Crystal structure of (1*S*,2*R*,5*R*,6*R*)-2-methoxy-6-(16-nitrophenylethynyl)-1-azabicyclo[3.2.2]nonane, $C_{17}H_{20}N_2O_3$

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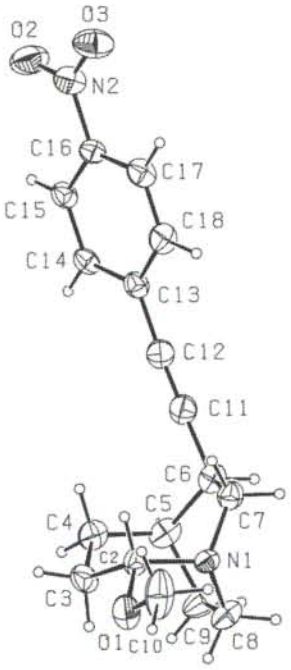
Received January 21, 2000, CCDC-No. 1267/387



Abstract

$C_{17}H_{20}N_2O_3$, orthorhombic, $P2_12_12_1$ (No. 19), $a = 7.096(1)$ Å, $b = 11.671(1)$ Å, $c = 19.277(2)$ Å, $V = 1596.5$ Å^3, $Z = 4$, $R_{gt}(F) = 0.032$, $wR_{ref}(F^2) = 0.040$, $T = 300$ K.

Source of material

p-NO_2-Phenyl substituted 10,11-didehydroquincorine [1] was transformed into its corresponding C9-iodide *via* mesylation and LiI-mediated iodination. The resulting 2-iodomethyl-5-(16-nitrophenylethynyl)-1-azabicyclo[3.2.2]-nonane (500 mg, 1.26 mmol, 1 eq) was dissolved in abs. MeOH (6 ml). After being stirred for 5 min at room temperature under argon freshly prepared silver benzoate (318 mg, 1.39 mmol, 1.1 eq) was added. The reaction mixture was stirred for 16 h at 323 K, diluted with MeOH and filtered. The remaining precipitate was washed with MeOH, the combined solutions were concentrated *in vacuo* and the resulting solid was dissolved in CH_2Cl_2. 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 (MTBE) furnished the desired substituted 1-azabicyclo[3.2.2]nonane (77 %, 292 mg, 0.97 mmol) which was recrystallized from MTBE / PE.

Discussion

Azabicyclic systems are common structural units in medicinal chemistry and in a large number of natural products, especially alkaloids including cinchona species [2]. Although azabicyclo[2.2.1]heptane and azabicyclo[2.2.2]octane systems have been subject to intensive studies, the next higher [3.2.2]-homologues have hardly been investigated [3-5]. Due to uncertain stereochemical and mechanistic details of the hetero-cinchona rearrangement these reactions were reinvestigated [6]. The resulting quinine and quinidine derivatives contain a 1-azabicyclo[3.2.2]nonane moiety. The mechanism of the rearrangement involves a 1,2-nucleophilic shift with generation of a strained non-planar iminium-ion and a stereoselective nucleophilic capture by the solvent. Likewise, silver salt-mediated ring enlargement of halogenated Quincorine® and Quincoridine® derivatives offers a short and stereoselective route to novel substituted 1-azabicyclo[3.2.2]nonanes containing four stereogenic centres [7]. In view of the high synthetic and therapeutic potential of 5-substituted quinuclidine derivatives we prepared (1*S*,2*R*,5*R*,6*R*)-2-methoxy-6-(16-nitrophenylethynyl)-1-azabicyclo[3.2.2]nonane and present its crystal structure.

Small torsion angles Φ_1 (N1–C7–C6–C5) = 6.3° and Φ_2 (N1–C8–C9–C5) = 2.4° suggest reduced conformational strain of the 1-azabicyclo[3.2.2]nonane moiety compared with related 1-azabicyclo[2.2.2]octanes which are strongly twisted to minimize eclipsing and ring strain [1]. The bridgehead nitrogen in the title compound is more flattened, with an expansion of bond angles, than in quincorine derivatives [8].

Table 1. Data collection and handling.

Crystal:	colourless, plate ‖ (010), size 0.09 × 0.18 × 0.33 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	0.86 cm^{-1}
Diffractometer, scan mode:	Stoe IPDS, 158 exposures, $\Delta\varphi = 1.3°$
$2\theta_{max}$:	48.24°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	10621, 2526
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 1139
$N(param)_{refined}$:	199
Programs:	SHELXS-86 [9], SHELXL-93 [10], PLATON [11]

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

Atom	Site	x	y	z	U_{iso}
H(1)	4*a*	0.8645(4)	0.2091(2)	0.2996(2)	0.078
H(2)	4*a*	0.9639(4)	0.3901(2)	0.3272(2)	0.095
H(3)	4*a*	0.8505(4)	0.3900(2)	0.3969(2)	0.095
H(4)	4*a*	0.6946(4)	0.4082(2)	0.2630(2)	0.095
H(5)	4*a*	0.6902(4)	0.5036(2)	0.3199(2)	0.095
H(6)	4*a*	0.3967(5)	0.4448(2)	0.3258(2)	0.091
H(7)	4*a*	0.2800(4)	0.2637(2)	0.3115(2)	0.087
H(8)	4*a*	0.4396(4)	0.1080(2)	0.3298(2)	0.086
H(9)	4*a*	0.5918(4)	0.1412(2)	0.2745(2)	0.086
H(10)	4*a*	0.6704(4)	0.2547(2)	0.4655(2)	0.097

Table 2. Continued.

Atom	Site	x	y	z	U_{iso}
H(11)	4*a*	0.4831(4)	0.1880(2)	0.4506(2)	0.097
H(12)	4*a*	0.3430(5)	0.3509(2)	0.4272(2)	0.121
H(13)	4*a*	0.5329(5)	0.4171(2)	0.4387(2)	0.121
H(14)	4*a*	1.1278(4)	0.0556(2)	0.4115(2)	0.161
H(15)	4*a*	1.0614(4)	0.0639(2)	0.3341(2)	0.161
H(16)	4*a*	0.9157(4)	0.0347(2)	0.3926(2)	0.161
H(17)	4*a*	0.3980(4)	0.4780(2)	0.0721(2)	0.075
H(18)	4*a*	0.3938(4)	0.4789(2)	–0.0471(2)	0.077
H(19)	4*a*	0.4085(4)	0.1353(3)	–0.0475(2)	0.086
H(20)	4*a*	0.4102(4)	0.1350(3)	0.0709(2)	0.093

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}
O(1)	4*a*	0.9889(3)	0.1968(2)	0.3905(1)	0.069(1)	0.087(1)	0.117(2)	–0.006(1)	–0.022(1)	0.036(1)
O(2)	4*a*	0.3836(4)	0.3960(2)	–0.1644(1)	0.213(3)	0.098(2)	0.077(2)	–0.010(2)	–0.022(2)	0.009(2)
O(3)	4*a*	0.4110(4)	0.2128(2)	–0.1631(1)	0.151(2)	0.103(2)	0.093(2)	0.019(2)	–0.015(2)	–0.032(2)
N(1)	4*a*	0.6635(3)	0.1844(2)	0.3705(1)	0.066(2)	0.050(1)	0.047(2)	0.003(1)	0.002(1)	0.002(1)
N(2)	4*a*	0.3999(3)	0.3048(3)	–0.1335(2)	0.092(2)	0.081(2)	0.083(3)	0.005(2)	–0.014(2)	–0.006(2)
C(2)	4*a*	0.8396(4)	0.2348(2)	0.3471(2)	0.068(2)	0.058(2)	0.068(2)	–0.003(2)	0.001(2)	0.013(2)
C(3)	4*a*	0.8479(4)	0.3650(2)	0.3490(2)	0.102(3)	0.052(2)	0.084(3)	–0.016(2)	–0.023(2)	0.009(2)
C(4)	4*a*	0.6819(4)	0.4216(2)	0.3124(2)	0.114(3)	0.043(2)	0.080(2)	0.005(2)	0.002(3)	0.005(2)
C(5)	4*a*	0.4841(5)	0.3815(2)	0.3350(2)	0.093(3)	0.064(2)	0.072(2)	0.029(2)	0.010(2)	0.007(2)
C(6)	4*a*	0.4099(4)	0.2767(2)	0.2961(2)	0.065(2)	0.075(2)	0.077(2)	0.011(2)	0.005(2)	0.013(2)
C(7)	4*a*	0.5264(4)	0.1679(2)	0.3157(2)	0.076(2)	0.064(2)	0.074(2)	0.001(2)	0.000(2)	0.010(2)
C(8)	4*a*	0.5746(4)	0.2402(2)	0.4306(2)	0.108(2)	0.073(2)	0.062(2)	0.017(2)	0.017(2)	0.012(2)
C(9)	4*a*	0.4739(5)	0.3553(2)	0.4130(2)	0.155(3)	0.082(2)	0.064(2)	0.048(2)	0.027(2)	0.008(2)
C(10)	4*a*	1.0265(4)	0.0781(2)	0.3814(2)	0.093(3)	0.088(2)	0.221(5)	0.010(2)	0.012(3)	0.067(3)
C(11)	4*a*	0.4052(4)	0.2935(3)	0.2202(2)	0.062(2)	0.084(2)	0.083(3)	–0.001(2)	–0.008(2)	0.016(2)
C(12)	4*a*	0.4047(4)	0.3038(3)	0.1596(2)	0.069(2)	0.077(2)	0.080(3)	0.001(2)	–0.010(2)	0.014(2)
C(13)	4*a*	0.4047(4)	0.3064(3)	0.0851(2)	0.053(2)	0.061(2)	0.071(2)	–0.002(2)	–0.009(2)	0.002(2)
C(14)	4*a*	0.3998(4)	0.4089(2)	0.0481(2)	0.065(2)	0.048(2)	0.075(2)	–0.002(2)	–0.012(2)	–0.009(2)
C(15)	4*a*	0.3977(4)	0.4101(2)	–0.0228(2)	0.071(2)	0.049(2)	0.072(2)	–0.003(2)	–0.010(2)	–0.001(2)
C(16)	4*a*	0.4015(3)	0.3065(3)	–0.0576(2)	0.057(2)	0.060(2)	0.057(2)	0.003(2)	–0.009(2)	–0.002(2)
C(17)	4*a*	0.4062(4)	0.2041(3)	–0.0232(2)	0.083(2)	0.046(2)	0.086(3)	0.007(2)	–0.010(2)	–0.005(2)
C(18)	4*a*	0.4074(4)	0.2045(3)	0.0473(2)	0.092(2)	0.050(2)	0.089(2)	0.005(2)	–0.009(2)	0.016(2)

Acknowledgment. Computing facilities of RRZN (Hannover) were used.

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