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SYNTHESIS OF A 2-PYRROLIDINOL METABOLITE OF OPC-51803, A VASOPRESSIN V_2 RECEPTOR AGONIST

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Abstract – The unstable 2-pyrrolidinol derivative (**2**), as a metabolite of a new vasopressin V_2 receptor agonist OPC-51803 (**1**), was synthesized by the cytochrome P-450 model reaction of **1** with the Fe-salen complex and iodosobenzene.

The benzazepine derivative, (*R*)-2-[1-(2-chloro-4-(1-pyrrolidinyl)benzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-yl]-*N*-isopropylacetamide (OPC-51803, **1**),[1] is a new vasopressin V_2 receptor agonist and is now under clinical trials (Figure 1). In the recent *in vitro* and *in vivo* metabolism studies in rats and dogs, eleven metabolites were isolated.[2] One of the metabolites was proposed to be the unstable 2-pyrrolidinol derivative (**2**) on the basis of NMR and MS spectral analyses.

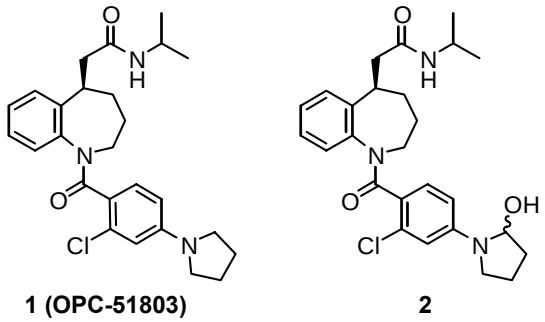


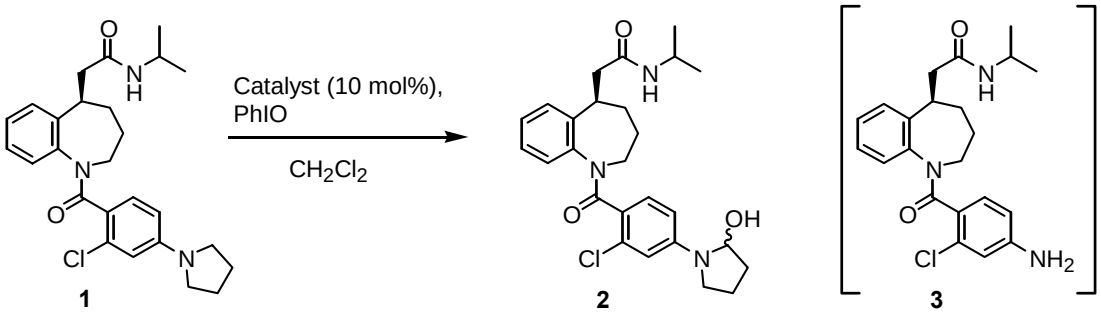
Figure 1

It has been well known that *N*-heterocyclic compounds as well piperidine, piperazine, morpholine and pyrrolidine can be metabolized to the unstable aminal, followed by oxidation to give the lactam or

amino acid. There are a few reports about synthesizing 2-pyrrolidinol compounds mainly by reduction of the corresponding lactams. S. Brandänge *et al*. reported the synthesis of the nicotine iminium salt, which is an intermediary metabolite of nicotine,[3] and the carbinolamine (aminal) was observed in strongly alkaline solution. K. Jankowski *et al*. reported the synthesis of 2-pyrrolidinol by reduction with Baker's Yeast.[4] G. A. Swan *et al*. reported the synthesis of 2-pyrrolidinol by reduction with lithium aluminum hydride.[5] In the studies of other aminal metabolites, we also succeeded in the synthesizing of the *N*-acetylhemiaminal metabolites.[6]

On the other hand, cytochrome P-450 plays an important role in metabolizing a wide variety of xenobiotics and biomolecules. In recent years, chemical models for P-450 have been developed and applied to drug metabolism studies.[7] The use of these model systems had an advantage in synthesizing the unstable metabolites. In previous papers,[8] we reported the application of chemical P-450 model systems for the synthesis of drug metabolites. We wish to describe here the preparation method of the unstable 2-pyrrolidinol metabolite.

We first examined the chemical P-450 model reaction with various catalysts and iodosobenzene in CH_2Cl_2 to find the most convenient reaction conditions as summarized in Table 1. In the screening test, the use of metalloporphyrin complexes or metallosalen complexes as the catalyst gave good results (entries 2,3,5,6 and 7). As the 2-pyrrolidinol derivative (**2**) was very unstable, the purification step was important for isolating **2**. We found that the 2-methoxy derivative (**4**) was more stable than **2**. The compound (**4**) was readily produced by treatment of the 2-hydroxy compound (**2**) with methanol, and can be converted to the 2-hydroxy compound by treatment with acetone and water. When metalloporphyrin complexes were used as the catalyst, it was difficult to remove the porphyrin derivative in the purification step. Therefore we chose commercially available Fe(salen) (*N*,*N'*-bis(salicylidene)ethylenediamine iron(II))as the catalyst to obtain **2**.

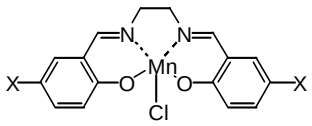


Scheme 1

Table 1. Chemical P-450 model reaction[a]

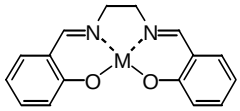
Entry	Catalyst	**2** (AP[b])	**3** (AP[b])	**1** (AP[b])
1	---	8	0	82
2	Fe(TPP)Cl	64	7	5
3	Mn(TPP)Cl	55	9	10
4	$VO(acac)_2$	16	0	65
5	Mn(4-Cl-salen)Cl [c]	53	5	15
6	Mn(4-Br-salen)Cl [d]	47	9	16
7	Fe(salen)	56	0	37
8	Co(salen)	12	0	80

a. The results were determined by HPLC monitored at 254 nm.
b. AP stands for HPLC area percent.
c. The catalyst was prepared according to ref. 9.
d. The catalyst was prepared according to ref. 10.



Mn(4-Cl-salen)Cl : X = Cl

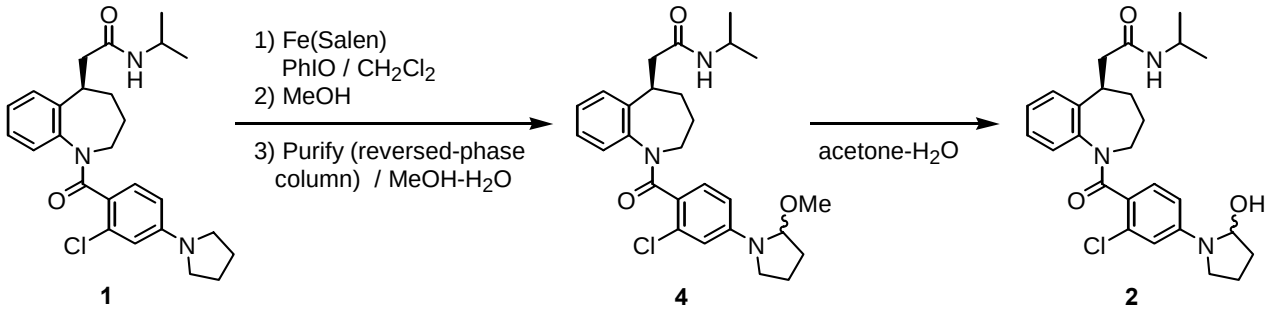
Mn(4-Br-salen)Cl : X = Br



Fe(salen) : M = Fe

Co(salen) : M = Co

The synthesis and purification procedure is as follows (Scheme 2). The compound (**1**) was treated with Fe(salen) and iodosobenzene in CH_2Cl_2 for 30 min, followed by adding MeOH. The reaction mixture including **4** was subjected to column chromatography on silica gel, and subsequently purified by column chromatography on silica gel with an amine-treated surface, and silica gel of reversed phase in this order to give **4** as the MeOH-H_2O solution. After evaporation of MeOH under 45 °C, the residue was diluted with acetone to convert the methoxy group to the hydroxy group. Evaporation of all the solvent gave the target compound (**2**) in 10% yield and 98.9% purity.



Scheme 2

In conclusion, the structure of the labile metabolite was identical with the corresponding synthetic compound based on the NMR, MS and high performance liquid chromatographic (HPLC) behavior,

moreover, the present study demonstrates a new preparation method for an unstable 2-pyrrolidinol metabolite from mother compound. This transformation might provide an alternative methodology for the construction of various metabolites containing the *N*-heterocyclic ring.

EXPERIMENTAL

To a solution of **1** (5.00 g, 11.0 mmol) in CH_2Cl_2 (100 mL) were added Fe(salen) (0.35 g, 1.09 mmol) and iodosobenzene (3.00 g, 13.6 mmol), and the mixture was stirred at rt for 30 min. Then MeOH (10 mL) was addeed to the mixture and the whole was stirred for 3 min. The reaction mixture was subjected to column chromatography on silica gel (solvent; CH_2Cl_2–MeOH = 20:1), and the product was subsequently purified by column chromatography on silica gel with an amine-treated surface (Fuji Silysia, NH-DM1020, solvent; Hex–EtOAc = 1:1 to 1:2), and silica gel of reversed phase (Fuji Silysia, ODS- DM1020T, solvent; MeOH–H_2O = 2:1) in this order to give **4** as the MeOH-H_2O solution. After evaporation of MeOH under 45 °C, the residue was diluted with acetone. Evaporation of all the solvent gave **2** (0.52 g, 10%) as a colorless crystalline powder, which was 98.9% purity by HPLC analysis using TSK Octyl-80Ts (solvent; CH_3CN–10 mM Na_2SO_4 aq = 45:55), mp 125 °C (decomp). ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 0.50 (3H, d, *J*=6.5 Hz, H-26), 0.96 (3H, d, *J*=6.5 Hz, H-27), 1.50-2.00 (4H, m, H-3,4), 2.05-2.15 (3H, m, H-19,22), 2.20-2.30 (2H, m, H-20), 2.50-2.80 (1H, m, H-22), 3.00-3.30 (2H, m, H-2,21), 3.40-3.60 (2H, m, H-5,21), 3.65 (1H, octet, *J*=6.9 Hz, H-25), 3.80-4.00 (1H, m, H-2), 5.35-5.40 (1H, m, H-18), 6.55 (1H, d, *J*=8.2 Hz, H-24), 6.78 (1H, dd, *J*=2.1, 8.2 Hz, H-15), 6.85 (1H, d, *J*=2.1 Hz, H-13), 7.15-7.40 (5H, m, H-6,7,8,9, and 16). IR (KBr): 3307, 1632, 1606, 1512, 1408, 1369, 1172 cm^{-1}. MS *m/z* (% rel. int.): 469 (M^+, 1), 453 (15), 452 (17), 451 (44), 446 (14), 245 (10), 208 (34), 206 (100). *Anal*. Calcd for $C_{26}H_{32}N_3O_3Cl{\cdot}H_2O$: C, 63.99; H, 7.02; N, 8.61. Found: C, 63.98; H, 6.91; N, 8.51.

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