THE SYNTHESIS OF *TRANS*-3,4-BIS-(3,4-DIHYDROXYPHENYL)PYRROLIDINE, A NOVEL DA_1 AGONIST

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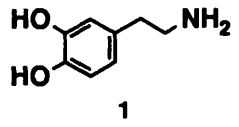
The synthesis of *trans*-3,4-bis-(3,4-dihydroxyphenyl)pyrrolidine by the Michael reaction of esterenolate with nitro olefin is described. This compound was expected to be the agonist toward dopamine (DA_1) receptor with equipotent affinity and to be more selective than dopamine itself.

KEYWORDS dopamine; DA_1 agonist; *trans*-3,4-bis-(3,4-dihydroxyphenyl)pyrrolidine; Michael reaction; renal blood flow; mean arterial pressure

Dopamine (1) is a fundamental sympathomimetic amine and is implicated in a wide variety of both central and peripheral functions.[1] An underproduction of dopamine, for example, causes Parkinson's disease,[2] while a hyperstimulation of its receptor associates with schizophrenia[3] in the brain. And it is suggested that 1 is linked with regulation of blood pressure cr renal blood flow peripherally.[4] The development of both dopamine agonists and antagonists may therefore be of interest in various fields of therapy. As of now, two pharmacologically distinct dopamine receptor subtypes are known,[5] and they exist both in the central nervous system (D_1 and D_2 receptors) and in the cardiovascular system (DA_1 and DA_2 receptors).[6] Although a number of agonists and antagonists of D_2 / DA_2 receptors have already been found,[7] no agonist which acts on D_1 / DA_1 receptors is known except for benzazepine derivatives.[8]

We have designed a novel DA_1 agonist, *trans*-3,4-bis-(3,4-dihydroxyphenyl)pyrrolidine (BDP, 2), whose skeleton is completely different from that of benzazepine derivatives. In this paper, we report an efficient synthesis of BDP(2) and its biological and pharmacological activities.



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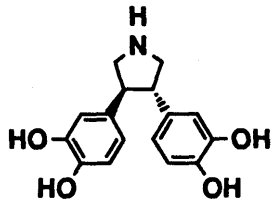

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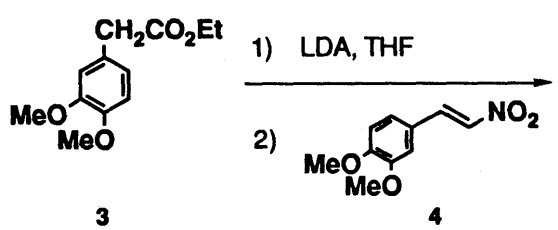
The first part of the synthesis of BDP(2) was the construction of the *trans*-γ-butyrolactam(8). The Michael reaction of ethyl 3,4-dimethoxyphenyl acetate(3)(20 mmol) with 2-(3,4-dimethoxyphenyl)-1-nitroethene(4)(20 mmol) prepared from 3,4-dimethoxybenzaldehyde and nitromethane[9] yielded ethyl 2,3- bis- (3,4- dimethoxyphenyl)- 4-nitrobutyrate (1.2 eq of LDA, THF, –78 °C, 87%). After purification by silica-gel chromatography, the NMR spectra of the adduct indicated that it was a mixture of the two diastereomers(1 : 1.1). The methyl proton of ethyl ester appeared at δ0.98 and δ1.21, respectively. The diastereomers could not be separated by TLC, but were separable by means of recrystallization from EtOH. The obtained crystalline adduct was determined to be the *erythro* form (5) for stereochemistry by X-ray analysis.[10] The ORTEP drawing is shown below. This conformational analysis accounts for the chemical shift of the methyl proton on the ethyl ester (δ = 0.98) of 5, which was shielded by the 2-phenyl ring.[11]



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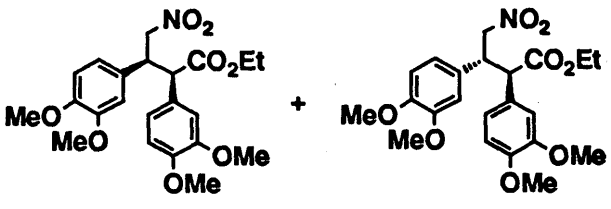

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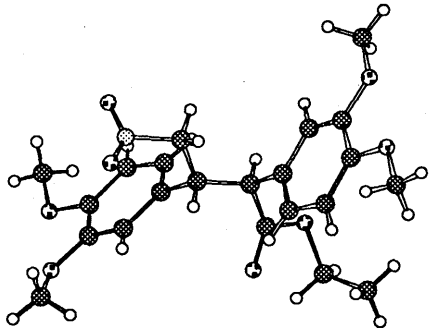
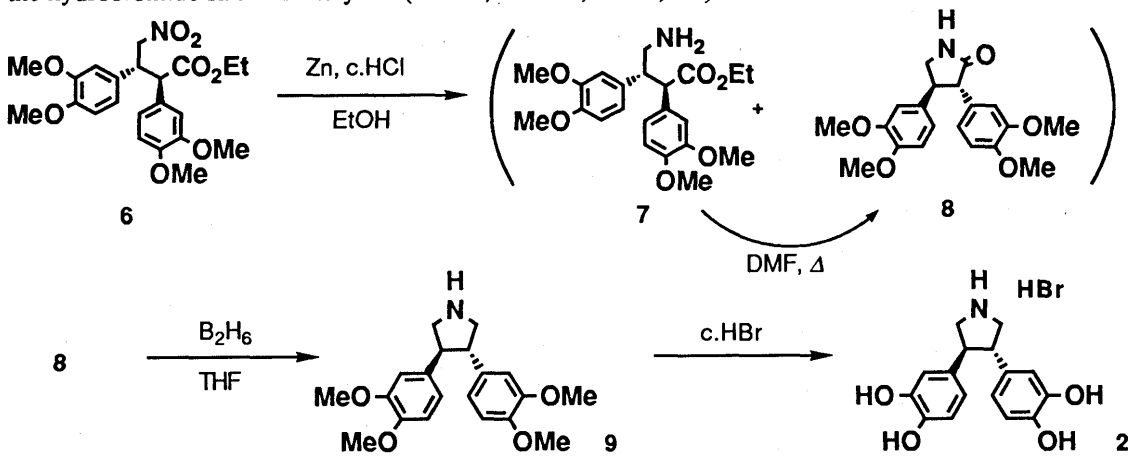


X-Ray Crystal Structure of **5**(*erythro* Form)

Ethyl *threo*-2,3-bis-(3,4-dimethoxyphenyl)-4-nitrobutyrate(**6**)(14.8mmol), which was obtained from mother liquor (*threo* / *erythro* = 11 / 1), was reduced with Zn(30mmol) and c.HCl(8.9ml) in EtOH(27ml) to afford a mixture of amino ester(**7**) and γ-butyrolactam(**8**). On heating the mixture in DMF, the amino ester(**7**) was cyclized to *trans*-γ-butyrolactam(**8**) and obtained in 61 % yield. The *trans*-γ-butyrolactam(**8**)(12.4 mmol) was treated with borane•THF complex (1M solution in THF, 50 ml) to afford the corresponding pyrrolidine(**9**) (60 %). The demethylation of the methoxyl group of **9** (5.0 mmol) gave BDP(**2**) as the hydrobromide salt in 80 % yield (c.HBr, 26.7 ml, reflux, 6h).[12]



The biological and pharmacological activities of BDP(**2**) were characterized by D_1 and D_2 binding assay and the test for the hemodynamics in anesthetised dogs. The binding affinities were determined by a replacement analysis in bindings of $D_1(DA_1)$ antagonist ([^{3}H]-Sch23390) and D_2 agonist ([^{3}H]-spiperone) to membranes of the rat neurostriatum using the methods described previously.[13] Renal blood flow and mean arterial pressure were measured in anesthetized dogs by intravenous administration.

Table I. Binding and Pharmacological Data of BDP(2)

Comp.	IC_{50},[a] μM		Ratio	ED_{15},[b] μg/kg	
	D_1binding[c]	D_2binding[d]	(D_1/D_2)	MAP	RBF
BDP (**2**)	7.2 ± 0.1	2.35	3.1	300	100
Dopamine (**1**)	3.7 ± 0.9	0.12	30.8	Hypertensive[e]	

a) Concentration of compound that decreased specific binding of [^{3}H]-Sch23390 or [^{3}H]-spiperone to rat striatum by 50 %. b) The effective dose required to produce 15% of reduction of mean arterial pressure (MAP) or 15 % of increase in renal blood flow (RBF) after intravenous administration to anesthetized dog. Effective doses were determined from at least three doses (N=5). c) Each value was determined from six concentration by linear regression analysis (N=3) expressed as ± SEM. d) Each value was determined from six concentration by linear regression analysis (N=2). e) Dopamine has α- and β- adrenergic activities in addition to DA_1 activity.

The data listed in the table show that BDP(2) has affinity toward both D_1 receptor and D_2 receptor. Since dopamine itself showed IC_{50} = 3.7 μM toward D_1 receptor in this test, it was to be estimated that BDP(2) have the equal (or scarcely low) binding affinity toward the D_1 receptor to dopamine. Moreover, D_2 binding affinity of BDP(2) is lower than that of dopamine itself (IC_{50} = 0.12 μM) and the D_1 / D_2 binding affinity ratio of BDP(2) is 3.1, whereas that of dopamine is 30.8. This resalt sugests that BDP(2) has more selective affinity toward D_1 receptor than dopamine. In order to clarify that BDP(2) was the agonist toward DA_1 receptor peripherally, we tried to examine the effect on renal blood flow and blood pressure. As shown in the table, BDP(2) increased RBF and reduced MAP at 300μg/kg of intravenous administration, and these effects fully disappeared after administration of the specific DA1 antagonist sch23390. These facts and the results of binding affinity indicated that BDP(2) is expected to be the agonist toward DA_1 receptor.

An extension of the present synthetic route and the synthesis of analogues of BDP(2) are now in progress.

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10) Crystal Data. **5**: $C_{22}H_{27}NO_8$; M = 433.36; monoclinic; $P2_1/n$(No.14); a=16.029(5)Å; b=11.574(4)Å; c=12.169(5)Å and β=101.93°(3); V=2208.9Å^3; z=4; μ(CuKα)=7.9cm^{-1}; no. of reflections with $I > 3\sigma(I)$= 2214; no. of refinement parameter=280; final R values, R=0.109; R_w=0.091.

11) The $J_{^2H\text{-}^3H}$ values of both adducts could not be measured directly from the signals of ^2H because the signals of ^2H overlapped with those of OMe proton. **5**: (NMR,400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J*= 7.1 Hz), 3.84-3.99(3H, m), 3.87(3H, s), 3.897(3H, s), 3.902(3H, s), 3.94(3H, s),4.04-4.16(1H, m), 4.32(1H, dd, *J*= 4.3 Hz, 12.4 Hz), 4.42(1H, dd, *J*= 10.1 Hz, 12.4 Hz), 6.80-6.89(4H, m), 6.99-7.03(2H, m). Mp 144-146 °C. **6**: (NMR,400 MHz, $CDCl_3$) δ 1.21(3H, t, *J*= 7.1 Hz), 3.73(3H, s), 3.76(3H, s), 3.78(3H, s), 3.71-3.95(3H, m), 4.06-4.21(1H, m), 4.78(1H, dd, *J*= 4.9 Hz, 12.4 Hz), 4.86(1H, dd, *J*= 10.1 Hz, 12.4 Hz), 6.52(1H, m), 6.60-6.68(5H, m).

12) **2**: NMR(400 MHz, D_2O) δ 3.50 (2H, t, *J*= 11 Hz), 3.50 - 3.62 (2H, m), 3.96(2H, dd, *J*= 7 Hz, *J*= 11 Hz), 6.82(2H, dd, *J*= 2 Hz, *J*= 8 Hz), 6.91(2H, d, *J*= 2 Hz), 6.93(2H, d, *J*= 8 Hz) Hz. Mp 208 - 210 °C. Calcd for $C_{16}H_{17}NO_4$.HBr C, 52.19; H 4.93; N, 3.80 %. Found C, 52.20; H, 5.17; N, 3.26 %. High resolution mass (FAB) calcd for $C_{16}H_{18}NO_4$; MH^+ 288.1236. Found MH^+ 288.1238.

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