

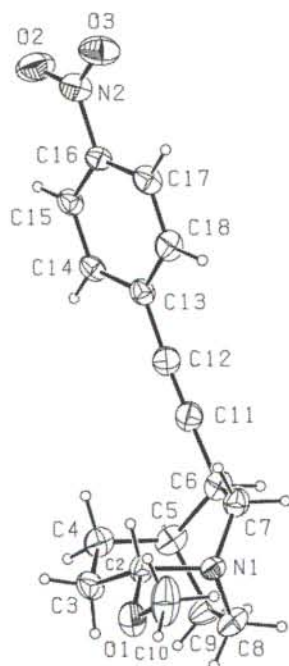
Crystal structure of (1*S*,2*R*,5*R*,6*R*)-2-methoxy-6-(16-nitrophenylethynyl)-1-azabicyclo[3.2.2]nonane, C₁₇H₂₀N₂O₃

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



Abstract

C₁₇H₂₀N₂O₃, orthorhombic, *P*2₁2₁2₁ (No. 19), *a* = 7.096(1) Å, *b* = 11.671(1) Å, *c* = 19.277(2) Å, *V* = 1596.5 Å³, *Z* = 4, *R*_g(*F*) = 0.032, *wR*_{ref}(*F*²) = 0.040, *T* = 300 K.

Source of material

p-NO₂-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 CH₂Cl₂. After addition of saturated aqueous NaHCO₃, the aqueous layer was extracted with CH₂Cl₂, and the combined organic layer dried (MgSO₄) 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, $\Delta\phi$ = 1.3°
$2\theta_{\max}$:	48.24°
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} :	10621, 2526
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 2 σ (<i>I</i> _{obs}), 1139
<i>N</i> (<i>param</i>) _{refined} :	199
Programs:	SHELXS-86 [9], SHELXL-93 [10], PLATON [11]

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Table 2. Atomic coordinates and displacement parameters (in Å²).

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

Table 2. Continued.

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

Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
O(1)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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)	4a	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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