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COMMUNICATION

Synthesis and Crystal Structure of 3-Quinuclidinyl α-(Cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate

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Abstract The title compound 3-quinuclidinyl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate was obtained by the reaction of methyl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate with 3-quinuclidinol in *n*-heptane. Its structure was characterized by ^{1}H, ^{13}C NMR, MS and X-ray single-crystal diffraction techniques: $C_{20}H_{25}NO_3$, $M_r = 327.41$, orthorhombic, space group $P2_12_12_1$ with $a = 8.547(2)$, $b = 11.428(4)$, $c = 18.288(5)$ Å, $V = 1786.3(9)$ Å^3, $Z = 4$. The title compound comprises a tertiary α-hydroxy acid and a bicyclo[2.2.2]octan moiety. The crystal structure shows the presence of the intermolecular O(1)–H(1)···N(1) hydrogen bonds.

Keywords Anticholinergic drug · Tertiary α-hydroxy acid · Crystal structure

Introduction

Over the past century classical anticholinergic drugs have been widely used for the treatment of certain diseases, such as chronic obstructive pulmonary diseases, Alzheimer's disease and urinary incontinence. Most of the muscarinic receptor antagonists comprise of a tertiary α-hydroxy acid as a key component [1]. We have engaged in the synthesis and biological activity study of anticholinergic drugs for many years [2]. Recently we synthesized a potent muscarinic receptor antagonist, 3-quinuclidinyl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate. The biological tests suggest that the title compound displays more effective treating centric and peripheral choline dysfunctions [3]. The title compound was obtained by the reaction of methyl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate with 3-quinuclidinol in *n*-heptane. Crystals of the title compound suitable for X-ray structure determination were obtained from the filtrate by slow evaporation of the CH_2Cl_2 solution.

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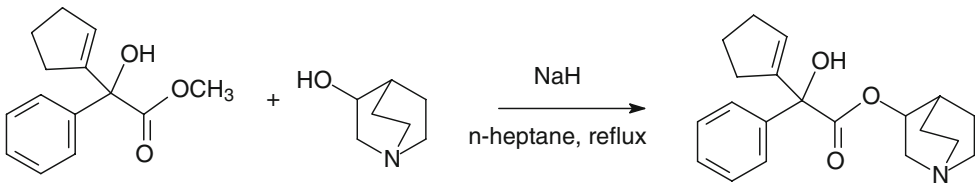
Experimental

Materials and Synthesis

All reagents were commercially available and used without further purification or purified by standard methods prior to use. Melting points were determined using a RY-1 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian UNITY INOVA 600 MHz and JNM-ECA-400 400 MHz instrument in the solvent indicated below. Chemical shift values are reported in parts per million (ppm) relative to those for tetramethylsilane used as an internal reference standard. Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; m, multiplet. Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Elemental analysis was carried at the CarloErba-1106. Methyl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate was synthesized as described in the literature [4]. The synthetic pathway for the title compound is outlined in Scheme 1.

Methyl α-(cyclopentyl-1-ene)-α-hydroxy-α-phenylacetate (2.6 g, 11.2 mmol) and 3-quinuclidinol (1.3 g, 10.2 mmol) were dissolved in anhydrous *n*-heptane (100 mL) and NaH

Scheme 1 Procedure of preparing the title compound



(0.5 g assay 80%) was added. Then the solution was refluxed for 3 h. After the solvent was removed under reduced pressure, the residue was dissolved in ether (150 mL), washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to dryness. The product was purified by flash-chromatography (chloroform/methanol, 9:1) and the title compound was isolated as a white solid (2.51 g, 76%). m.p.: 183–185 °C. ^{1}H-NMR (ppm, $CDCl_3$, 25 °C) δ: 7.55 (2H, m), 7.33 (3H, m), 4.91 (1H, s), 3.93 (s, 1H), 3.24 (m, 1H), 2.76 (m, 5H), 2.41 (m, 4H), 2.05 (s, 1H), 1.92 (m, 3H), 1.64 (m, 1H), 1.52 (m, 1H), 1.26 (m, 2H). ^{13}C-NMR δ ($CDCl_3$): 173.91, 144.48, 140.07, 127.93, 127.80, 126.46, 78.25, 73.65, 55.07, 47.08, 46.20, 32.52, 32.05, 25.24, 24.26, 23.48, 19.47. ESI-MS: 328.2 (M + 1). Anal. Calcd. (%) For $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found (%): C, 73.28; H, 7.61; N, 4.32.

Crystallographic Study

A colorless crystal of the title compound with dimensions of 0.28 × 0.24 × 0.20 mm^3 was mounted on a glass fiber in a random orientation. The data were collected by a Bruker CCD-1000 diffractometer with a graphite-monochromated Mo$K\alpha$ radiation ($\lambda = 0.71073$ Å) by using a ω scan mode in the range of $2.23 \leq \theta \leq 26.51°$ at 293(2) K. The structure was solved by direct methods with SHELXL-97 program [5] and all data were corrected by using semi-empirical (SADABS) method [6]. Unit cell dimensions were obtained with least-squares refinements. A total of 10,442 reflections were collected with 2,125 unique ones ($R_{int} = 0.0486$), of which 1558 with $I > 2\sigma(I)$ were considered as observed and used in the succeeding refinements. All the other non-hydrogen atoms were located in successive difference Fourier syntheses. The final refinement was carried out by full-matrix least-squares methods with anisotropic thermal parameters for non-hydrogen atoms on F^2. The hydrogen atoms were added theoretically, and allowed to ride on the concerned atoms and refined with fixed thermal factors. The final refinement gave $R = 0.0518$ and $wR = 0.1228$ for 2,125 observed reflections ($w = 1/[\sigma^2(F_o)^2 + (0.0788P)^2 + 0.2078P]$, where $P = (F_o^2 + 2F_c^2)/3$), $S = 1.021$, $(\Delta/\sigma)_{max} = 0.000$, $(\Delta\rho)_{max} = 0.341$ and $(\Delta\rho)_{min} = -0.226$ e/Å^3.

Results and Discussion

The ^{1}H, ^{13}C NMR, MS and elemental analysis for the product are in good agreement with the title compound. Crystallographic data and experimental details for structural analyses are summarized in Table 1. The selected bond distances and angles are listed in Table 2, respectively. Figure 1 shows the molecular structure of the title compound and molecular packing together with the hydrogen bonds.

The X-ray ORTEP structure of the title compound with atomic labeling is shown in Fig. 1a. X-ray structure analytical data show that the title compound is composed of a 3-quinuclidinol structure and a tertiary hydroxy acid moiety. The three six-membered rings of the bicyclo[2.2.2]octan structure have twist boat conformations along C(16)···N(1) axis. The torsion angles of N(1)–C(20)···C(16)–C(19) = 7.6°, N(1)–C(15)···C(16)–C(14) = 6.0° and N(1)–C(18)···C(16)–C(17) = 8.4° are similar to those found in some monosubstituted quinuclidine compound [7]. In the quinuclidine ring system the C–N distances (N(1)–C(15) = 1.456(4), N(1)–C(18) = 1.467(4) and N(1)–C(20)

Table 1 Crystallographic data and structure refinement summary for the title compound

CCDC deposit no.	245331
Empirical formula	$C_{20}H_{25}NO_3$
Molecular weight	327.41
Temperature (K)	293(2)
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a (Å) = 8.547(2)
	b (Å) = 11.428(4)
	c (Å) = 18.288(5)
Volume, V (Å^3)	1786.3(9)
Z	4
Calculated density (mg m^{-3})	1.217
Absorption coefficient (mm^{-1})	0.081
F (000)	704
Crystal size (mm^3)	0.20 × 0.20 × 0.18
Reflections collected/unique	10,442/2,125
Max. and min. transmission	1.0000 and 0.9841
Data/restraints/parameters	2125/0/235
R_{int}	0.0486
Goodness of fit on F^2	1.029
Final R indices [$I > 2\sigma$(I)]	$R_1 = 0.0518$, $wR_2 = 0.1228$
R indices (all data)	$R_1 = 0.0793$, $wR_2 = 0.1360$
Largest diff. peak and hole (eÅ^{-3})	0.341 to −0.226

Table 2 Selected bond lengths (Å) and bond angles (°)

Bond	Distance	Bond	Distance	Bond	Distance
O(1)–C(7)	1.412(3)	N(1)–C(20)	1.470(4)	C(5)–C(6)	1.361(5)
O(2)–C(13)	1.195(4)	C(1)–C(2)	1.373(7)	C(6)–C(7)	1.525(4)
O(3)–C(13)	1.337(4)	C(1)–C(6)	1.378(6)	C(8)–C(12)	1.328(5)
O(3)–C(14)	1.447(4)	C(2)–C(3)	1.381(8)	C(8)–C(9)	1.497(5)
N(1)–C(15)	1.456(5)	C(3)–C(4)	1.350(8)	C(17)–C(18)	1.531(5)
N(1)–C(18)	1.466(5)	C(4)–C(5)	1.400(6)	C(19)–C(20)	1.546(5)
Angle	(°)	Angle	(°)	Angle	(°)
C(13)–O(3)–C(14)	117.5(2)	C(6)–C(5)–C(4)	121.3(4)	N(1)–C(15)–C(14)	112.0(3)
C(15)–N(1)–C(18)	108.9(3)	C(5)–C(6)–C(1)	118.4(4)	C(14)–C(16)–C(19)	107.3(2)
C(15)–N(1)–C(20)	108.6(3)	C(5)–C(6)–C(7)	122.6(3)	C(14)–C(16)–C(17)	109.5(3)
C(18)–N(1)–C(20)	109.9(3)	C(1)–C(6)–C(7)	118.8(3)	C(19)–C(16)–C(17)	108.7(3)
C(2)–C(1)–C(6)	121.0(4)	O(1)–C(7)–C(8)	110.4(3)	C(16)–C(17)–C(18)	108.7(3)
C(1)–C(2)–C(3)	119.7(5)	O(1)–C(7)–C(6)	106.4(2)	N(1)–C(18)–C(17)	111.2(3)
C(4)–C(3)–C(2)	120.3(5)	C(8)–C(7)–C(6)	114.5(2)	C(16)–C(19)–C(20)	108.5(3
C(3)–C(4)–C(5)	119.3(4)	O(1)–C(7)–C(13)	109.3(2)	N(1)–C(20)–C(19)	110.8(3)

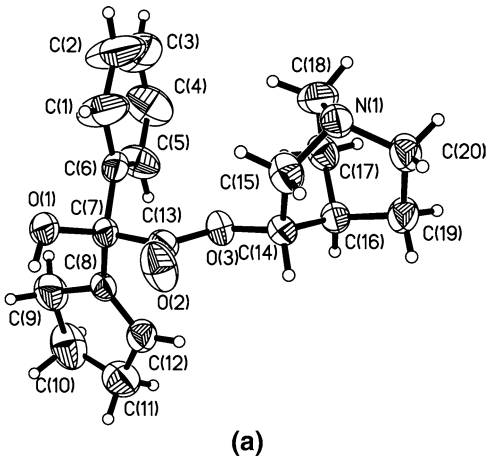


Fig. 1 (**a**) Molecular structure of the title compound with the 50% probability of the thermal ellipsoids; (**b**) Molecular packing in a unit cell showing the one-dimensional structure with hydrogen bonds

1.468(3) Å) are slightly shorter compared with cinchonine alkaloid [8]. No significant difference was found in the bond lengths, but the bond angle of C(18)–N(1)–C(20)(110.0(2)°) was slightly larger than C(15)–N(1)–C(18)(108.7(2)°) and C(15)–N(1)–C(20) (108.5(2)°) because of the 3-substituted ester group.

As shown in Fig. 1b, a *zig-zag* one-dimensional linear structure is formed through N···H–O hydrogen bonds in which the O atom of hydroxyl groups link the N atom of 3-quinuclidinol in the adjacent molecule. The N···O separation is 2.761 Å with the H···N separations of 1.954 Å, and the bond angles are 167.50°, falling into the normal range of N···O separation for hydrogen bonds [9].

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