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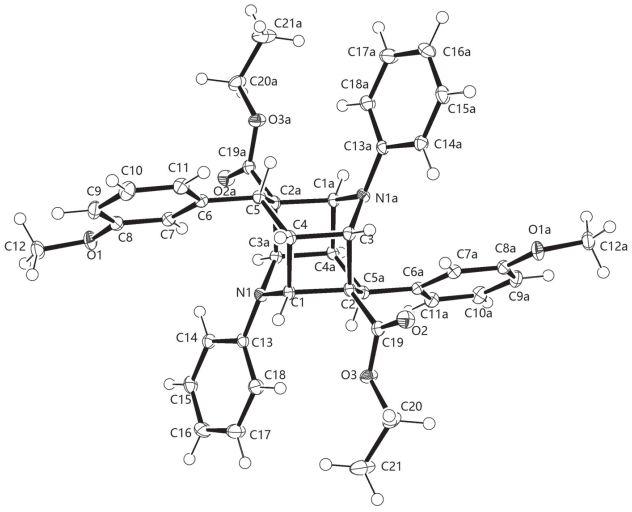
Crystal structure of diethyl 3,9-diphenyl-6,12-bis(3-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,11-dicarboxylate, $C_{42}H_{42}N_2O_6$



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Abstract

$C_{42}H_{42}N_2O_6$, monoclinic, $P2_1/c$ (no. 14), $a = 6.9848(14)$ Å, $b = 20.816(4)$ Å, $c = 11.543(2)$ Å, $\beta = 99.745(5)°$, $V = 1654.1(6)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0377$, $wR_{ref}(F^2) = 0.1019$, $T = 113(2)$ K.

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The centrosymmetric cage dimeric title structure is shown in the figure. Tables 1 and 2 contain details of the measurement method and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

The title compound was synthesized by ethyl 1-phenyl-1,4-dihydro-4-(3-methoxyphenyl)pyridine-3-carboxylate under irradiation of UV-light in methanol/THF solution. After approximately 48 h irradiation was stopped and the product was purified by TL chromatography using ethyl acetate-petroleum ether (1:30 v/v). After concentration in vacuum, colorless solids were collected, dried, and recrystallized from methanol. Colorless crystals were obtained 3 days later.

Table 1: Data collection and handling.

Crystal:	Colourless prism
Size:	0.20 × 0.18 × 0.12 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.9 cm^{-1}
Diffractometer, scan mode:	Rigaku XtaLAB P200, φ and ω
$2\theta_{max}$, completeness:	55°, >99.6%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	16568, 3779, 0.0352
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 3129
$N(param)_{refined}$:	228
Programs:	Rigaku [1], SHELX [2]

Experimental details

All H atoms were placed in idealized positions (C—H = 0.95-1.00 Å) and refined as riding atoms. The U_{iso} values were set to be $1.5U_{eq}$ of the carrier atom for nitrogen H atoms and $1.2U_{eq}$ for the remaining H atoms. The hydrogen atoms attached to carbon were placed on calculated positions with the help of the SHELX program (AFIX 23, 43 or 137 option) [2].

Discussion

The title compound is a derivative of 3,9-diazatetraasteranes and plays important roles in synthetic, therapeutic, and bioorganic chemistry, for example, it shows anti-HIV PR activity [3]. As competitive inhibitors [4], 3,9-diazatetraasteranes are among the most promising classes of novel inhibitors of HIV-1 PR. In general, they have unique caged structures as well as lipophilic properties [5]. Furthermore, cage dimeric HIV-1 PR inhibitors have been introduced as novel lead structures [6]. Only a small number of 3,9-diazatetraasteranes have been reported so far [7]. In order to search for new 3,9-diazatetraasteranes, the title compound was synthesized and its crystal structure was determined.

The molecular structure of the title compound is shown in the figure. It displays exact centrosymmetry. The substitution at the central cage is such that at the C2—C5a—C4a joint of the piperidine rings there is one bulky substituent

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
O1	−0.27129(13)	0.55565(5)	0.95362(8)	0.0195(2)
O2	0.44732(12)	0.39885(4)	0.42556(8)	0.0192(2)
O3	0.22737(12)	0.33065(4)	0.47684(8)	0.0185(2)
N1	−0.08299(13)	0.44852(5)	0.62036(8)	0.0123(2)
C1	0.11432(16)	0.44996(6)	0.59723(10)	0.0121(2)
H1	0.2030	0.4217	0.6522	0.015*
C2	0.13796(16)	0.43926(6)	0.46339(10)	0.0118(2)
C3	0.21163(16)	0.50990(6)	0.45941(10)	0.0120(2)
H3	0.3490	0.5121	0.4456	0.014*
C4	0.19616(16)	0.51902(6)	0.59185(10)	0.0124(2)
H4	0.3271	0.5234	0.6419	0.015*
C5	0.05948(16)	0.57366(6)	0.61423(10)	0.0121(2)
H5	0.1119	0.6143	0.5856	0.015*
C6	0.05427(17)	0.58228(6)	0.74456(10)	0.0131(2)
C7	−0.10626(17)	0.56572(6)	0.79516(10)	0.0142(2)
H7	−0.2196	0.5494	0.7470	0.017*
C8	−0.10255(17)	0.57283(6)	0.91574(11)	0.0155(2)
C9	0.06284(18)	0.59590(6)	0.98779(11)	0.0186(3)
H9	0.0668	0.6002	1.0701	0.022*
C10	0.22239(18)	0.61260(7)	0.93666(11)	0.0198(3)
H10	0.3358	0.6287	0.9850	0.024*
C11	0.22006(18)	0.60635(6)	0.81700(11)	0.0169(3)
H11	0.3306	0.6184	0.7841	0.020*
C12	−0.2689(2)	0.55604(7)	1.07762(11)	0.0217(3)
H12A	−0.1643	0.5281	1.1162	0.033*
H12B	−0.3938	0.5404	1.0942	0.033*
H12C	−0.2469	0.5999	1.1076	0.033*
C13	−0.15685(17)	0.39275(6)	0.66632(10)	0.0131(2)
C14	−0.33332(17)	0.39502(6)	0.70993(10)	0.0152(2)
H14	−0.4056	0.4339	0.7052	0.018*
C15	−0.40215(18)	0.34088(6)	0.75966(11)	0.0184(3)
H15	−0.5227	0.3430	0.7872	0.022*
C16	−0.2986(2)	0.28370(7)	0.77002(12)	0.0221(3)
H16	−0.3461	0.2471	0.8054	0.027*
C17	−0.1241(2)	0.28105(7)	0.72769(12)	0.0233(3)
H17	−0.0513	0.2423	0.7342	0.028*
C18	−0.05509(18)	0.33461(6)	0.67579(11)	0.0183(3)
H18	0.0635	0.3317	0.6462	0.022*
C19	0.28929(16)	0.38898(6)	0.45105(10)	0.0133(2)
C20	0.36169(19)	0.27741(6)	0.47523(12)	0.0217(3)
H20A	0.4945	0.2903	0.5121	0.026*
H20B	0.3645	0.2637	0.3934	0.026*
C21	0.2896(2)	0.22368(7)	0.54347(15)	0.0309(3)
H21A	0.2915	0.2374	0.6248	0.046*
H21B	0.3738	0.1861	0.5425	0.046*
H21C	0.1565	0.2125	0.5075	0.046*

at C2 and C5a, while at the C3—N1a—C1a joint there is only one non-H substituent. Apart from this group, the N1a atom bears no other substituent, not even a hydrogen atom. This generates much more crowding at C4 and C2 of the cyclobutane ring than at C3 and C1. Because of the Csp^2 nature of the substituent at C5a, the orientation of the phenyl ring around the C5a—C6a bond is characterized by the following torsion angles: C4a—C5a—C6a—C7: 108.93°, C2—C5a—C6a—C7: −13.91°. The C2—C5a—C4a prow is inclined at very similar angles to the bottoms of both piperidinyl moieities (134.7° and 135.7°). The corresponding C—C5a distances are 1.535(2) Å, and the C2—C5a—C4a angle is 107.14(9)°. At the same time, the piperidinyl C—C—C5a valence angles are all very similar (113.0(2)−113.7(1)°, average 113.3° and correspond very well to the substituent angles in planar cyclobutane rings (113.1(6)°) calculated by Allen [8]. All bond lengths and angles are within normal ranges [9].

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References

1. Rigaku: RAPID-AUTO. Rigaku Corporation, Tokyo, Japan (1998).
2. Sheldrick, G. M.: Crystal structure refinement with SHELX. Acta Crystallogr. **C71** (2015) 3–8.
3. Hilgeroth, A.; Tykarska, E.; Jaskolski, M.: Crystal structure of a novel synthetic inhibitor of HIV-1 protease. J. Mol. Struct. **605** (2002) 63–70.
4. Wollmann, J.; Baumert, C.; Erlenkamp, G.; Sippl, W.; Hilgeroth, A.: Novel insight into inhibitor binding of highly symmetric HIV-1 protease. ChemBioChem **9** (2008) 874–878.
5. Hilgeroth, A.; Fleischer, R.; Wiese, M.; Heinemann, F. W.: Comparison of azacyclic urea A-98881 as HIV-1 protease inhibitor with cage dimeric *N*-benzyl 4-(4-methoxyphenyl)-1,4-dihydropyridine as representative of a novel class of HIV-1 protease inhibitors: A molecular modeling study. J. Comput. Aid. Mol. Des. **13** (1999) 233–242.
6. Wlodawer, A.; Vondrasek, J.: Crystal structure of a novel synthetic inhibitor of HIV-1 protease. Ann. Rev. Biophys. Biomol. struct. **27** (1998) 249–284.
7. Hilgeroth, A.; Billich, A.: Cage dimeric 4-aryl-1,4-dihydropyridines as promising lead structures for the development of a novel class of HIV-1 protease inhibitors. Cheminform. **332** (1999) 3–5.
8. Allen, F. H.: The geometry of small rings. VI. Geometry and bonding in cyclobutane and cyclobutene. Acta Crystallogr. **40** (1984) 64–72.
9. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R.: Tables of bond lengths determined by X-ray and neutron diffraction. Part 1. Bond lengths in organic compounds. Perkin Trans. 2. **2** (1987) S1–S19.