4.32.

4*a*-Hydroxy-8-(*p*-dimethylaminophenyl)-2,3,8*a*-trimethyldecahydro-6-isoquinolone (3) was obtained in 40% yield (1.05 g) analogously using 4-dimethylaminobenzalacetone (1.51 g, 8 mmol); mp 219-221°C (2-propanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (the coupling constants are given in Table 1): 0.89 (3H, s, 8*a*-CH_3); 1.07 (3H, d, 3-CH_3); 1.40 (1H, dd, H-4); 1.73 (1H, d, H-5); 1.80 (1H, dd, H-4); 2.00 (1H, d, H-1); 2.10 (1H, d, H-1); 2.13 (3H, s, N–CH_3); 2.25 (1H, ddq, H-3); 2.36 (1H, dd, H-7); 2.90 (1H, d, H-5); 2.92 (6H, s, $N(CH_3)_2$); 2.92 (1H, dd, H-7); 3.82 (1H, dd, H-8); 6.66 and 7.11 (4H, m, Ar–H). Found, %: C 72.51; H 9.32; N 8.26. $C_{20}H_{30}N_2O_2$. Calculated, %: C 72.72; H 9.09; N 8.48.

4*a*-Hydroxy-3,3-dimethyl-8-phenyldecaisochromen-6-one (5). Benzalacetone (0.46 g, 3.2 mmol) in ethanol (10 ml) was added dropwise over 25 min to a solution of 2,2-dimethyl-4-tetrahydropyrone (0.5 g, 3.9 mmol) and 85.5% aqueous KOH (0.24 g) in absolute ethanol (5 ml). The reaction mixture was poured into water. The light-yellow crystals were filtered off, washed repeatedly with water, and recrystallized from 2-propanol to give 0.24 g (27%) compound **5**; mp (base) 229-231°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (the coupling constants are given in Table 1): 1.04 (3H, s, 3-CH_3); 1.26 (3H, s, 3-CH_3); 1.49 (1H, d, H-4); 1.64 (1H, d, H-4); 2.15 (1H, dd, H-7); 2.22 (1H, d.d, H-1); 2.30 (1H, d, H-5); 2.65 (1H, d, H-5); 2.67 (1H, dd, H-1); 2.83 (1H, dd, H-7), 3.00 (1H, ddd, H-8*a*); 3.45 (1H, ddd, H-8); 4.89 (1H, s, 4*a*-OH); 7.08-7.40 (5H, m, Ar–H). Found, %: C 74.64; H 7.85. $C_{17}H_{22}O_3$. Calculated, %: C 74.45; H 8.02.

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