Synthesis and crystal structure of quinuclidin-3-yl 2-cyclopentyl-2-hydroxy-2-phenylacetate

He Liu*, Xiang-yu Han, Bo Wu, Bo-hua Zhong and Ke-liang Liu

No.7 Department, Beijing Institute of Pharmacology and Toxicology, Beijing 100850. P. R. China

Quinuclidin-3-yl 2-cyclopentyl-2-hydroxy-2-phenylacetate, a more effective the muscarinic receptor antagonist, was synthesised and its crystal structure was first elucidated by X-ray crystallography.

Keywords: synthesis, crystal structure, muscarinic receptor antagonist

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 synthesised a potent muscarinic receptor antagonist, quinuclidin-3-yl 2-cyclopentyl-2-hydroxy-2-phenylacetate which comprise of a tertiary α-hydroxy acid and a 1-aza bicyclo[2.2.2]octane moiety. The biology results suggest that the tile compound display more effective treating centric and peripheral choline dysfunctions.[3] The title compound was synthesised by methyl 2-cyclopentyl-2-hydroxy-2-phenylacetate and quinuclidin-3-ol. 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.

An ORTEP plot showing the X-ray structure of the title compound with atomic labelling is shown in Fig. 1(a). X-ray structure analytical data showed that the title compound is composed of a quinuclidin-3-ol structure and a tertiary hydroxy acid moiety. The three six-membered rings of the 1-aza bicyclo[2.2.2]octane structure have a twist boat conformation; the molecule is seen in Fig. 1(a) along C16…N1 axis. The N1–C20…C16–C19 = 8.8°, N1–C15…C16–C14 = 5.9° and N1–C18…C16–C17 = 8.9° torsion values are similar to those found in some monosubstituted 1-azabicyclo[2,2,2]octane compound.[4] In the quinuclidine ring system the C–N distances [N(1)–C(15) 1.462(2), N(1)–C(18) 1.473(3) and N(1)–C(20) 1.476(3) Å] are slightly shorter compared with cinchonine alkaloid.[5] No significant difference was found in the bond angles[C(18)–N(1)–C(20) 108.84(16)°, C(15)–N(1)–C(18) 108.25(15) (2)° and C(15)–N(1)–C(20) 108.36(16)°].

As shown in Fig. 1(b), a zigzag quasi-one dimensional linar structure was formed through N…H–O hydrogen bonds in which the O atom of the hydroxyl groups link the N atom of quinuclidin-3-ol in the adjacent molecule. The N…O separation is 2.860 Å with the H…N separations is 2.041 Å, the bond angles are 177.17°, falling into the normal range of the N…O separation for hydrogen bonding.[6]

Experimental

All the reagents for syntheses 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. Elemental analyses were performed on a Perkin-Elmer 240C analyzer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using a multinuclear FT-NMR spectrometer ARX300 (Bruker). Mass spectra were obtained from Micromass ZabSpec and API3000 instruments. Methyl 2-cyclopentyl-2-hydroxy-2-phenylacetate was synthesised by addition of Grignard reagents to dimethyl oxalate as described in the literature.[7]

Synthesis of quinuclidinyl-3-yl 2-cyclopentyl-2-hydroxy-2-phenylacetate

Methyl 2-cyclopentyl-2-hydroxy-2-phenylacetate (4.7g, 20mmol) and quinuclidin-3-ol (2.1g, 18mmol) were dissolved in anhydrous *n*-heptane (200 ml), NaH(1g assay 80%) was added. The solution was reflux for 3 hours. 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 an white solid (4.4g, 74%). m.p. 121–123 °C. ^{1}H NMR ($CDCl_3$): 7.56(2H, m), 7.32 (3H, m), 5.69(1H, s), 4.91 (1H, s), 3.99(s, 1H), 3.16 (m, 1H), 2.75(m, 5H), 2.05(s, 1H), 1.91–1.70(m, 9H) 1.55(m, 1H), 1.39(m, 2H). ^{13}C NMR δ($CDCl_3$), 173.92, 144.47, 140.06, 127.94, 127.81, 126.46, 79.50, 73.71, 55.10, 47.11, 46.24, 32.53, 32.05, 25.25, 24.29, 23.48, 19.49. ESI-MS: 330.2 (M+1). Anal. calc. For $C_{20}H_{27}NO_3$: C 72.92, H 8.26, N 4.25; found: C 72.88, H 8.31, N4.22.

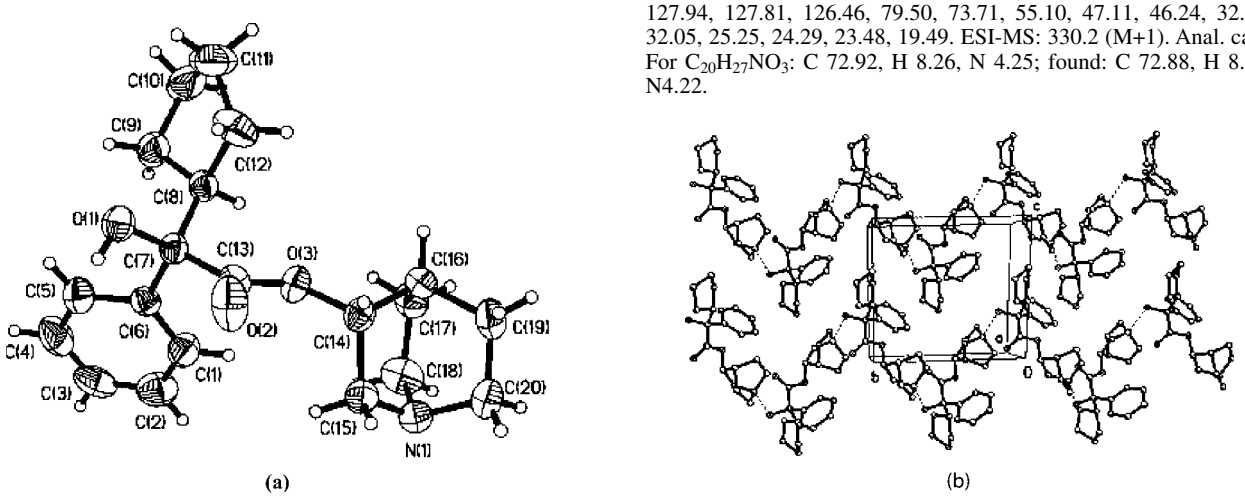
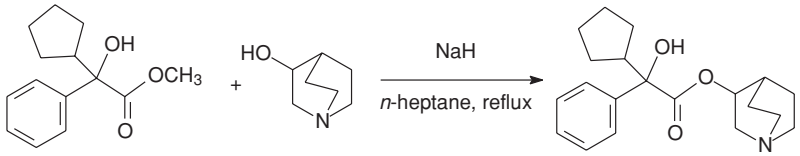


Fig.1 (a) Molecular structure of the title compound; (b) molecular packing in a unit cell showing the quasi-one dimensional structure with hydrogen bonding.

* Correspondent. E-mail: hliuamms@yahoo.com



Scheme 1

Crystal data: $C_{20}H_{27}NO_3$, M*r* = 329.43, Monoclinic, $P2_1$, *a* = 8.926(6) Å, *b* = 10.458(7) Å, *c*= 10.320(7) Å, β = 112.140(10). *V* = 892.3(10) Å^3, D_x = 1.226 g cm^{-3}, *Z* = 2, μ= 0.082 mm^{-1}, *T* = 293(2) K. A colourless crystal with dimensions of 0.38 mm × 0.22 mm × 0.18 mm was mounted on a Bruker Smart 1000 CCD diffractometer equipped with a graphite monochromator for data collection. The determination of unit cell parameters and data collections was performed with Mo Kα radiation (λ = 0.71073 Å) and unit cell dimensions were obtained with least-squares refinements. A total of 4644 reflections with 3092 independent ones with R_{int} = 0.0171 and 2718 observed reflections with $I > 2\sigma(I)$ were collected in the range of $2.13 < \theta < 25.01°$ by an ω/θ scan mode at 293(2) K. All data were corrected by using SADABS method[8]. The structure was solved by direct methods with SHELXL-97 program[9]and all data were corrected by using semi-empirical absorption corrections (SADABS) method. 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 riding on the concerned atoms and refined with fixed thermal factors. The weighting scheme was $w = 1/[\sigma^2(F_o^2) + (0.0533P)^2 + 0.0268P]$, where $P = (F_o^2 + 2F_c^2)/3$. The refinement converged to the final $R = 0.0331$ and $wR = 0.0818$. $S = 0.999$.

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications (CCDC No. 245530). Copies of available materials can ben obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 int. code (+44)(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

This work was financially supported by the National Natural Science Foundation of China (No. 203900508).

Received 2 June 2005; accepted 8 July 2005
Paper 05/3283

References

1 (a) M. Mitsuya, Y. Ogino, N. Ohtake and T. Mase, *Tetrahedron,* 2000, **56**, 9901; (b) M. Mitsuya, K. Kawakami, Y. Ogino, K. Miura and T. Mase, *Bioorg. Med. Chem. Lett*., 1999, **9**, 2037.

2 (a) H. Liu, X.Y. Han, B.H. Zhong and K.L. Liu, *J. Chem. Res.,* 2005, 322; (b) X.Y. Han, H. Liu, C.H. Liu, B. Wu, L.F. Chen, B.H. Zhong and K.L. Liu, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 1979; (c) Y.Q. Liu, H. Liu, B.H. Zhong, Y.L. Deng and K.L. Liu, *Synth. Commun.,* 2005, **35**, 1403; (d) (e) H. Liu, C.H. Liu, X.Y. Han, B.H. Zhong and K.L. Liu, *J. Chem. Res.,* 2004, 482; (f) H. Liu, X.Y. Han, C.H. Liu, B.H. Zhong and K.L. Liu, *Anal. Sci.,* 2004, **20**, x121.

3 L.P. Liu, PhD Thesis. Institute of Pharmacology and Toxicology Academy, Beijing, 2002.

4 (a) M.S. Arias-Pérez, A. Cosme, E. Gálver, F. Florencio, I. Fonseca and J. Sanz, *Magn. Res. Chem.,* 1991, **29**, 1130; (b) L. Brammer, J.C.M. Rivas and D. Zhao, *Inorg. Chem.,* 1998, **37**, 5512; (c) T. Borowiak, G. Dutkiewicz and J. Thiel, *Z.Naturforsch,* 2002, **57b**, 586.

5 P. Kumaradhas, P. Kalyanam and K.A. Niramala, *Cryst. Res. Technol., 2001, **36**, 1435.*

6 (a) G.R. Desiraju, *Acc. Chem. Res*., 1991, **24**, 290; (b) *Hydrogen bonding in Biological Structure*. G.A. Jeffrey, W. Saenger, eds. Springer: Berlin., pp.29-32, 1991.

7 (a) J.S. Ninita and H.S. Mosher, *J. Org. Chem.,* 1981**, 46**, 211; (b) C.C. Chiu and F. Jordan, *J. Org. Chem.,* 1994, **59**, 5763.

8 G.M. Sheldrick, SADABS, program for Empirical Absorption Correction of Area Detector Data, University of Göttingen 1996.

9 G.M. Sheldrick, *SHELXS-97, Program for X-ray Crystal Structure Solution*; Göttingen University: Germany, 1997; Sheldrick, G. M. *SHELXL-97, Program for X-ray Crystal Structure Refinement*; University of Göttingen: Germany, 1997.