New Synthesis and Structure Determination of 13-Aza-4,4,8,8,12,12-hexamethyl-2,6,10-trioxatricyclo[7,3,1,0^{5,13}]tridecane

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Dedicated to Prof. H. P. Fritz on the occasion of his 65th birthday

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Asinger Condensation, C₃-Symmetric Heterocycle, 5,6-Dihydro-2H-1,3-oxazine,
Crystal Structure

A new 13-Aza-4,4,8,8,12,12-hexamethyl-2,6,10-trioxatricyclo[7,3,1,0^{5,13}]tridecane synthesis and the crystal structure are reported. It crystallizes in the monoclinic space group P2₁/n with *a* = 1201.9(1) pm, *b* = 1436.6(1) pm, *c* = 1726.2(2) pm, β = 90.74(1)° and *Z* = 8.

Introduction

The highly symmetric 13-aza-4,4,8,8,12,12-hexamethyl-2,6,10-trioxatricyclo[7,3,1,0^{5,13}]tridecane is of general interest regarding several aspects. First, the molecule belongs to the rare point group C₃. Second it is being discussed as a possible complexing agent [1]. Furthermore the title compound is quite inert against some drastic reaction conditions, *e.g.* it does not react with lithium aluminium hydride in refluxing ether during four hours [2].

Starting in the 1950's, the first synthesis of 13-aza-4,4,8,8,12,12-hexamethyl-2,6,10-trioxatricyclo[7,3,1,0^{5,13}]tridecane included 3-hydroxy-2,2-dimethyl-propionaldehyde as one of the starting materials [3, 2]. Hasek and Martin isolated **III** by destructive distillation of the self-condensation product **IV** after removal of formaldehyde, isobutyraldehyde and other volatile products [4] (see

Scheme 1. Formation of **III** by the distillation of **IV**.

Scheme 1). Analogous compounds were synthesized by H. P. Fritz *et al.* [5] by reaction of acrolein or crotonaldehyde with solutions of ammonium sulfate in aqueous sulfuric acid.

Discussion

In this paper we describe a new approach for the C₃-symmetrical target molecule and for the first time present its X-ray structural analysis. Type **I** 5,6-dihydro-2H-1,3 oxazines are easily accessible *via* Asinger condensation [6]. Hereby, 3-hydroxy-2,2-dimethylpropionaldehyde reacts with a second oxo component and ammonia under dehydration to form **I** [7]. Starting from oxazines **I**, our goal was to synthesize 4-oxazine acetic acids **II** by addition of malonic acid and subsequent decarboxylation [8]. When we used oxazines with a methyl- or an ethyl-group at the 2-position, however, we found that tridecane **III** is formed (see Scheme 2).

The obvious explanation for this is an opening of the oxazine ring, which is much faster than the addition of malonic acid to the azomethine double bond, thus the formation of **III** can be rationalized as a retro Asinger reaction **2** followed by an Asinger reaction with 3-hydroxy-2,2-dimethylpropionaldehyde **IV** and a condensation with a second equivalent of 3-hydroxy-2,2-dimethylpropionaldehyde (see Scheme 3).

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Scheme 2. The reaction of 5,6-dihydro-2,5,5-trimethyl-2H-1,3-oxazine and 2-ethyl-5,6-dihydro-5,5-dimethyl-2H-1,3-oxazine with malonic acetic acid.

The structure of **III** was confirmed by mass-, infrared- and NMR-spectroscopy and also verified by elemental analysis and X-ray structure determination (Fig. 1).

Scheme 3. Proposed mechanism of the formation of **III**.

Fig. 1. The structure of **III**. Selected bond lengths [pm]: N–C 145(1)–149(1); O–C 140(1)–143(1); C–C 149(1)–157(1).

The NMR-spectra are rather simple because of the molecule's C₃-symmetry. However, the molecules in the crystal reveal no crystallographic symmetry, due to the influence of the crystal environment [9]. The compound crystallizes with two crystallographically independent molecules A and B in the asymmetric unit with no significant deviations in their geometries.

Experimental

3-Hydroxy-2,2-dimethylpropionaldehyde (Aldrich, techn., 70%) was used without further purification. 5,6-Dihydro-2,5,5-trimethyl-2H-1,3-oxazine and 2-ethyl-5,6-dihydro-5,5-dimethyl-2H-1,3-oxazine were prepared according to [7].

NMR spectra were recorded on a Bruker AM 360 (360.134 MHz) spectrometer, TMS as internal standard. Mass spectra were obtained by electron impact (EI) and chemical ionisation (CI, isobutane ionisation) on a Varian MAT CH 5 (70 eV). IR spectra were recorded on a Perkin-Elmer 157 G. The elemental analysis was performed in the micro-analytical laboratory of this Institute.

13-Aza-4,4,8,8,12,12-hexamethyl-2,6,10-trioxatricyclo[7,3,1,0^{5,13}]tridecane

To a solution of malonic acid (20.8 g, 0.20 mol) in ethanol (120 ml) the corresponding oxazine (0.13 mol) is added and refluxed for three hours. While refluxing, the formed product precipitates. The precipitates are collected, washed with ether and dried *in vacuo*.

Yield: 19.3 g (55%) colourless needles, m.p.: 186 °C.

Analysis for C₁₅H₂₇NO₃ (269.36 g/mol)

Calcd C 66.91 H 10.04 N 5.20%,

Found C 66.79 H 9.98 N 5.22%.

¹H-NMR (CDCl₃): 0.8 (s, 3H, –CH₃); 1.15 (s, 3H, –CH₃); 3.18 (d, 1H, ²*J* = 11.3 Hz, –CH₂); 3.2 (s, 1H, –CH); 3.5 (d, 1H, ²*J* = 11.3 Hz, –CH₂). – ¹³C-NMR (CDCl₃): 18.6 (–CH₃); 21.34 (–CH₃); 36.6 (–C); 76.45 (–CH₂); 95.93 (–CH). – MS (70 eV), *m/z* (%) 270 (M⁺ + 1, 100); 269 (M⁺, 1); 213 (7); 158 (4); 128 (2); 85 (1.5). – IR (KBr) (cm^{−1}): 2800 (m, –N); 1400 (s, –CH₃); 1160 (s, –O–).

Crystal structure determination of III

The compound crystallizes as colourless needles. A single crystal with the approximate dimensions 0.06 × 0.12 × 0.5 mm was chosen for the X-ray investigations, which were performed on a CAD 4 (ENRAF-NONIUS) with MoK α radiation (graphite monochromator) at low temperature of 211 K. The lattice parameters were determined with 100 precisely centered high-angle reflections. For the structure determination 5384 intensities were measured with an ω/θ -scan from $\theta = 3$ –27°. Intensity data were corrected for Lorentz and polarization effects [9]. The structure was solved by direct methods [10]. Hydrogen atoms were calculated in idealized positions [11]. In order to keep the re-

Table I. Crystal data and structure refinement for **III**.

Empirical formula	C ₁₅ H ₂₇ NO ₃
Formula weight	269.38
Temperature	211(2) K
Wavelength	71.073 pm
Crystal system	monoclinic
Space group	P2 ₁ /n
Unit cell dimensions	<i>a</i> = 1201.9(1) pm <i>b</i> = 1436.6(1) pm <i>c</i> = 1726.2(2) pm β = 90.74(1)°
Volume	2.980(1) nm ³
<i>Z</i>	8
Density (calculated)	1.201 Mg/m ³
Absorption coefficient	0.082 mm ^{−1}
<i>F</i> (000)	1184
Crystal size	0.06 × 0.12 × 0.5 mm
θ range for data collected	3.07–24.96°
Index ranges	−14 ≤ <i>h</i> ≤ 14, 0 ≤ <i>k</i> ≤ 17, 0 ≤ <i>l</i> ≤ 20
Reflections collected	5384
Reflections unique	5209
Reflections observed	1369 [<i>F</i> > 4 σ (<i>F</i>)]
Refinement method	Full-matrix least-squares on <i>F</i> ²
No. of parameters	165
Goodness-of-fit on <i>F</i> ²	1.451
Final <i>R</i> indices [<i>F</i> > 4 σ (<i>F</i>)]	<i>R</i> 1 = 0.0831, <i>wR</i> 2 = 0.2209
Largest diff. peak and hole	365 and −312 e [−] · nm ^{−3}

Table II. Atomic coordinates (×10⁴) and isotropic displacement parameters *U*_{iso} [pm² × 10^{−1}].

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>U</i> _{iso}
Molecule A				
N(1)	1044(7)	5659(5)	7971(4)	24(2)
O(1)	1014(5)	5717(4)	9331(3)	28(2)
O(1)	1066(5)	4208(5)	7319(3)	33(2)
O(2)	1022(5)	7069(4)	7249(3)	31(2)
C(1)	1391(8)	4774(6)	9388(5)	31(2)
C(2)	986(8)	4207(6)	8701(5)	20(2)
C(3)	1429(8)	4696(6)	7990(5)	27(2)
C(4)	1450(8)	4636(6)	6633(5)	29(2)
C(5)	1015(9)	5650(6)	6529(5)	33(3)
C(6)	1446(8)	6157(6)	7269(5)	29(2)
C(7)	1378(8)	7593(6)	7898(4)	25(2)
C(8)	977(8)	7151(7)	8648(5)	26(2)
C(9)	1420(8)	6148(6)	8661(5)	25(2)
C(21)	1494(8)	3232(6)	8760(5)	33(2)
C(22)	– 263(8)	4127(7)	8689(5)	34(2)
C(51)	1587(9)	6064(7)	5829(6)	48(3)
C(52)	– 223(8)	5648(7)	6462(5)	38(3)
C(81)	1542(9)	7718(7)	9327(5)	42(3)
C(82)	– 263(9)	7181(7)	8712(6)	44(3)
Molecule B				
N(2)	1028(7)	9381(5)	2930(4)	23(2)
O(201)	1068(5)	9354(4)	4315(3)	28(2)
O(202)	1019(5)	7977(4)	2232(3)	29(2)
O(203)	980(5)	10809(4)	2274(3)	26(2)
C(201)	1456(8)	8415(5)	4312(5)	25(2)
C(202)	1051(8)	7880(7)	3617(5)	29(3)
C(203)	1441(8)	8413(6)	2900(5)	25(2)
C(204)	1430(9)	8427(6)	1552(5)	37(3)
C(205)	1048(8)	9436(6)	1512(5)	25(2)
C(206)	1410(8)	9899(6)	2257(4)	23(2)
C(207)	1392(9)	11297(7)	2943(5)	35(3)
C(208)	1028(9)	10856(7)	3687(5)	30(3)
C(209)	1439(8)	9840(6)	3651(5)	25(2)
C(221)	1544(8)	6895(7)	3610(5)	41(3)
C(222)	– 244(8)	7821(7)	3609(5)	35(2)
C(251)	1576(8)	9918(6)	814(5)	37(3)
C(252)	– 235(9)	9450(7)	1427(6)	45(3)
C(281)	1530(8)	11337(6)	4382(5)	32(2)
C(282)	– 264(8)	10845(7)	3729(5)	30(2)

flections/parameters ratio in an acceptable range, isotropic instead of anisotropic displacement parameters were used in the final full-matrix refinement which led to *R*-values *R*1 = 0.0831 and *wR*2 = 0.2209 [11].

Crystallographic details are given in Table I, positional and isotropic displacement parameters in Table II, the range of bond distances and angles in Fig. 1*.

* Further details may be obtained from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, by quoting the Registry-No. CSD 58078, the names of the authors and the journal citation.

Conclusions

In the present study, a new synthesis of 13-aza-4,4,8,8,12,12-hexamethyl-2,6,10-trioxatricyclo[7,3,1,0^{5,13}]tridecane starting from the Asinger heterocycle 5,6-dihydro-2,5,5-trimethyl-2*H*-1,3-oxazine and 2-ethyl-5,6-dihydro-5,5-dimethyl-2*H*-1,3-oxazine is described. The target compound can be obtained in a yield comparable to the literature procedure. Mechanistically, this reaction rep-

resents an acid induced retro Asinger followed by an Asinger reaction and a second condensation to the title compound.

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