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SYNTHESIS OF N-ACETYLHEMIAMINAL METABOLITES OF OPC-21268, VASOPRESSIN V1 RECEPTOR ANTAGONIST

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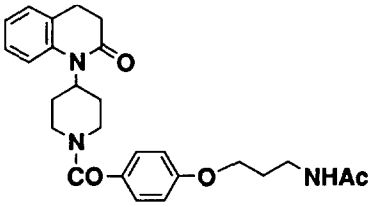
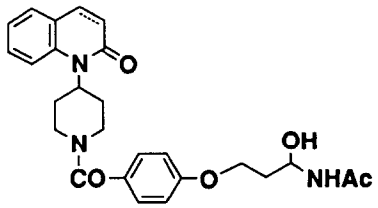
Abstract : N-Acetylhemiaminal metabolites of 1-{1-[4-(3-acetylaminopropoxy)benzoyl]-4-piperidyl}-3,4-dihydro-2(1*H*)-quinolinone (OPC-21268) (**1**), which is a new vasopressin V1 receptor antagonist were synthesized by oxidative decarboxylation of the corresponding α -amino acid derivatives with lead tetraacetate.

An orally effective, nonpeptide, vasopressin V1 receptor antagonist, OPC-21268, (1-{1-[4-(3-acetylaminopropoxy)benzoyl]-4-piperidyl}-3,4-dihydro-2(1*H*)-quinolinone) (**1**) has been identified by Y. Yamamura and H. Ogawa et al [1] and is now under clinical trial. In recent studies [2] on the metabolism of OPC-21268, labile metabolites (**2a** and **2b**)[3] were isolated from biological fluids of rat, dog and human, whose nuclear magnetic resonance (NMR) and mass (MS) spectral data indicated the structure of the N,O-acetal.



1 (OPC-21268)



2a, b

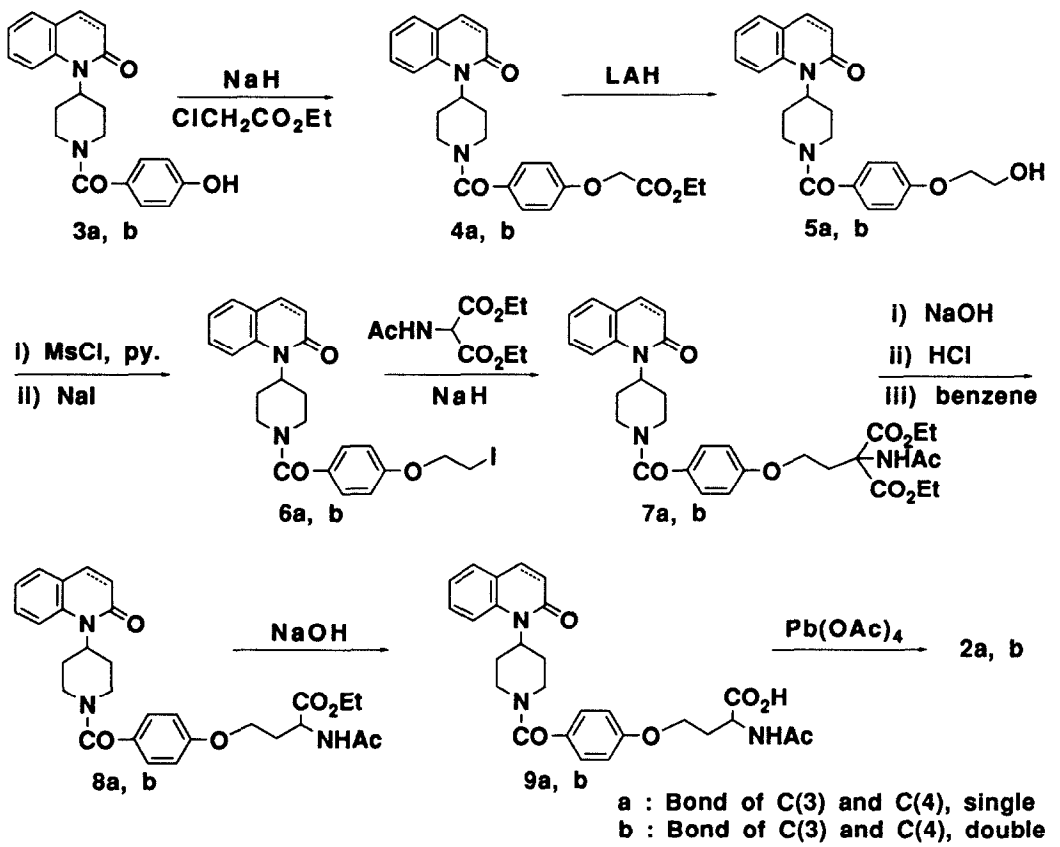
a : Bond of C(3) and C(4), single
b : Bond of C(3) and C(4), double

It has been well known that aminoalkyl compounds can be metabolized to the unstable N,O-acetals, followed by oxidative deamination to give the ketone compounds. In the cases of most aminoalkyl drugs, the hemiacetal metabolites could not be isolated. These N,O-acetal compounds are of interest in the study of the metabolism of xenobiotic aminoalkyl compounds. Recently, the oxidative decarboxylation of N-acylated α -amino acids with lead tetraacetate to give the O-acetyl-N,O-acetal has been briefly reported by Corcoran and Green.[4] In this paper we describe the synthesis of N-acetylhemiaminal metabolites of OPC-21268.

Synthesis

Alkylation of phenol derivative (**3a**)[5] with ethyl chloroacetate in the presence of sodium hydride afforded the ester compound (**4a**) in quantitative yield. Reduction of **4a** with lithium aluminum hydride (LAH) gave the alcohol (**5a**) in 88% yield. The alcohol (**5a**) was treated with methanesulfonyl chloride in pyridine to give the mesylate, which was converted to the iodide (**6a**) by replacement with sodium iodide in 65% yield. Condensation of the iodide (**6a**) with diethyl acetamidomalonate in the presence of sodium hydride afforded the amido derivative (**7a**) in 47% yield, which was hydrolyzed with sodium hydroxide, followed by decarboxylation in benzene to give the amino acid ethyl ester (**8a**) in 76% yield. Hydrolysis of the ester compound (**8a**) with sodium hydroxide gave the N-acetylated amino acid (**9a**) in 55% yield. Target compound (**2a**, 18%) [6] was synthesized by treatment of N-acetylated amino acid (**9a**) with lead tetraacetate in dry dimethyl formamide (DMF) (Scheme 1). Formation of a small amount of O-acetyl N,O-acetal, which was the major product in the case of Corcoran and Green,[4] was also observed.

Scheme 1



Another metabolite (**2b**) was obtained similarly from phenol derivative (**3b**),[5] via **7b**, which was hydrolyzed with sodium hydroxide. The resulting N-acetylated amino acid (**9b**) was treated with lead tetraacetate to give the desired hemiaminal metabolite (**2b**, 14%).[7]

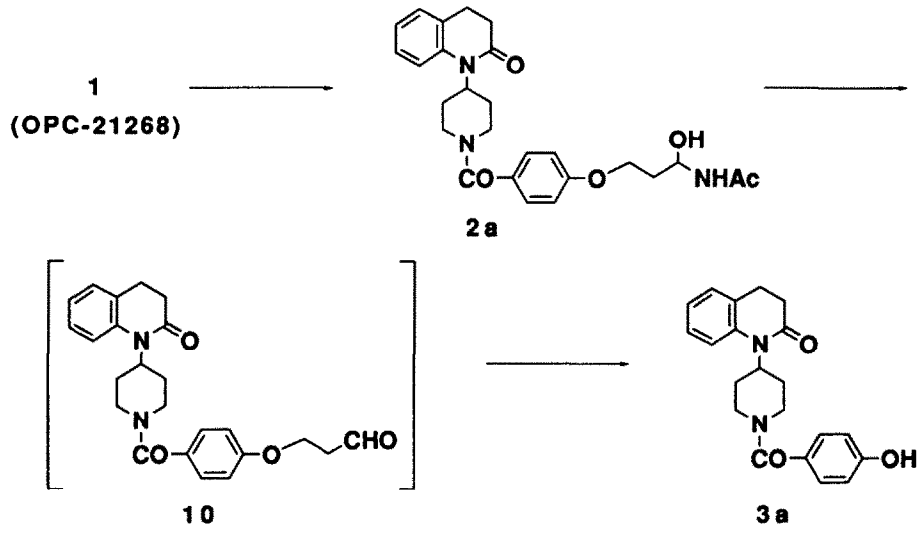
Results

The structure of the labile metabolites were identical with the corresponding synthetic compounds based on the NMR, MS and high performance liquid chromatographic (HPLC) comparison.

Vasopressin V1 receptor antagonistic activity of these N-acetylhemiaminal metabolites (**2a** and **2b**) was tested by the same method as described in a previous paper.[1] The results showed that the metabolite **2a** was a little less active (IC_{50}: 0.6 μ mol) and the metabolite **2b** was less active (IC_{50}: 3.3 μ mol) than the parent compound (**1**) (IC_{50}: 0.44 μ mol).

These compounds are of interest in the study of the metabolism of **1**. The degradation metabolite (**3a**) was isolated as a significant urinary metabolite in animal species. It was suggested that the hemiaminal metabolite (**2a**) apparently undergoes further metabolism to give the degradation product (**3a**) via very unstable intermediate (**10**). We have clarified one of the mode of metabolism by isolating and synthesizing of the hemiaminal metabolite (Scheme 2).

Scheme 2



The hemiaminal metabolites (**2a** and **2b**) have an asymmetric carbon at the N-acetyl hemiaminal moiety. The synthetic hemiaminal metabolite (**2a**) was analyzed by HPLC using a chiral stationary phase column.[8] The

chromatogram showed two peaks with almost the same area intensity, and the retention times were 14.7 min and 22.4 min.[9] After OPC-21268 (**1**) was administered orally to beagle dogs, the separated urinary metabolite (**2a**) was subjected to HPLC analysis under the same condition. It was found that the urinary metabolite showed the same two peaks as the synthetic sample did.[9] From these results, it was considered that OPC-21268 was not preferentially metabolized to one of the two possible enantiomers of the hemiaminal metabolite (**2a**) in beagle dogs, resulting in the formation of nearly racemic **2a**. The reason for this non-stereoselective biological hydroxylation of **1** to give racemic **2a** is unclear.

Acknowledgement : We are grateful to Professor K. Mori of the Department of Agricultural Chemistry, the University of Tokyo, for helpful advice.

References and notes

1) Y. Yamamura, H. Ogawa, T. Chihara, K. Kondo, T. Onogawa, S. Nakamura, T. Mori, M.Tominaga, and Y. Yabuuchi, *Science*, **1991**, 252, 572.

2) K. Okada and G. Miyamoto, unpublished data.

3) Half-life of the metabolite (**2a**) in $CDCl_3$ at room temperature was about 1 week.

4) R. C. Corcoran and J. M. Green, *Tetrahedron Lett.*, **1990** 31, 6827.

5) H. Ogawa, H. Miyamoto, K. Kondo, H. Yamashita, K. Nakaya, M. Tominaga and Y. Yabuuchi, **1990**, EP Patent 382185 (*Chem. Abstr.*, **1991**, 114, 81619f).

6) ^{1}H NMR (200 MHz, $CDCl_3$) δ : 1.65-1.90 (2H, br s), 2.00 (3H, s), 2.12 (2 H, q, J=5.8 Hz), 2.50-3.10 (8H, m), 4.00-5.00 (5H, m), 5.56 (1H, q, J=6.4 Hz), 6.80 (1H, d, J=8.6 Hz), 6.91 (2 H, d, J=8.6 Hz), 7.03-7.30 (4H, m), 7.44 (2H, d, J=8.6 Hz); FAB-MS (Pos.) m/z: 466 $[M-H]^+$; IR (KBr): 3400, 3300, 2950, 1670, 1600, 1250 cm^{-1}.

7) ^{1}H NMR (200 MHz, $CDCl_3$) δ : 1.70-1.90 (2 H, br s), 2.01 (3 H, s), 2.13 (2 H, q, J=5.6 Hz), 2.30-3.70 (6H, m), 3.90 (1H, br s), 4.10-4.40 (2 H, br s), 4,40-5.20 (3 H, m), 5.57 (1 H, m), 6.64 (1 H, d, J=9.4 Hz), 6.75 (1 H, br s), 6.93 (2 H, d, J=8.8 Hz), 7.23 (1 H, m), 7.45-7.70 (6 H, m).

8) Column, CHIRALCEL OJ (4.6 mm I. D. x 250 mm); solvent, n-hexane : EtOH: diethylamine = 600: 400: 1; detector, UV 254 nm.

9) Synthetic **2a**: tR 14.7 min (49.9 %), tR 22.4 min (50.1 %); **2a** obtained as the metabolite: tR 14.8 min (49.8 %), 22.4 min (50.2 %).