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SILA-PHARMACA. II[1] STRUCTURE OF METHYL-IODIDE SALTS OF DIMETHYLPHENYLPIPERIDINOMETHYLSILANE AND N-(β-PHENYLETHYL)PIPERIDINE

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Abstract

X-ray structures of the methyliodide salts of (N–(β–phenylethyl)piperidine (N–(β–phenylethyl)–N–methyl–piperidiniumiodide) and dimethylphenyl–piperidinomethyl-silane (N–methyl–N–(phenyldimethylsilyl)–methyl– piperidinium iodide) are reported.

Keywords: structure of methyl–iodide salts of dimethylphenylpiperidinomethylsilane and N–(β–phenylethyl)piperidine; sila-pharmaca.

Introduction

Molecules containing the phenylethylamine skeleton (Ph–C–C–N=) possess a wide range of pharmacological properties. Phenylethylamine itself has psychostimulant effect, which can be tuned and modified by a variety of substituents [1, 2]. We have synthesized N–(β–phenylethyl)piperidine (I) and its sila-analogue (II). PÓRSZÁSZ et al. showed that I has enhanced curare-like effect [3]. The sila-analogue is different by one $-CH_2-$ group from the compound (III) which was found to have as effective tumor-inhibiting properties as 5–fluorouracil though it is toxic [4]. The methyliodide salts were prepared for X-ray structure determination.

Experimental

Synthesis

Several routes are known for the synthesis of N–(β–phenylethyl)piperidine (I) [5–9]. The method of NAMYOTKIN et al. [9] has been chosen, starting

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[1] Part I.: [1]

from piperidine and butyllithium and finally reacting it with styrene. The quaternary ammonium salt was yielded by methyliodide.

Dimethylphenylpiperidinomethylsilane (II) was obtained from phenyldimethylchloromethylsilane with piperidine and the salt was formed with methyliodide [1].

Crystal Structure Analysis

Crystal data and data collection parameters are summarized in *Table 1.*

Table 1

Crystal data, data collection parameters and least-squares parameters

	I	II
Empirical formula	$C_{14}H_{22}NI$	$C_{15}H_{26}NISi$
Formula weight (a. m. u.)	331.24	375.37
F(000)	664	760
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	Cc
a (Å)	7.087(1)	7.621(1)
b (Å)	11.960(1)	19.758(1)
c (Å)	17.163(1)	12.206(1)
β (°)		105.64(2)
V (Å)	1454.70(4)	1769.9(6)
Z	4	4
ρ_X (g cm^{-3})	1.51	1.41
μ[Cu–K$_\alpha$–] (cm^{-1})	172.8	149.1
Scan type	$\omega - 2\Theta$	
Scan rate (deg/min^{-1} in ω)	$1 - 20$	
Scan width (°)	$0.3 + 0.14\tan(\Theta)$	$0.5 + 0.14\tan(\Theta)$
Scan range (°)	$3 - 150.0$	
No. of reflexions measured:	1760	3849
No. of unique reflexions	1620	1919
Reflexion averaging agreement on I (%)	0.02	0.03
Reflexions used in refinement (NO)	1541($I > 3\sigma$)	1720($I > 3\sigma$)
Least-squares weights	$4Fo^2/\sigma(Fo^2)^2$	
No of parameters (NV)	145	163
R	0.038	0.053
$R(w)$	0.050	0.075
R(tot)	0.041	0.067
S^*	1.90	3.19
Largest shift/esd	0.040	0.421

* $\left[\sum w|F_o| - |F_c|)^2/(NO - NV)\right]^{1/2}$

X-ray measurements were performed on a computer-controlled four-circle Enraf–Nonius CAD4 diffractometer with monochromated Cu–K_α–radiation ($\lambda = 1.5418$ Å), at room temperature. Approximate crystal sizes were 0.25 × 0.25 × 0.30 mm (I) and 0.15 × 0.20 × 0.30 mm (II). Unit cell parameters were determined by least-squares from the setting angles of 25 ($30 < \Theta < 33°$) carefully centered reflexions. Three intensity check reflexions were measured every hour and these indicated a 5.9% total loss of intensity for II. A linear decay correction was therefore applied for the intensity data of II (the correction factors on intensity ranged from 0.983 to 1.086 with an average value of 1.030).

The structures were solved by the heavy atom method and weighted Fourier syntheses and were refined by full matrix anisotropic least-squares. At the end of isotropic refinements an empirical spherical absorption correction [10] was applied for both crystals. The minimum, maximum, and average relative transmission coefficients were as follows: 0.866, 1.552, 1.049 for I, and 0.427, 1.599, 1.009 for II. Hydrogen atomic positions were calculated from assumed geometries and they were added as fixed contributions ($B_H = B_{eq,C}$+1 Å^2) to structure factor calculations. Final atomic parameters are given in *Tables 2* and *3*[2]. Atomic scattering factors were taken from [11].

The molecular diagrams are depicted in *Figs. 1* and *2*, the relevant data of the molecular geometries are shown in *Tables 4* and *5*.

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[2] Lists of observed and calculated structure factors and anisotropic thermal parameters can be obtained from the authors.

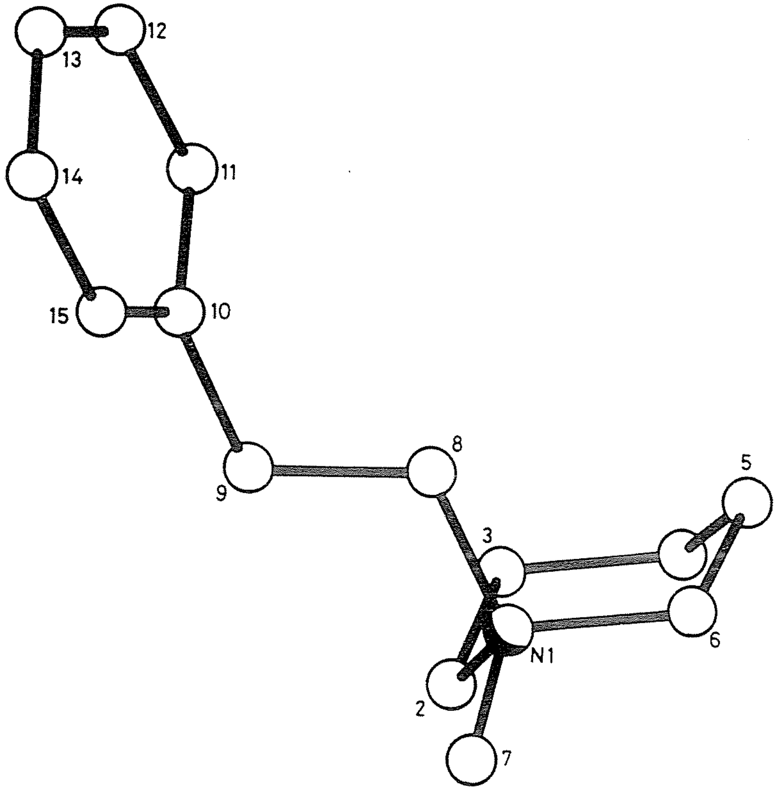


Fig. 1. The molecular diagram of compound I

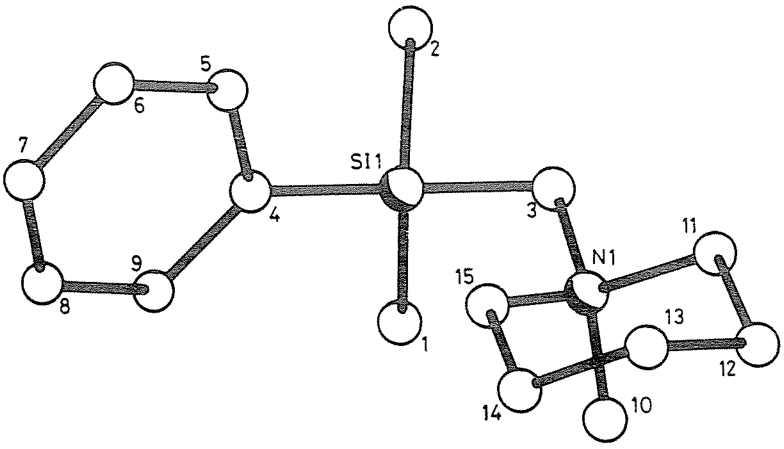


Fig. 2. The molecular diagram of compound II

Table 2
Final atomic coordinates and B(eq) (B for the hydrogen atoms) (Å^2) values for compound I

Atom	x/a	y/b	z/c	$B_{(eq)}/B$
I	0.41785(6)	0.38978(3)	0.84830(2)	2.55(1)
N1	0.0664(7)	0.6587(3)	0.6391(2)	1.4(1)
C2	−0.1209(8)	0.5994(4)	0.6323(3)	1.9(2)
C3	−0.158(1)	0.5221(5)	0.6998(4)	2.8(2)
C4	−0.157(1)	0.5841(6)	0.7759(4)	3.4(2)
C5	0.027(1)	0.6481(5)	0.7852(3)	2.8(2)
C6	0.0681(9)	0.7222(4)	0.7163(3)	1.8(1)
C7	0.080(1)	0.7443(5)	0.5754(3)	3.0(2)
C8	0.2331(8)	0.5810(4)	0.6346(3)	1.7(1)
C9	0.225(1)	0.4991(5)	0.5662(3)	2.9(2)
C10	0.404(1)	0.4307(4)	0.5617(2)	1.7(1)
C11	0.434(1)	0.3423(5)	0.6122(3)	2.4(2)
C12	0.591(1)	0.2747(4)	0.6049(3)	2.8(2)
C13	0.724(1)	0.2984(5)	0.5482(3)	3.0(2)
C14	0.698(1)	0.3891(5)	0.4982(3)	2.8(2)
C15	0.539(1)	0.4532(5)	0.5054(3)	2.6(2)
H2a	−0.218	0.654	0.630	2.9
H2b	−0.122	0.557	0.586	2.9
H3a	−0.278	0.488	0.693	3.8
H3b	−0.063	0.466	0.701	3.8
H4a	−0.260	0.635	0.777	4.4
H4b	−0.170	0.532	0.818	4.4
H5a	0.019	0.693	0.831	3.8
H5b	0.127	0.596	0.791	3.8
H6a	0.189	0.755	0.723	2.8
H6b	−0.025	0.779	0.714	2.8
H7a	0.198	0.782	0.579	4.0
H7b	0.072	0.708	0.526	4.0
H7c	−0.020	0.797	0.581	4.0
H8a	0.344	0.625	0.630	2.7
H8b	0.239	0.539	0.682	2.7
H9a	0.121	0.450	0.573	3.9
H9b	0.211	0.540	0.519	3.9
H11	0.345	0.328	0.652	2.7
H12	0.608	0.212	0.639	2.7
H13	0.833	0.253	0.543	2.7
H14	0.789	0.406	0.460	2.7
H15	0.521	0.515	0.471	2.7

The equivalent isotropic temperature factor is defined as $B_{(eq)} = 4/3$ *trace* ($\underline{\mathbf{B}}\ \underline{\mathbf{G}}$) where $\underline{\mathbf{B}}$ is the thermal motion tensor and $\underline{\mathbf{G}}$ is the direct metric tensor.

Table 3
Final atomic coordinates and B(eq) (B for the hydrogen atoms) (Å^2) for compound II

Atom	x/a	y/b	z/c	$B_{(eq)}/B$
I	0	0.17225(3)	0	4.51(1)
Si	0.4174(3)	0.0703(1)	0.3644(2)	3.32(5)
N	0.571(1)	0.18010(3)	0.2488(7)	3.7(2)
C1	0.415(1)	-0.0029(5)	0.269(1)	5.5(3)
C2	0.199(1)	0.0730(6)	0.409(1)	5.3(3)
C3	0.417(1)	0.1553(4)	0.2929(8)	3.8(2)
C4	0.610(1)	0.0636(3)	0.4958(7)	2.7(1)
C5	0.623(1)	0.1110(4)	0.5850(7)	3.6(2)
C6	0.757(1)	0.1062(5)	0.6857(8)	4.1(2)
C7	0.885(1)	0.0566(5)	0.7009(9)	5.2(2)
C8	0.882(1)	0.0101(5)	0.616(1)	5.3(3)
C9	0.745(1)	0.0130(4)	0.5150(9)	4.0(2)
C10	0.595(1)	0.1342(6)	0.158(1)	5.1(3)
C11	0.515(1)	0.2497(5)	0.1977(9)	4.9(2)
C12	0.664(2)	0.2837(6)	0.159(1)	5.6(3)
C13	0.837(2)	0.2931(8)	0.265(1)	6.2(4)
C14	0.893(1)	0.2219(7)	0.312(1)	5.7(4)
C15	0.744(1)	0.1886(5)	0.3426(8)	4.2(2)
H1a	0.316	0.001	0.203	6.6
H1b	0.526	-0.004	0.248	6.6
H1c	0.401	-0.044	0.308	6.6
H2a	0.098	0.077	0.344	6.3
H2b	0.188	0.033	0.450	6.3
H2c	0.201	0.111	0.457	6.3
H3a	0.312	0.155	0.230	4.7
H3b	0.403	0.188	0.347	4.7
H5	0.537	0.147	0.575	3.7
H6	0.760	0.138	0.745	3.7
H7	0.977	0.054	0.771	3.7
H8	0.973	-0.024	0.628	3.7
H9	0.741	-0.020	0.457	3.7
H10a	0.692	0.150	0.130	6.1
H10b	0.622	0.090	0.188	6.1
H10c	0.486	0.133	0.097	6.1
H11a	0.412	0.245	0.134	5.8
H11b	0.486	0.277	0.254	5.8
H12a	0.625	0.327	0.127	6.6
H12b	0.698	0.257	0.103	6.6
H13a	0.808	0.321	0.321	7.3
H13b	0.936	0.314	0.242	7.3
H14a	0.993	0.225	0.377	6.6
H14b	0.925	0.196	0.255	6.6
H15a	0.715	0.214	0.402	5.2
H15b	0.784	0.145	0.371	5.2

Table 4
Bond distances (Å), bond angles (°) and relevant torsion angles for I

Bond lengths (Å)

N1–C2	1.510(8)	C3–C4	1.50(1)	C10–C11	1.384(8)
N1–C6	1.527(7)	C4–C5	1.52(1)	C10–C15	1.39(1)
N1–C7	1.501(8)	C5–C6	1.506(9)	C11–C12	1.38(1)
N1–C8	1.504(8)	C8–C9	1.531(8)	C12–C13	1.38(1)
C2–C3	1.505(9)	C9–C10	1.51(1)	C13–C14	1.394(9)
				C14–C15	1.37(1)

Bond angles (deg.)

C2–N1–C6	107.9(7)	N1 –C6 –C5	112.7(9)
C2–N1–C7	108.8(8)	N1 –C8 –C9	114.0(9)
C2–N1–C8	113.3(7)	C8 –C9 –C10	111(1)
C6–N1–C7	107.0(8)	C9 –C10 –C11	121(1)
C6–N1–C8	110.3(7)	C9 –C10 –C15	121(1)
C7–N1–C8	109.4(8)	C11 –C10 –C15	119(1)
N1–C2–C3	112.5(9)	C10 –C11 –C12	121(1)
C2–C3–C4	111(1)	C11 –C12 –C13	120(1)
C3–C4–C5	110(1)	C12 –C13 –C14	120(1)
C4–C5–C6	112(1)	C13 –C14 –C15	119(1)
		C10 –C15 –C14	122(1)

Torsion angles (deg.) with e. s. d.'s

C4–C3–C2–N1	59(1)	C8 –N1 –C2–C3	65.3(9)
C4–C5–C6–N1	-55(1)	C8 –N1 –C6–C5	-69.3(8)
C5–C4–C3–C2	-55(1)	C9 –C8 –N1–C2	48.8(9)
C5–C6–N1–C2	54.9(9)	C9 –C8 –N1–C6	170(1)
C6–N1–C2–C3	-57.0(8)	C9 –C8 –N1–C7	-73(1)
C6–C5–C4–C3	53(1)	C10 –C9 –C8–N1	175(1)
C7–N1–C2–C3	-173(1)	C11 –C10 –C9–C8	77(1)
C7–N1–C6–C5	172(1)	C15 –C10 –C9–C8	-105(1)

Table 5

Bond distances (Å), bond angles (°) and relevant torsion angles for II

Bond lengths

SI–C1	1.85(1)	N –C11	1.52(1)	C7 –C8	1.38(2)
SI–C2	1.89(1)	N –C15	1.51(1)	C8 –C9	1.39(2)
SI–C3	1.89(1)	C4–C5	1.42(1)	C11–C12	1.50(2)
SI–C4	1.865(8)	C4–C9	1.41(1)	C12–C13	1.59(2)
N–C3	1.50(1)	C5–C6	1.38(1)	C13–C14	1.53(2)
N–C10	1.48(2)	C6–C7	1.36(1)	C14–C15	1.45(2)

Bond angles

C1 –SI –C2	110.2(9)	SI –C4 –C5	119(1)
C1 –SI –C3	113.8(8)	SI –C4 –C9	124(1)
C1 –SI –C4	110.9(7)	C5 –C4 –C9	117(1)
C2 –SI –C3	102.6(8)	C4 –C5 –C6	121(1)
C2 –SI –C4	107.6(8)	C5 –C6 –C7	121(2)
C3 –SI –C4	111.2(6)	C6 –C7 –C8	121(2)
C3 –N –C10	110(1)	C7 –C8 –C9	120(2)
C3 –N –C11	107(1)	C4 –C9 –C8	121(2)
C3 –N –C15	112(1)	N –C11–C12	113(2)
C10–N –C11	109(1)	C11–C12–C13	109(2)
C10–N –C15	112(1)	C12–C13–C14	106(2)
C11–N –C15	107(1)	C13–C14–C15	111(2)
SI –C3–N	124(1)	N –C15–C14	116(2)

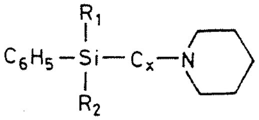
Torsion angles

C1 –SI –C3–N	-65(1)	C12–C11–N –C3	175(2)
C2 –SI –C3–N	176(1)	C12–C11–N –C10	-67(2)
C4 –SI –C3–N	61(1)	C13–C12–C11–N	-61(2)
C5 –C4–SI–C1	-173(1)	C13–C14–C15–N	59(2)
C5 –C4–SI–C2	-53(1)	C14–C13–C12–C11	60(2)
C5 –C4–SI–C3	59(1)	C14–C15–N –C3	-171(2)
C9 –C4–SI–C1	5(1)	C14–C15–N –C10	65(2)
C9 –C4–SI–C2	126(2)	C14–C15–N –C11	-54(2)
C9 –C4–SI–C3	-122(1)	C15–N –C3 –SI	-63(1)
C10–N –C3–SI	62(1)	C15–N –C11–C12	55(2)
C11–N –C3–SI	180(1)	C15–C14–C13–C12	-58(2)

Discussion

Organosilicon compounds with known structures related to II are listed in *Table 6*. Of the organic derivatives, 3–phenethyl–3–azabicyclo(3.2.1)octan–8–α–ol (VII), the structure of which has been recently determined [15], is worth mentioning. This compound is a derivative of I containing a condensed and OH–substituted piperidine ring.

Table 6
Related organosilicon compounds



Compound	R_1	R_2	$-C_x-$	Ref.
III	CH_3	CH_3	$-CH_2CH_2-$	[4]
IV	C_6H_5	OH	$-CH_2OCH_2CH_2-$	[12]
V	C_6H_5	OH	$-CH_2CH_2CH_2-$	[13]
IV	C_6H_5	OH	$-CH_2CH_2-$	[14]
II*	CH_3	CH_3	$-CH_2-$	this work

* CH_3I salt

Due to the presence of the iodine atoms in both structures, the e.s.d's of bonds lengths and angles are rather high. In view of the high uncertainties of the molecular geometry, no significant deviations can be detected when the two structures are compared. The piperidine ring, which might be the biologically important part of the structures, is of chair conformation in both structures ($^1C_4$ [I] and $^4C_1$ [II]).

The overall shape and conformation of the molecules are completely different (c.f. *Figs. 1* and *2*), the solid state conformation, therefore cannot be directly related to the biological activity. Starting from the final atomic coordinates, a molecular mechanic energy minimization was carried out using the MM2 program [16]. The refinement, apart from idealizing hydrogen atomic positions, slightly changed bond distances, angles, and torsion angles, but left the overall conformation intact.

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