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Original paper

Monophenolic 2-amino-1-indanone and 2-amino-1-tetralone derivatives: synthesis and assessment of dopaminergic activity

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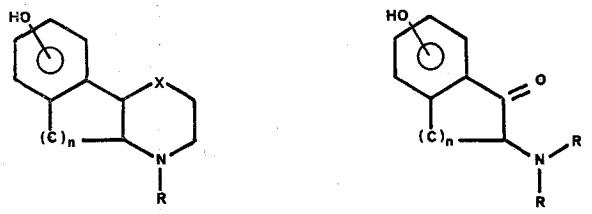
Summary — Monophenolic 2-amino-1-indanones and 2-amino-1-tetralones having various substituents on the nitrogen atom were prepared and their activities *in vitro* on D_1 and D_2 dopaminergic receptors were assayed. All compounds were inactive in binding assays and this inactivity is discussed.

Résumé — **Amino-2 indanones-1 et amino-2 tétralones-1 monophénoliques: synthèse et appréciation de l'activité dopaminergique.** *Des amino-2-indanones-1 et amino-2-tétralones-1 monophénoliques diversement substituées sur l'atome d'azote ont été préparées et leurs activités* in vitro *essayées sur les récepteurs dopaminergiques D_1 et D_2. Tous les composés se sont révélés inactifs dans les essais de liaison et cette inactivité est discutée.*

amino-indanones / amino-tetralones / dopaminergic activity / D_1 and D_2 receptors

Introduction

Among the great number of dopamine (DA)-rigid congeners studied by different researchers, some *trans*-octahydrobenzo-[f]quinolines **Ia** (Fig. 1) have been shown to be potent receptor agonists [1—4]. In order to examine the corresponding oxygen isosters, we studied and described [5—7] a synthetic method for obtaining naphtho- and indeno[1,4]oxazines (***Ib***).



I a: X = C
b: X = O

II

$n = 1, 2$

Fig. 1.

During these investigations, Jones *et al.* [8], Dykstra *et al.* [9] and Martin *et al.* [10] reported to have noted a CNS—dopaminergic activity for the same naphthoxazine derivatives that we had synthesized [7].

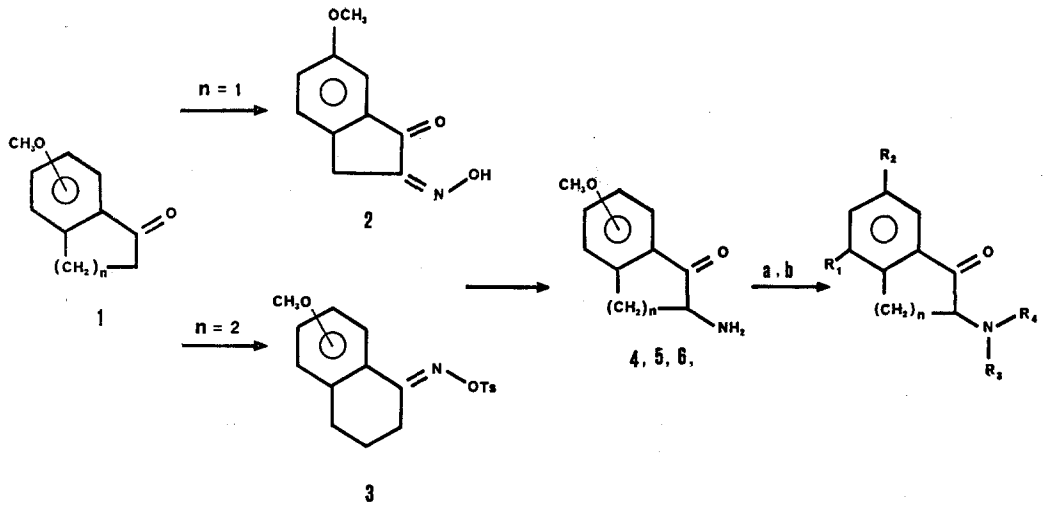
In particular the (+)**Ib** (R = *n*Pr, 9-OH, $n = 2$) was shown to be remarkably potent at both pre- and post-synaptic D_2 receptors, causing turning in the 6-OH DA rat, inducing emesis in dogs and inhibiting DOPA (3-(3,4-dihydroxy phenyl) alanine) accumulation in the γ-butirolactone (GBL)-treated rat.

Some naphtho—oxazines therefore, even if having different conformational freedom compared to known DA-agonists such as ADTN (aminodihydroxytetrahydronaphthalenes), are very active.

In order to evaluate how sensitive the DA-receptor is to conformational freedom of the DA-framework in rigid congener structures, we have considered 1-oxo-2-amino-tetraline derivatives that are ADTN derivatives with an oxygen atom placed in the same position as in the naphtho—oxazines. The preliminary investigation carried out on racemic compounds, was limited to the activity on CNS D_1 and D_2 dopamine receptors determined using binding assays against the SCH 23390 and spiperone.

Chemistry

The 2-amino-5-methoxy and 2-amino-7-methoxy-1-tetralone, **5** and **6** respectively, have been prepared using the corresponding α-tetralones, commercially available, *via* Neber-transposition, as previously reported [7]. The 2-amino-6-methoxy-1-indanone **4** has been prepared starting from



Scheme 1. Reagents: **a:** Reductive alkylation with A, B and C method; **b:** HBr 48% reflux. See Table I.

6-methoxy-1-indanone, obtained as reported [11] (Scheme 1). This compound was reacted with ethyl nitrite to yield 2-isonitroso-6-methoxy-1-indanone **2** that by reduction over a Pd-C catalyst gave the 2-amino-6-methoxy-1-indanone **4**. The primary amino ketones **4**, **5** and **6** were *N*-alkylated and each preparative method of *N*-alkylation is illustrated by a representative example under experimental protocols. Pertinent data for all compounds are summarized in Table I. The phenols presented in Table I were prepared from the corresponding methoxy compounds *via* *O*-demethylation in 48% aqueous HBr (Scheme 1). Spectral data (IR and NMR) of all intermediates and final products were consistent with the proposed structures.

Pharmacology

We decided to initially evaluate the dopaminergic activity with an *in vitro* binding assay in order to avoid pharmacokinetic problems, such as absorption and metabolism.

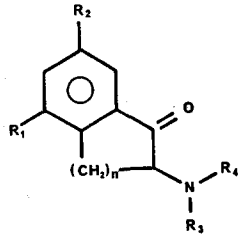
The monophenolic aminoketones described in Table I were evaluated for D_1 and D_2 dopaminergic activities by determining, for each compound, the ability to displace [^{3}H]SCH 23390 and [^{3}H]spiperone, respectively, from specific binding sites on rat striatal membranes [12, 13].

At the dose tested (10^{-6} M) all compounds were unable to displace either [^{3}H]SCH 23390 or [^{3}H]spiperone from their specific sites.

The same concentration of SCH 23390 and haloperidol was tested as internal controls of the inhibition studies and elicited a reduction in the binding of 90% and 76%, respectively.

The inactivity found in compounds reported herein can be due to: 1) conformational factors because, with the presence of the carbonyl group that makes bicyclic systems more rigid compared to naphtho—oxazine derivatives, we have a conformation quite different from the one necessary for the DA-receptor; 2) electronic factors due to influence of the carbonyl group.

Table I. Preparation and properties of 2-amino-1-indanone and 2-amino-1-tetralone derivatives.



Compound	n	R_1	R_2	R_3	R_4	Method	Yield %	mp, °C (MeOH/Et_2O)	Formula
7	1	H	OCH_3	CH_3	CH_3	A	80	169-71	$C_{12}H_{16}ClNO_2$
8		H	OH	H	H		65	237-39(dec.)	$C_9H_{10}BrNO_2$
9		H	OH	CH_3	CH_3		60	191-93(dec.)	$C_{11}H_{14}BrNO_2$
10	2	OCH_3	H	CH_3	CH_3	A	75	204-6	$C_{13}H_{18}ClNO_2$
11		OCH_3	H	H	nPr	C	60	205-7	$C_{14}H_{20}ClNO_2$
12		OCH_3	H	H	isoPr	B	50	202-4	$C_{14}H_{20}ClNO_2$
13		OH	H	H	H		80	216-18	$C_{10}H_{12}BrNO_2$
14		OH	H	CH_3	CH_3		70	209-11	$C_{12}H_{16}BrNO_2$
15		OH	H	H	nPr		90	221-23	$C_{13}H_{18}BrNO_2$
16		OH	H	H	isoPr		65	202-4	$C_{13}H_{18}BrNO_2$
17		H	OCH_3	CH_3	CH_3	A	60	178-80	$C_{13}H_{18}ClNO_2$
18		H	OCH_3	H	nPr	C	70	170-72	$C_{14}H_{20}ClNO_2$
19		H	OCH_3	H	isoPr	B	65	185-87	$C_{14}H_{20}ClNO_2$
20		H	OH	H	H		90	211-12	$C_{10}H_{12}BrNO_2$
21		H	OH	CH_3	CH_3		80	216-18	$C_{12}H_{16}BrNO_2$
22		H	OH	H	nPr		90	203-5	$C_{13}H_{18}BrNO_2$
23		H	OH	H	isoPr		70	218-20	$C_{13}H_{18}BrNO_2$

Experimental protocols

Chemistry

Melting points were determined in open capillaries using a Büchi—Tottoli apparatus and are uncorrected. Microanalyses were performed by the Microanalytical Section of our Department: the analytical results (C, H, N) were within ± 0.4% of the theoretical values and are not

reported in the present paper. ^1H NMR spectra were recorded on a Varian EM-390 instrument, using D_2O as the solvent and DSS (2,2-dimethyl-2-silapentane-5-sulfonate) as the internal standard, unless otherwise indicated, and all values are reported in ppm (δ). IR spectra were measured with a Perkin—Elmer Model 283 spectrometer. IR and ^1H NMR spectra of all compounds reported in Table I were similar to those of the compounds described under Methods A, B and C.

2-Isonitroso-6-methoxy-1-indanone **2**

Freshly prepared ethyl nitrite was bubbled through a solution of 10 g of 6-methoxy-1-indanone in 100 ml of EtOH saturated with HCl gas, for 2 h at 35°C. Then the reaction mixture left at room temperature, gave a crystalline solid, 8.2 g (69%), with mp = 210—212°C (EtOH). IR (KBr): 1640 (C=N), 1710 (C—O), 3280 br (OH) cm^{-1}. NMR (DMSO-d_6): 3.6 (s, 2H, CH_2); 3.8 (s, 3H, OCH_3); 7.1—7.6 (m, 3H, Ar). Anal. $C_{10}H_9NO_3$.

2-Amino-6-methoxy-1-indanone hydrochloride **4**

A suspension of 5 g of **2** in 20 ml of EtOH and 2 ml of conc. HCl was hydrogenated, under stirring, in the presence of 10% Pd/C (0.1 g) at room temperature and normal pressure until the incorporation of hydrogen was complete. The filtrate was evaporated under reduced pressure and the residue purified by dissolving in hot acidified (HCl) water and cooling. A white crystalline product was collected, 3.5 g (65%), with mp = 263—265°C (dec) (MeOH/Et_2O). IR(KBr): 1720 (C=O) cm^{-1}. NMR(D_2O): 2.9—3.7 (m, 2H, CH_2); 3.8 (s, 3H, OCH_3); 4.30 (m, 1H, CH—N); 7.10—7.55 (m, 3H, Ar). Anal. $C_{10}H_{12}ClNO_2$.

N-*Alkylation reactions*

Reductive alkylation of primary amines with formaldehyde under catalytic reductive conditions (method A)

This procedure is illustrated for 2-dimethylamino-6-methoxy-1-indanone hydrochloride **7**.

A mixture of 0.7 g (0.0035 mol) of **4**, 15 ml of 37% aqueous formaldehyde, and 0.1 g of 5% Pd/C in 50 ml of EtOH was hydrogenated at room temperature at an initial pressure of 50 psi. When 2 equivalents of H_2 were absorbed, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue, in methanol, was decolored with charcoal. Addition of ether to the solution gave white crystals. IR(KBr): 1700 (C=O) cm^{-1}. NMR(D_2O): 2.80 (s, 6H, $2CH_3$); 2.95—3.40 (m, 2H, CH_2); 4.30 (m, 1H, CH—N). Anal. $C_{12}H_{16}ClNO_2$.

Reductive alkylation of primary amine with acetone and $NaCNBH_3$ (method B)

This procedure is illustrated for 2-isopropylamino-5-methoxy-1-tetralone **12**. To a stirred solution of 0.8 g (0.0035 mol) of **5** in 10 ml of dry acetone and 80 ml of dry methanol, at 0°C under N_2, 0.6 g of $NaCNBH_3$ wet with 1 ml of dioxane was added. After 3 h, 1 N HCl was added to bring the pH to 2 or lower. The reaction mixture was evaporated under reduced pressure and the residue was made basic with 1 M NaOH. The mixture was extracted repeatedly with ether. The pooled ethereal extracts were washed with water and dried over Na_2SO_4. Gaseous HCl was added to the dried ethereal extract and the resulting mixture was evaporated under reduced pressure. The residue was crystallized. IR(KBr): 1700 (C=O) cm^{-1}. NMR(D_2O): 1.3 (dd, 6H, $2CH_3$); 1.9—2.7 (m, 2H, CH_2); 2.7—3.3 (m, 2H, CH_2—Ar); 3.6 (q, 1H, $CH(CH_3)_2$); 3.8 (s, 3H, OCH_3); 4.35 (m, 1H, CH—C=O); 7.0—7.5 (m, 3H, Ar): Anal. $C_{14}H_{20}ClNO_2$.

Reductive alkylation of primary amine with propionaldehyde under catalytic reduction conditions (method C)

This procedure is illustrated for 2-*n*-propylamino-5-methoxy-1-tetralone hydrochloride **11**. To a solution of 0.8 g (0.0035 mol) of **5** in 50 ml of EtOH, 10 ml of propionaldehyde was added and the mixture was catalytically hydrogenated over 5% Pd/C (0.1 g) under atmospheric pressure at room temperature until the absorption of the calculated amount of hydrogen was complete. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure. The residue in methanol was decolored with charcoal. Addition of ether to the solution gave white crystals. IR(KBr): 1700 (C=O) cm^{-1}. NMR(D_2O): 0.95 (t, 3H, CH_3); 1.7 (m, 2H, CH_2—CH_3); 2.0—2.6 (m, 2H, endoCH_2); 3.0 (m, 4H, CH_2—Ar and CH_2—N); 3.80 (s, 3H, OCH_3); 4.30 (m, 1H, CH—N); 7.0—7.20 (m, 3H, Ar). Anal. $C_{14}H_{20}ClNO_2$.

Demethylation of methoxy compounds

The phenols were obtained by heating the appropriate methoxy hydrochloride compounds in 48% aqueous HBr for 2 h at 125°C under nitrogen. The reaction mixture was evaporated under reduced pressure and H_2O was removed by successive azeotropic distillation with EtOH. The resulting brown oil was decolored with charcoal in MeOH and then crystallized.

Pharmacology

Dopamine receptor studies: inhibition of [^3H]SCH 23390 (D_1 activity) and [^3H]spiperone (D_2 activity) binding to caudate membrane preparations

Adult male Sprague—Dawley rats (Charles River, Italy) were killed by decapitation and caudates were rapidly dissected and kept frozen until use. The tissues were weighed and mechanically homogenized (ultra-Turrax) in ice cold buffer (Tris-HCl 50 mM, pH 7.6) and the homogenate was centrifuged at 50 000 × *g* for 10 min at 4°C. The pellet was washed twice and resuspended in 70 μl/mg tissue of 50 mM Tris-HCl buffer, pH 7.7, containing NaCl (120 mM), KCl (5 mM), $CaCl_2$ (2 mM), $MgCl_2$ (1 mM), pargyline (10 μM) and ascorbic acid (0.1%, w/v).

Inhibition of [^3H]spiperone (0.5 nM) and [^3H]SCH 23390 (1 nM) binding was performed by incubating 500 μl of the membrane preparation for 30 min at 37°C with the appropriate radioligand in the absence (total binding) or in the presence of the compound to be tested (samples) at the final concentration of 10^{-6} M.

The non-specific binding was obtained by displacement with 10^{-6} M haloperidol for the D_2 binding studies and 10^{-6} M cold SCH 23390 for the D_1 binding assay.

Bound radioactivity was separated under vacuum through Whatman GF/B glass fiber filters and measured in a β counter in the presence of scintillation cocktail.

Results are expressed as the percent of specifically bound radioactivity, which is defined as follows:

$$\frac{\text{cpm sample—cpm non-specific binding}}{\text{cpm total binding—cpm non-specific binding}} \times 100$$

and for all compounds the obtained values are 0.

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