Crystal structure of (1*S*,2*R*,4*S*)-2-bromomethyl-1-azabicyclo[2.2.2]-octan-5-one, $C_8H_{12}BrNO$

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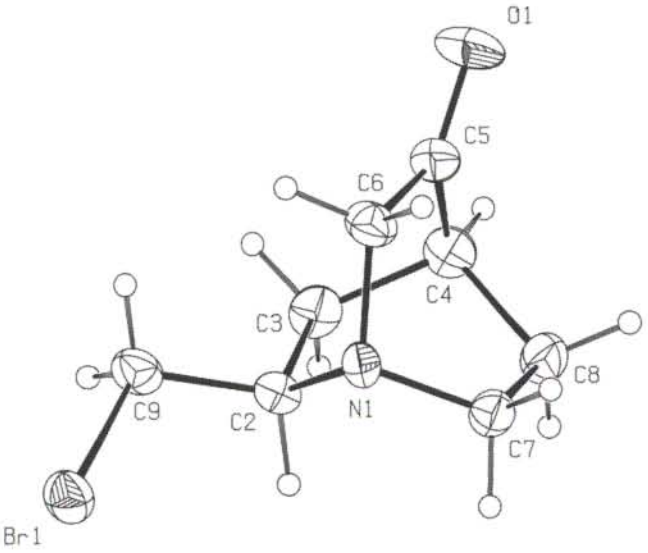

Abstract

$C_8H_{12}BrNO$, orthorhombic, $P2_12_12_1$ (No. 19), a = 7.002(1) Å, b = 7.432(1) Å, c = 16.762(2) Å, V = 872.3 Å^3, Z = 4, $R_{gt}(F)$ = 0.031, $wR_{all}(F^2)$ = 0.050, T = 300 K.

Source of material

Methanesulfonyl chloride (0.39 ml, 5.0 mmol) was added to (1*S*,2*R*,4*S*)-2-hydroxymethyl-1-azabicyclo[2.2.2]octan-5-one (600 mg, 3.9 mmol) and Et_3N (1.08 ml, 7.7 mmol) in absolute CH_2Cl_2 (10 ml) at 273 K. The reaction mixture was stirred for 10 h at room temperature, diluted with CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$. The organic layer was dried, the solvent evaporated and the crude product (83 %, 748 mg, 3.21 mmol) dissolved in abs. dioxan (5 ml). Powdered lithium bromide (838 mg, 9.64 mmol, 3.0 eq) was added and the mixture was refluxed for 24 h at 383 K. After addition of saturated aqueous $NaHCO_3$ the aqueous layer was extracted with CH_2Cl_2, and the combined organic layer dried ($MgSO_4$) and evaporated. Purification by chromatography (EtOAc / MeOH 20:1) furnished the desired brominated ketone which was recrystallized from MTBE / acetone.

Experimental details

Completeness of Laue data set in class *mmm* 100%, but Friedel pairs kept separate in the refinement. The empirical absorption corerection was based on a function of the mean intensity of the imaging plate versus angle φ improving the R_{int} from 0.201 to 0.076. A spherical absorption correction with μ·r = 0.34 was applied too. The Flack parameter was found to be –0.01(2).

Discussion

Substituted quinuclidines possess interesting and diverse pharmacological activities as the quinuclidine nucleus has been found to be a good mimic for the quaternary nitrogen in acetylcholine [1]. The synthetic methods most frequently used for the preparation of quinuclidine-based pharmaceutical lead structures have started from quinuclidin-3-one [2, 3]. In the course of our investigations on the synthesis of chiral quinuclidinone analogs the title compound has been prepared from Quincoridine® [4] in enantiopure form following an eight step pathway [5]. Because of their low molecular weight and their compact azabicyclic structure quincoridine-derivatives are of general interest [6, 7]. Oxidative degradation of the vinylic side chain of quincoridine was carried out by double bond shift, 1,2-dihydroxylation and subsequent diol cleavage. *O*-Mesylation of resulting (1*S*,2*R*,4*S*)-2-hydroxymethyl-1-azabicyclo[2.2.2]octan-5-one followed by LiBr-promoted S_N2 displacement furnished the desired γ-amino δ-bromo ketone of which we present the crystal structure.
(1*S*,2*R*,4*S*)-2-Bromomethyl-1-azabicyclo[2.2.2]-octan-5-one contains a prochiral carbonyl group and three stereogenic centres including the chiral *S*-configurated bridgehead nitrogen. The analysis of N,C-bond angles shows a less developed pyramidalization of the bridgehead nitrogen than in 10,11-didehydroquincorine and -quincoridine [8, 9, 10].

Table 1. Data collection and handling.

Crystal:	colourless plate ll (100), size 0.06 × 0.17 × 0.20 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	46.55 cm^{-1}
Diffractometer, scan mode:	Stoe IPDS, 150 exposures, Δφ = 1.5°
$2\theta_{max}$:	48.36°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	6270, 1378
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 897
$N(param)_{refined}$:	101
Programs:	SHELXS-86 [11], SHELXS-93 [12], PLATON [13], PROMETHEUS [14]

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Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(1)	4a	0.4330(7)	0.0982(8)	0.4440(3)	0.044
H(2)	4a	0.5098(8)	0.0706(8)	0.3166(2)	0.056
H(3)	4a	0.3215(8)	-0.0361(8)	0.2962(2)	0.056
H(4)	4a	0.325(1)	0.2594(8)	0.2324(3)	0.056
H(5)	4a	-0.0929(7)	0.262(1)	0.3927(3)	0.059
H(6)	4a	-0.0419(7)	0.058(1)	0.3789(3)	0.059

Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(7)	4a	0.350(2)	0.3974(6)	0.4631(2)	0.052
H(8)	4a	0.152(2)	0.4670(6)	0.4315(2)	0.052
H(9)	4a	0.2907(8)	0.5159(7)	0.3153(2)	0.062
H(10)	4a	0.4773(8)	0.4154(7)	0.3429(2)	0.062
H(11)	4a	0.359(1)	-0.2063(6)	0.4141(2)	0.056
H(12)	4a	0.142(1)	-0.1528(6)	0.4134(2)	0.056

Table 3. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(1)	4a	0.2543(2)	-0.15708(7)	0.55172(2)	0.0582(3)	0.0530(3)	0.0470(2)	-0.0031(7)	0.0001(7)	0.0118(3)
O(1)	4a	-0.0388(7)	0.2448(6)	0.2380(2)	0.098(4)	0.096(4)	0.057(2)	0.002(3)	-0.046(2)	0.002(2)
N(1)	4a	0.1707(6)	0.1969(6)	0.4326(2)	0.040(3)	0.030(3)	0.032(2)	0.004(2)	0.003(2)	0.002(2)
C(2)	4a	0.3185(7)	0.0655(8)	0.4136(3)	0.035(4)	0.043(4)	0.032(2)	0.005(3)	-0.002(2)	0.000(3)
C(3)	4a	0.3721(8)	0.0693(8)	0.3231(2)	0.060(4)	0.051(4)	0.028(3)	0.000(4)	0.012(2)	-0.009(3)
C(4)	4a	0.284(1)	0.2423(8)	0.2877(3)	0.064(6)	0.054(4)	0.023(2)	-0.006(5)	0.008(3)	0.002(2)
C(5)	4a	0.076(1)	0.2243(9)	0.2918(3)	0.065(4)	0.045(5)	0.043(3)	0.000(4)	-0.017(4)	-0.003(3)
C(6)	4a	0.0082(7)	0.180(1)	0.3771(3)	0.037(3)	0.057(5)	0.052(3)	-0.002(4)	-0.008(2)	0.011(3)
C(7)	4a	0.252(2)	0.3784(6)	0.4230(2)	0.054(3)	0.042(4)	0.033(2)	-0.005(6)	0.001(5)	-0.001(2)
C(8)	4a	0.3394(8)	0.4061(7)	0.3391(2)	0.072(4)	0.044(4)	0.039(3)	-0.013(3)	-0.002(3)	0.004(2)
C(9)	4a	0.266(1)	-0.1238(6)	0.4363(2)	0.058(3)	0.050(3)	0.031(2)	0.008(5)	-0.005(4)	-0.002(2)

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References

1. Wadsworth, H. J., Jenkins, S. M.; Orlek, B. S.; Cassidy, F.; Clark, M. S. G.; Brown, F.; Riley, G. J.; Graves, D.; Hawkins, J.; Naylor, C. B.: Synthesis and Muscarinic Activities of Quinuclidin-3-yltriazole and -tetrazole Derivatives. J. Med. Chem. **35** (1992) 1280-1290.
2. Nordvall, G.; Sundquist, S.; Nilvebrant, L.; Hacksell, U.: 3-Lithioquinuclidin-2-ene: A Novel Intermediate for the Synthesis of Muscarinic Agonists and Antagonists. Bioorg. Med. Chem. Lett. **4** (1994) 2837-2840.
3. Johansson, G.; Sundquist, S.; Nordvall, G.; Nilsson, B. M.; Brisander, M.; Nilvebrant, L.; Hacksell, U.: Antimuscarinic 3-(2-Furanyl)-quinuclidin-2-ene Derivatives: Synthesis and Structure-Activity Relationships. J. Med. Chem. **40** (1997) 3804-3819.
4. Quincoridine® is available from Buchler GmbH, Harxbütteler Str. 3, D-39110 Braunschweig.
5. Frackenpohl, J.; Hoffmann, H. M. R.: Synthesis of Enantiopure Quinuclidin-3-one Analogs with Three Stereogenic Centres: (1*S*,2*R*,4*S*)- and (1*S*,2*S*,4*S*)-2-Hydroxymethyl-1-azabicyclo[2.2.2]octan-5-one and Stereocontrol of Nucleophilic Addition to Carbonyl Group. J. Org. Chem. submitted.
6. Hoffmann, H. M. R., Schrake, O.: Acylation and *O*-Sulfonylation of Quincorine® and Quincoridine®. Efficient Intramolecular Catalysis. Tetrahedron: Asymmetry **9** (1998) 1051-1057.
7. Schrake, O.; Rahn, V. S.; Frackenpohl, J.; Braje, W. M.; Hoffmann, H. M. R.: Novel Bridged Bicyclic α-Amino Acid Esters and Key Derivatives from Quincorine® and Quincoridine®. Org. Lett. **1** (1999) 1607-1610.
8. Schrake, O.; Braje, W.; Hoffmann, H. M. R.; Wartchow, R.: Synthesis of 10,11-Didehydro- and 10,11-Dihydro-quincorine and of the Quincoridine analogs: Functionalized and Enantiopure 1-Azabicyclo[2.2.2]octanes with Four Stereogenic Centres. Tetrahedron: Asymmetry **9** (1998) 3717-3722.
9. Wartchow, R.; Schrake, O.; Braje, W. M.; Hoffmann, H. M. R.: Crystal structure of (1*S*,2*S*,4*S*,5*R*)-2-hydroxymethyl-5-ethynyl-1-azabicyclo[2.2.2]octane. Z. Kristallogr. NCS **214** (1999) 285-286.
10. Wartchow, R.; Frackenpohl, J.; Hoffmann, H. M. R.: Crystal Structure of (1*S*,2*R*,4*S*,5*R*)-2-Hydroxy-methyl-5-ethynyl-1-azabicyclo[2.2.2]octane. Z. Kristallogr., to be submitted.
11. Sheldrick, G. M.: SHELXS-86, program for crystal structure determination University of Göttingen, Germany 1986.
12. Sheldrick, G. M.: SHELXL-93, program for refining crystal structures University of Göttingen, Germany 1993.
13. Spek, A. L.: PLATON, an integrated tool for the analysis of the results of a single crystal structure determination. Acta Crystallogr. Suppl. A**46** (1990) C-34.
14. Zucker, U. H.; Perenthaler, E.; Kuhs, W. F.; Bachmann, R.; Schulz, H.: PROMETHEUS, a program system for investigation of anharmonic thermal vibrations in crystals J. Appl. Crystallogr. **16** (1983) 358.