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Synthesis and theoretical study of 2-amino-2,3,3a,4,5,6-hexahydro-1*H*-phenalene and its biological evaluation on central dopaminergic system

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Abstract

Compound **2** considered as a rigid non-hydroxylated 2-amino tetralin was synthesized and biologically evaluated. Central administration of compound **2** (50 μg or 100 μg/10 μl) induced a reduction in urinary sodium and potassium excretion at 3 and 6 h of urine collection. We speculate that compound **2** may be acting as a dopamine receptor antagonist. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Antagonist; Receptor; Dopamine

1. Introduction

The central nervous system (CNS) dopaminergic system in mammalian brain has been the subject of extensive studies in the past two decades. Dopamine (DA) systems and their associated receptors in the brain are important in modulating motor, endocrine and emotional functions [1,2]. Furthermore, both DA neurons and DA receptors are markedly reduced by normal aging and Parkinson's disease [3,4] and have been implicated in a variety of other disorders, including schizophrenia and drugs abuse [5]. Structure–activity relationship studies of many classes of dopamine receptor agonists allow some generalization regarding dopaminergic activity. Considering this fact, compound **1** was synthesized as a rigid non-hydroxylated amino indan and evaluated biologically. The results showed that **1** is a novel compound that acts on the dopaminergic central system [6,7] and also as a MAO-enzyme inhibitor [8]. As a consequence in the present study, we show the synthetic pathway for the preparation of the 2-amino-2,3,3a,4,5,6-hexahydro-1*H*-phenalene (**2**), a non-hydroxylated rigid derivative of 2-aminotetralin which possess inside its structure, the partial fragment of the dopaminergic receptor pharmacophore (phenylethylamino) and an additional carbon atom with respect to compound **1**. On the other hand, it has been shown that compound **3** is an agonist of the D-2 receptor [9] and its skeleton is an isoster of the phenalene nucleus present in **2**. Taking the above-mentioned aspects into consideration, we propose that compound **2** should show a similar biological activity as compound **1**, possibly through a dopaminergic mechanism (Fig. 1).

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2. Chemistry

The 2-amino-2,3,3a,4,5,6-hexahydro-1*H*-phenalene (**2**) have been prepared following the steps depicted in Schemes 1 and 2 by the intermediacy of the unknown amino alcohol **12** obtained in two ways (Scheme 2). In order to have access to this latter derivative, we started from the condensation of the α-tetralone **4** with diethyl succinate using sodium *t*-butoxide as the condensing agent. Following, the half ester **5** was decarbethoxylated by the action of a mixture of hydrochloric and acetic acids to give the unsaturated acid **6** [10]. Catalytic hydrogenation of **6** afforded the known 1,2,3,4-tetrahydro-1-naphthyl-propionic acid (**7**) [11]. Cyclization of this latter acid **7** proceeded rapidly by the polyphosphoric acid method to give ketone **8** [12]. In the first approach, route A (Scheme 2), for the introduction of the amino group at the α position of ketone **8**, a bromination reaction with pyridinium hydrobromide perbromide in $CHCl_3$ was carried out. The resulting α-bromoketone **9** was later converted into the azide derivative **10** by a treatment with NaN_3 in aqueous DMF. Subsequent catalytic hydrogenation of **10** in acidic medium (HCl–EtOH) over 10% Pd–C followed by reduction with $NaBH_4$, afforded the desired amino alcohol **12** with an overall yield of 38% from **8** [13]. Another but less efficient route B was used to prepare this key intermediate **12**, where the formation of the keto oxime **13** is involved through the treatment of compound **8** with *n*-butyl nitrite in basic medium using sodium *t*-butoxide [14]. Subsequent catalytic reduction in solution of HCl–EtOH over 10% Pd–C afforded the desired amino alcohol **12** with an overall yield of 16% from **8** [15]. As the last step, a catalytic reduction of **12** with a mixture of acetic and sulfuric acids over 10% Pd–C gave the final compound **2** as a diasteromeric mixture [7].

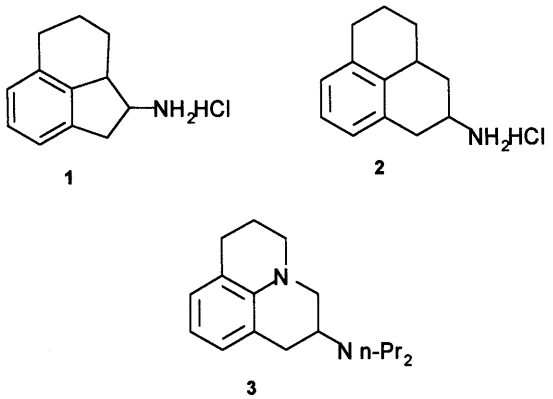
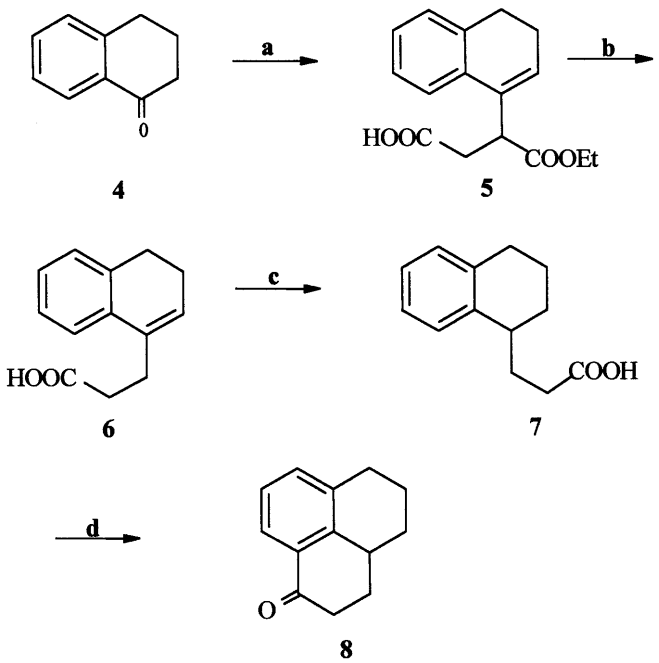


Fig. 1. Structures of compounds **1**–**3**.



Scheme 1. Synthetic pathway of compound **8**. Reagents: (a) $EtO_2C–CH_2–CH_2–CO_2Et$, $NaOC(CH_3)_3$, $HOC(CH_3)_3/\Delta$; (b) HCl–AcOH–H_2O/Δ; (c)H_2/10% Pd–C–ethanol; (d) PPA, 60°C.

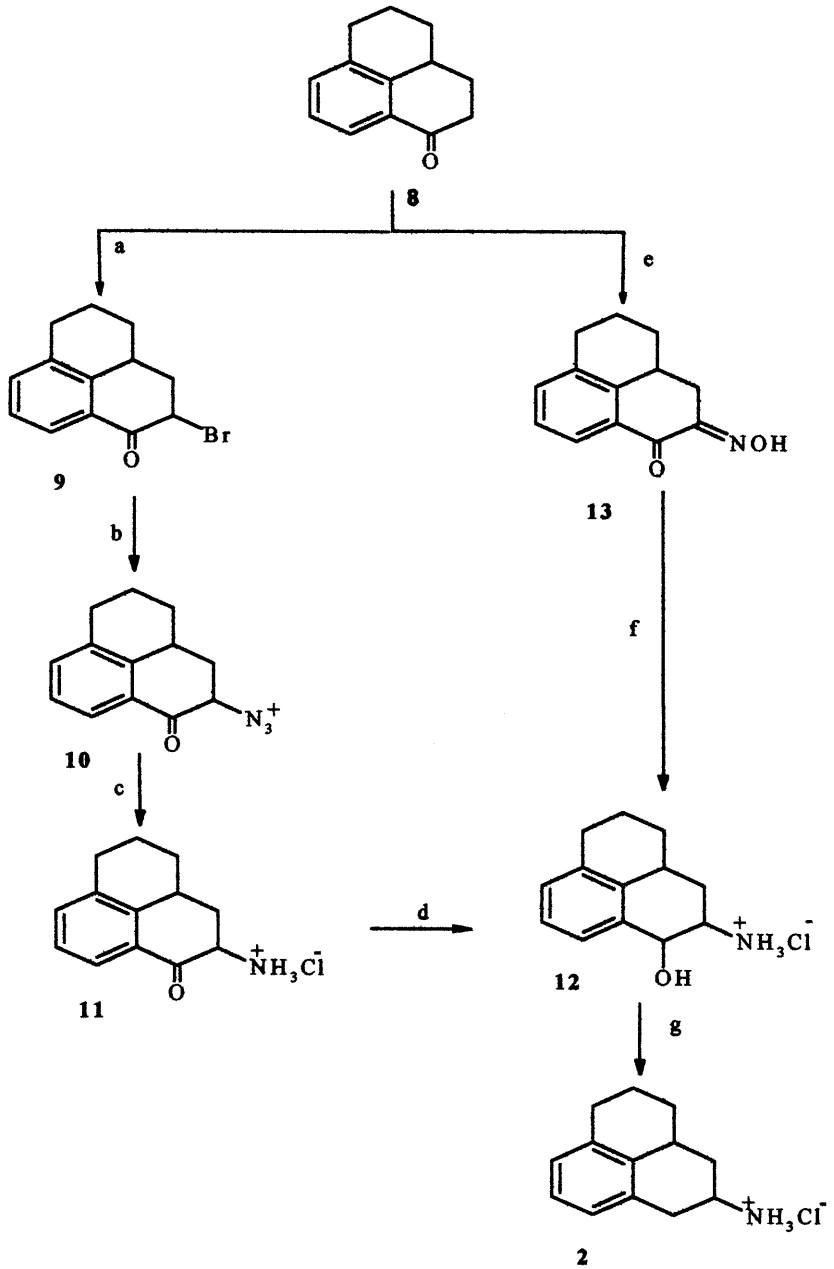
3. Experimental

3.1. Chemistry

Uncorrected melting points were determined using a Thomas Hoover capillary melting point apparatus. ^{1}H NMR spectra were recorded using a JEOL GSX (270 MHz) and reported in ppm (δ) downfield from TMS as an internal standard. Infrared spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer. Carbon, Hydrogen and Nitrogen elemental analyses were performed by Atlantic Microlab Laboratories, Atlanta, GA, and were within $\pm 0.4\%$ of the theoretical values. Mass spectra were recorded on a Hewlett–Packard 5995 mass spectrometer. The purity of all compounds was assessed by thin layer chromatography using several solvents of different polarity. All solvents were distilled and dried in the usual manner.

3.1.1. β-Carbetoxy-β-(3,4-dihydro-1-naphtyl)-propionic acid (5)

A solution of α-tetralone **4** (14.6 g, 0.1 mol), ethyl succinate (26.1 g, 0.15 mol) in *t*-butyl alcohol (20 ml) was added to a solution of metallic sodium 2.6 g (0.11 mol) in *t*-butyl alcohol (40 ml). The resulting mixture was refluxed for 4 h. After cooling, the mixture was acidified using diluted hydrochloric acid (10%) under vigorous stirring. The organic phase was extracted with diethyl ether. The organic extract was washed several times with sodium bicarbonate (10%) and water. The organic extracts were dried over anhydrous magnesium



Scheme 2. Synthetic pathway of compound **2**. Reagents: (a) $Py^{+}HBr_3$–$CHCl_3$ 50°C; (b) NaN_3–DMF–H_2O–AcOH; (c) H_2/10% Pd–C EtOH–HCl; (d) $NaBH_4$–MeOH; (e) *n*-BuONO–$NaOCMe_3$–$HOCMe_3$; (f) H_2/10% Pd–C HCl–EtOH; (g)) H_2/10% Pd–C AcOH–H_2SO_4.

sulfate. The solvent was removed under reduced pressure to give a red crude (22 g) that later turned brown (m.p. 65–70°C). Recrystallization of the crude product from ethanol–water produced a white solid (17 g, 65%), m.p. 68–69°C (Lit. [10] m.p. 64–69°C). IR (KBr, cm^{-1}): 3311–2138 (COOH), 1711 (CO). ^1H NMR ($CDCl_3$): 1.00 (t, 3H, CH_3CH_2O), 1.78 (m, 2H, $ArCH_2CH_2$), 2.00–2.78 (m, 4H, CH_2COOH, $ArCH_2CH_2$), 3.26 (m, 1H, CCHCO), 3.94 (m, 2H, CH_3CH_2O), 5.78 (t, 1H, =CH), 6.73–7.31 (m, 4H, ArH), 10.73 (s, 1H, CO_2H).

*3.1.2. β-(3,4-Dihydro-1-naphtyl)-propionic acid (**6**)*

A solution of compound **5** (18 g, 0.06 mol), in acetic acid (126 ml), hydrochloric acid (63 ml), and water (90 ml), was refluxed for 24 h. During the first 3 h of heating, evolution of CO_2 was observed. The mixture was concentrated under reduced pressure. To the semisolid residue, extracted with diethyl ether, diluted solution of sodium hydroxide was added. The resulting basic solution was acidified using concentrated sulfuric acid to give a brown solid that recrystallized from ethanol–water. 83% Yield; m.p. 105–107°C; (Lit. [10]

106.8–107.5°C). IR (KBr, cm^{-1}): 3500–2000 (COOH), 1703 (CO). ^1H NMR ($CDCl_3$): 2.00–2.52 (m, 2H, $ArCH_2CH_2C=$), 2.52–3.79 (m, 6H, $=CCH_2CH_2CO$, $=CCH_2CH_2CO$, $ArCH_2CH_2C=$), 5.89–6.21 (m, 1H, ArC=CH), 7.10–8.47 (m, 4H, ArH), 11.26 (s, 1H, COOH).

3.1.3. β-(1,2,3,4-Tetrahydro-1-naphtyl)-propionic acid (7)

Compound **6** (2.5 g, 12,3 mmol), was hydrogenated over 10% Pd–C (0.25 g) in ethanol at room temperature (r.t.), under an initial pressure of 50 psi. After the absorption of the calculated amount of hydrogen, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. A total of 87% yield of a white solid recrystallized from a mixture of ethanol–water, m.p. 80–81°C (Lit. [10] 83°C). IR (KBr, cm^{-1}): 3400, 2000 (COOH), 1700 (CO). ^1H NMR ($CDCl_3$): 0.68–2.00 (m, 6H, $ArCH_2CH_2CH_2$, $ArCH_2CH_2CH_2$, CH_2CH_2COOH); 2.00–2.26 (m, 2H, CH_2COOH); 2.28–2.84 (m, 2H, $ArCH_2$), 3.10–3.52 (m, 1H, ArCH–), 6.51–7.89 (m, 4H, ArH), 9.73–10.15 (s, 1H, COOOH).

3.1.4. 2,3,3a,4,5,6-Hexahydro-phenalen-1-one (8)

To polyphosphoric acid (24 g) heated previously to 60°C, compound **7** (2 g, 9.8 mmol) was added, and the mixture was stirred manually for 30 min in an oil bath, keeping the temperature between 90 and 120°C. Then, crushed ice was added and the stirring produced precipitation of the product, which was extracted with dichloromethane. The organic extracts were washed with water, sodium bicarbonate, and water again and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, to give a yellow solid that recrystallized from a mixture of ethanol–water. 82% yield of a white solid. m.p. 68–69°C (Lit. [10] 69.2–70°C). IR (KBr, cm^{-1}): 3054 (ArH), 1676 (CO). ^1H NMR ($CDCl_3$): 0.52–2.21 (m, 6H, $ArCH_2CH_2CH_2$, $ArCH_2CH_2CH_2$, $ArCOCH_2CH_2$), 2.23–3.19 (m, 5H, $ArCOCH_2$, $ArCH_2$, ArCH), 6.73–7.36 (m, 2H, ArH), 7.52–7.94 (m, 1H, ArH).

3.1.5. 3a,4,5,6-Tetrahydro-1H-phenalene-1,2(3H)-dione-2-oxime (13)

A solution of compound **8** (1.68 g, 9 mmol), *n*-butyl nitrite (1.57 g, 15.2 mmol) in *t*-butyl alcohol (20 ml) was added to a solution of metallic sodium (0.34 g, 15.2 mmol) in *t*-butyl alcohol (20 ml). The resulting mixture was stirred for 4 h at 50°C during the first hour, and at r.t. the rest of the time. The solvent was evaporated at reduced pressure and the resulting solid was dissolved in water (25 ml). The aqueous solution was extracted with benzene and then saturated with carbon dioxide, producing the formation of a red semisolid residue that after extraction with diethyl ether and evaporation of the solvents gave a solid that was recrystallized from acetone–water. 20% yield of a red precipitate, m.p. 144–145°C. IR (KBr, cm^{-1}): 3600–3046 (OH), 1679 (CO). ^1H NMR (DMSO-d_6): 0.68–2.26 (m, 4H, CH_2CH_2), 2.47–3.10 (m, 3H, $ArCH_2$, ArCH), 3.21–3.73 (m, 2H, $CH_2C=NOH$), 6.84–7.36 (m, 3H, ArH), 7.36–7.94 (bb, 1H, =NOH).

3.1.6. 2-Bromo-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-one (9)

A solution of the previously synthesized pyridine hydrobromide perbromide complex (3.42 g, 10.7 mmol), compound **8** (1.5 g, 8 mmol), in chloroform (50 ml) was heated. The temperature was kept at 50°C for 15 min. The mixture was poured over ice and benzene. The organic phase was separated, washed several times with water and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, to obtain a brown crude, that was purified using chromatographic column with silica gel 60 (0.040–0.060 mesh) and benzene as the eluant. 70% Yield, m.p. 57–58°C. IR (KBr, cm^{-1}): 1682 (CO). ^1H NMR ($CDCl_3$): 0.63–2.21 (m, 6H, CH_2CH_2, $CHCH_2$), 2.23–3.36 (m, 3H, $ArCH_2$, ArCH), 4.42 (t, 1H, COCHBr), 6.78–7.31 (m, 2H, ArH), 7.52–7.94 (m, 1H, ArH).

3.1.7. 2-Azido-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-one (10)

A solution of sodium azide (0.677 g, 10 mmol) in water (5 ml) was added to a solution of compound **9** (1.38 g, 5.2 mmol) in DMF (20.8 ml) and acetic acid (1.0 ml). The resulting mixture was kept at 5°C under constant stirring. When the temperature reached 20°C, the reaction was stopped after 1 h. Next, water was added and the organic phase separated, washed several times with water, and then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained crude was purified through chromatography column using silica gel 60 (0.040–0.060 mesh) using ethyl acetate as the eluant to give purple oil. 84% Yield, r_f 0.61 (ethyl acetate). IR (film, cm^{-1}): 2104 (N_3), 1692 (CO). ^1H NMR ($CDCl_3$): 0.52–2.42 (m, 4H, CH_2CH_2), 2.44–3.47 (m, 5H, CH_2CHN_3, $ArCH_2$, ArCH), 3.57–4.73 (m, 1H, CHN_3), 7.0–7.52 (m, 2H, ArH), 7.73–8.36 (m, 1H, ArH). $C_{13}H_{13}N_3O$ (227.26). *Anal.* Calc.: C, 68.71; H, 5.76; N, 18.49. Found: C, 69.03; H, 5.83; N, 18.49%.

3.1.8. Diasteromeric mixture of 2-amino-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-one chlorhydrate (11)

A solution of compound **10** (0.72 g, 3.1 mmol) in hydrochloric acid (2 ml), and ethanol (98 ml) was used to perform a hydrogenation reaction over 10% Pd/C

(0.072 g) at r.t. under an initial pressure of 50 psi. After absorption of the calculated amount of hydrogen, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give an orange solid that was recrystallized from a mixture of isopropanol–ether. 80% yield, m.p. 175°C (highly hygroscopic). IR (film, cm^{-1}): 1655–1587 ($NH_3^+Cl^-$), 1682 (CO), 1281, 1260 (C–CO–C).

3.1.9. Diasteromeric mixture of 2-amino-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-ol (**12**)

3.1.9.1. Route A. A solution of recently prepared compound **11** (0,67 g, 2.8 mmol) in methanol (10 ml), was added dropwise, to a suspension of sodium borohydride (0.2137 g, 5.6 mmol) in methanol (10 ml). The resulting mixture was kept at 5°C under constant stirring for 1 h. The mixture was acidified with 2 **N** hydrochloric acid and the solvent was evaporated under reduced pressure; water (10 ml) was added and the solution made basic using 2 **N** sodium hydroxide. The mixture was extracted with chloroform, and the organic phase washed with water several times; then dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, to obtain a light brown oil, which gave a solid after transformation with Et_2O–HCl in the corresponding chlorhydrate that was purified by recrystallization from isopropanol–ether. 80% yield of a white solid, m.p. 205–206°C. IR (KBr, cm^{-1}): 3367 (OH), 1520–1461 ($NH_3^+Cl^-$). ^1H NMR (DMSO-d_6): 0.789–2.42 (m, 6H, CH_2CH_2, $CHCH_2$), 2.63–3.84 (m, 4H, $ArCH_2$, $ArCH,CHNH_3^+Cl^-$), 5.05 (d, 1H, $J = 9.47$ Hz, ArCHOH), 7.21–8.1 (m, 4H, $(ArH)_3$, OH), (bs, 3H, $NH_3^+Cl^-$). EM m/z: 239 ($M^{\bullet+}$, $C_{13}H_{18}NOCl$, 21%); 221 ($C_{13}H_{16}NCl$, 11%); 202 ($C_{13}H_{17}NO$, 20%); 185 ($C_{13}H_{15}N$, 20%); 175 ($C_{12}H_{17}N$, 17%); 160 ($C_{11}H_{12}O$, 14%); 145 ($C_{10}H_9O$, 18%); 130 ($C_{10}H_{10}$, 20%); 115 (C_9H_7, 16%); 91 (C_7H_7, 20%); 77 (C_6H_5, 16%). $C_{13}H_{17}NO{\cdot}HCl$ (239.74). *Anal*. Calc.: C, 65.13; H, 7.57; N, 5.84. Found: C, 64.88; H, 7.58; N, 5.84%.

3.1.9.2. Route B. A solution of compound **13** (0.4 g, 1.86 mmol) in hydrochloric acid (2 ml) and ethanol (98 ml) was used to perform a hydrogenation reaction over 10% Pd–C (0.04 g) at r.t. under an initial pressure of 50 psi. After absorption of the calculated amount of hydrogen, the catalyst was removed by filtration and the solvent evaporated under reduced pressure to give a white solids that was recrystallized from mixture of isopropanol–ether.79% yield, m.p. 205–206°C.

3.1.10. Diasteromeric mixture of 2-amine 2,3,3a,4,5,6-hexahydro-1H-phenalen chlorhydrate (**2**)

A solution of compound **12** (0.5 g, 2 mmol) in acetic acid (90 ml) and sulfuric acid (10 ml), was hydrogenated over 10% Pd–C (0.05 g) at r.t., under an initial pressure of 50 psi. After absorption of the calculated amount of hydrogen, the catalyst was removed by filtration and the solvent evaporated under reduce pressure. The residue was diluted with water, and made basic to pH 10 with a sodium hydroxide (20%) solution, then extracted with dichloromethane. The organic extracts were combined, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The yellow oil obtained, was dissolved in chloroform and treated with Et_2O–HCl, to produce an amorphous solid that was recrystallized from isopropanol–ether. 60% yield of a white solid, m.p. 202–203°C. IR (KBr, cm^{-1}): 2986, 1583 ($NH_3^+Cl^-$). ^1H NMR (DMSO-d_6): 1.45 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 2.52 (m, 1H, CH), 3.12 (m, 1H, $CHNH_3^+$), 3.35 (m, 2H, CH_2), 6.28 (dd, 1H, ArH, $J_1 = 8.03$, $J_2 = 2.77$ Hz), 6.40 (dd, 1H, ArH $J_1 = 8.03$, $J_2 = 2.77$ Hz), 6.52 (m, 1H, ArH), 7.66 (bs, NH_3^+Cl). EM m/z: 187 ($M-1$, $C_{13}H_{16}N$, 2%); 186 ($C_{13}H_{15}N$, 11%); 170 ($C_{13}H_{14}$, 74%); 169 ($C_{13}H_{13}$, 100%); 144 ($C_{11}H_{12}$, 48%); 129 ($C_{10}H_9$, 79%); 115 (C_9H_7, 18%); *Anal*. Calc.: C, 69.79; H, 8.11; N, 6.26. Found: C, 70.01; H, 8.12; N, 6.21%.

3.2. Pharmacology

Adult male Sprague-Dawley rats 250–300 g were housed under controlled conditions of temperature and light (light on from 06:00 to 18:00 h) and provided with free access to laboratory chow and water. A cannula was implanted in the left lateral ventricle of the rat, under pentobarbital anesthesia (40 mg kg^{-1}, i.p.). Single intracerebroventricular (ICV) injection was made with a Hamilton syringe fitted with a stopper to prevent needle penetration past cannula tip. Three days after ventricular cannulation the animals were randomly distributed into two groups. Animals were weighed and placed in metabolic cages. At 09:00 half of the rats were injected, as a bolus in 10 s, with saline solution (5 μl) or with freshly prepared **2** in saline solution (50 μg/10 μl and 100 μg/10 μl) followed by orally administration of water (20 ml water/kg). Urine was collected at 3 and 6 h. The bladder was emptied after 6 h by gentle suprapubic massage. Food and water were not available during the experiment. Ventricular cannula placement was confirmed postmortem by examining the distribution of an ICV injection of 5 μl of a fast green dye, given before the animals were killed. Data were used only if the dye was distributed in the lateral, third and fourth ventricles. Urine samples were assayed for sodium and potassium concentrations by flame photometry. Statistical differences between groups were analyzed using a two-way analysis of variance and by the Newman–Keul's range statistics.

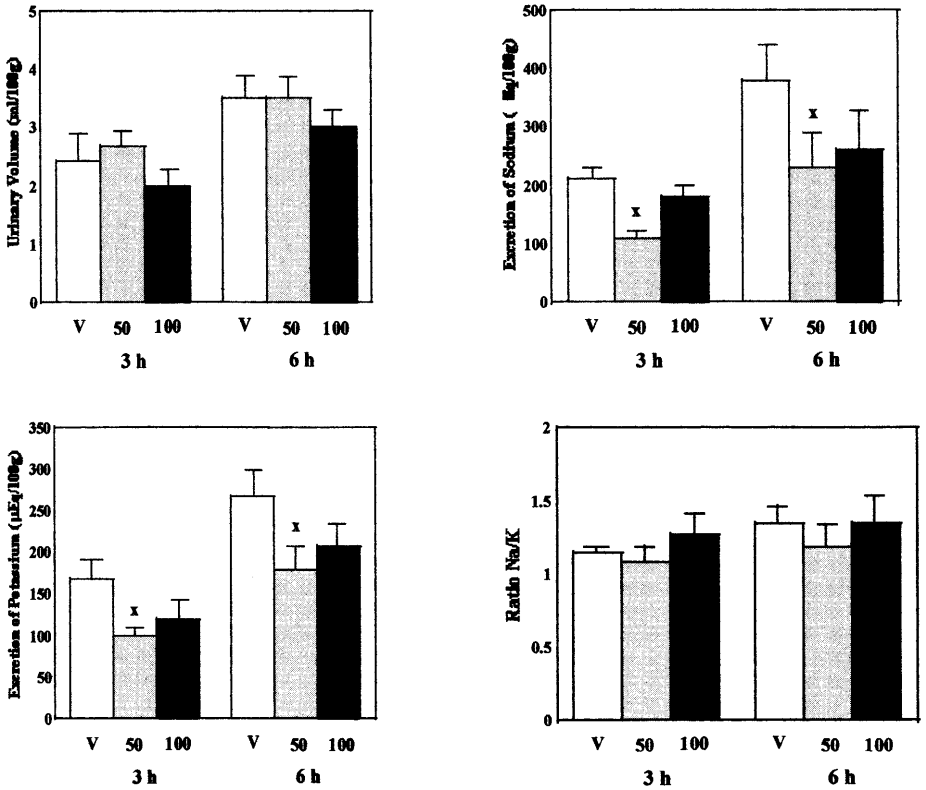


Fig. 2. Urinary responses to ICV administration of compound **2** in rats. A group of rats were ICV treated with compound **2** at doses of 50 or 100 µl/10 µl; control rats received ICV saline (10 µl). The results revealed a significant decrease (**x**) of urinary sodium and potassium excretion after 3 and 6 h (50 µl/100 µl) ($P^* < 001$).

3.3. Computational method

Computational calculation was performed using the Hartree–Fock AM1 method [16]. The computational program used for optimizations was AMPAC (SUNUNIX) and the display was carried out with the programs DMM [17] and PLUTO [18].

4. Results and discussion

Compound **2,** like compound **1**, is considered a rigid non-hydroxylated 2-amino indane, which also presents the partial moiety of the phenylethylamine pharmacophore. Despite the fact that compound **1** possesses one carbon atom less on its skeleton than compound **2**, we hypothesized that it should show a similar biological activity as the one described previously for compound **1**. In effect, we have shown that central administration of dopamine and compound **1** induces diuresis and natriuresis [7,19]. The involvement of the brain dopaminergic system in the centrally mediated renal action of compound **1** was strongly supported by the fact that the natriuretic and diuretic response was inhibited by haloperidol and when the endogenous dopamine levels were reduced after selective dopamine denervation [6,7]. However and unexpectedly, our present results demonstrated that central administration of compound **2**, not only did not show the diuretic and natriuretic effects, but on the contrary, compound **2** induced a dose dependent reduction in urinary sodium and potassium excretion (Fig. 2 and Table 1). The exact mechanisms by which central administration of compound **2** gives rise to an antinatriuretic and antikaliuretic effect are unknown.

It was reported in the synthesis and pharmacological evaluation of several tricyclic amines that compound **3** showed dopaminergic activity through the stimulation of the dopamine D-2 receptor [9]. In this respect we could point out that the basic nucleus of compound **2** is

Table 1
Effect of compound **2** on electrolyte urinary excretion [a]

Urinary excretion	Dose administrated (µg)	Inhibition (%)	
		3 h	6 h
Sodium	50	52	36
Sodium	100	14	27
Potassium	50	43	33
Potassium	100	31	23

[a] Results are expressed as percentage on inhibition compared with the basal excretion.

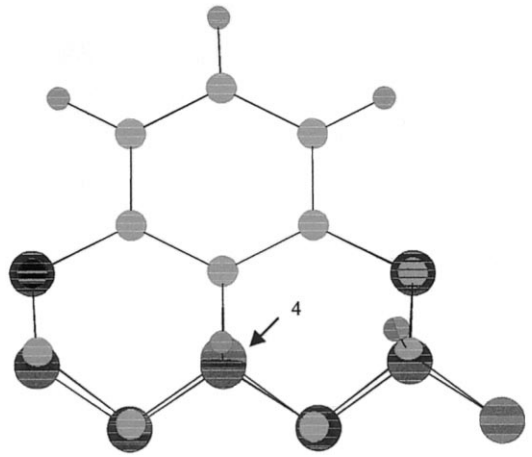


Fig. 3. Overlapping of the nuclei of compounds **2** and **3** using AM1 semiempirical method. Compound **3** possesses the nitrogen atom at position 4. Shrinking of the molecular area is observed.

an isoster of compound **3**; differing only at the nitrogen atom at position 4 in the benzo-[*ij*]-quinolizine system. Furthermore, compound **2** is a primary amine, while compound **3** is a dipropylated tertiary amine. Thus, apparently, these two compounds should have the same area. As a consequence of this fact, we could postulate that the nitrogen atom at position 4 in compound **3** would modify the base nucleus geometry, shrinking the area. This result was confirmed through a theoretical study using the AM1 method [16] when comparing both compounds as primary amines. In this work, the geometry of **2** and **3** was calculated and the results are summarized in Fig. 3. We can observe how the substitution of a carbon atom for nitrogen caused the mentioned shrinking of area.

Taking into consideration these findings, we could speculate that compound **2** occupancy of the D-2 receptor with no intrinsic activity induces a dopaminergic antagonism on urinary sodium and potassium excretion. Furthermore, the inhibition of urinary electrolyte excretion observed in the present results may indicate that the blockade of the brain dopaminergic receptor by compound **2** inhibits the tonic endogenous dopamine regulation of sodium and potassium balance. Consequentially, stimulation of the D-1 receptor would result in a reduction in urinary sodium and potassium excretion. In this respect, there is evidence of oppositional D-1:D-2 interactions which appears to constitute another general mode of dopaminergic regulation. Indeed, while tonic activity, through D-1 receptor is necessary for the expression of typical D-2 stimulated behavior, via the well-known cooperative/synergic D-1:D-2 interactions [20], D-1 tone normally inhibits via oppositional D-1:D-2 interactions, the expression of atypical D-2 — stimulated behaviors such as jerking [21]. Furthermore, It has been shown that D-1:D-2 receptors act differentially on body temperature, and that they influence a common output system, but in opposite directions: D-1 receptor induced hyperthermia and stimulation of D-2 receptor, hypothermia [22].

Future studies are carried out to confirm our hypothesis and to suggest which stereoisomer of diasteromeric mixture is responsible for that particular activity.

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