Sila-Pharmaca. Part 32.[1] Crystal and Molecular Structures of the (*R*)-Enantiomer and the Racemate of the Antimuscarinic Agent (Cyclohexyl)-phenyl[2-(pyrrolidin-1-yl)ethyl]silanol (Sila-Procyclidine)†

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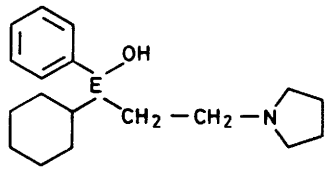
The crystal structures of the (*R*)-enantiomer (**2b**) and the racemate (**1b**) of (cyclohexyl)phenyl[2-(pyrrolidin-1-yl)ethyl]silanol (sila-procyclidine) have been determined by *X*-ray structural analysis. The absolute configuration of (**2b**) was established. (**2b**) crystallizes in the orthorhombic space group $P2_12_12_1$, with $a = 15.221(1)$, $b = 17.967(1)$, $c = 6.463(1)$ Å, and $Z = 4$. (**1b**) crystallizes in the monoclinic space group $P2_1/c$, with $a = 6.441(1)$, $b = 17.182(7)$, $c = 16.707(4)$ Å, $\beta = 103.86(2)°$, and $Z = 4$. The structures were refined to respective *R* factors of 0.044 and 0.058. The molecular conformation of sila-procyclidine is identical in the two different structures. Intermolecular O–H ··· N hydrogen bonding is observed in both crystal lattices. In (**1b**) (*R*)- and (*S*)-configurated molecules form centrosymmetric dimers, in (**2b**) the (*R*)-configurated molecules are linked into infinite chains parallel to the *c* axis. The (*R*)-configurated sila-procyclidine (**2b**) has higher affinity for ileal and atrial muscarinic receptors of the guinea pig than the (*S*)-configurated enantiomer (**3b**).

In the course of our systematic investigations on sila-substituted drugs (sila-pharmaca) we have recently synthesized racemic sila-procyclidine (**1b**),[2] a silicon analogue of the racemic antimuscarinic agent procyclidine [1-cyclohexyl-1-phenyl-3-(pyrrolidin-1-yl)propan-1-ol] (**1a**), which is applied therapeutically as an antiparkinsonian drug. Starting from (**1b**), the enantiomers (**2b**) and (**3b**) could be obtained with the help of a classical resolution method *via* crystalline salts using L(+)- and D(−)-tartaric acid, respectively, as resolving agents.[3] To our knowledge, this is the first example for a chiral silanol, from which both enantiomers could be obtained with high purity in the form of crystals.

Comparative pharmacological studies[2] on the isolated guinea pig ileum demonstrated that the racemates (**1a**) and (**1b**) possess approximately the same antimuscarinic potency: sila-procyclidine (**1b**) exhibits about two-fold greater affinity for ileal muscarinic receptors than procyclidine (**1a**). Whereas (−)-procyclidine (**2a**) and (−)sila-procyclidine (**2b**) (the direction of rotation was determined for solutions in $CHCl_3$) also have approximately the same antimuscarinic potency, the pharmacological properties of the dextrorotatory enantiomers are dramatically different from one another: (+)-sila-procyclidine (**3b**) is about 100 times more potent than the carbon analogue (**3a**).[4] In contrast to the high stereoselectivity index of 375[5] for the procyclidine enantiomers (**2a**) and (**3a**), a value of only < 10 was found for the analogous silanols (**2b**) and (**3b**).[4] This remarkably pronounced biological sila-substitution effect suggested the need for further investigations, during the course of which it became necessary to determine the absolute configurations of (**2b**) and (**3b**) and to compare these with the known[6] absolute configurations of the carbon analogues (**2a**) and (**3a**). In this paper we report the *X*-ray structural analysis of the laevorotatory silanol (**2b**) and the racemate (**1b**). In addition to the absolute configuration of (**2b**) we were particularly interested in establishing whether the necessary differences in molecular packing and possibly intermolecular hydrogen bonding in the crystal lattices of (**1b**) and (**2b**) lead to the adoption of differing conformations by the sila-procyclidine molecule.



(a) E = C, (b) E = Si
(1) racemate
(2) (-)- enantiomer
(3) (+)- enantiomer

Experimental

Preparation of Crystals of (**1b**).—Racemic sila-procyclidine (**1b**) was prepared using a reported method.[2] Crystals suitable for *X*-ray analysis were obtained by slow cooling of a warm solution of (**1b**) in anhydrous tetrahydrofuran (thf)–diethyl ether (1:1) to room temperature.

Preparation of Crystals of (**2b**).—Resolution method (description of a typical experiment; further details will be published elsewhere[3b]): a mixture of (**1b**) (0.15 mol, 45.5 g), L(+)-tartaric acid (0.15 mol, 22.5 g), and ethanol–propan-2-ol (1:3.2) (230

† *Supplementary data available* (No. SUP 56232, 7 pp.): H-atom coordinates, thermal parameters. See Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1985, Issue 1, pp. xvii—xix. Structure factors are available from the editorial office.

Table 1. Crystal and refinement data

Compound	(1b)	(2b)
Formula	$C_{18}H_{29}NOSi$	$C_{18}H_{29}NOSi$
Space group	$P2_1/c$	$P2_12_12_1$
a/Å	6.441(1)	15.221(1)
b/Å	17.182(7)	17.967(1)
c/Å	16.707(4)	6.463(1)
α/°	90	90
β/°	103.86(2)	90
γ/°	90	90
U/Å^3	1 795.1(8)	1 766.8(3)
Z	4	4
M	303.5	303.5
D_c/g cm^{-3}	1.12	1.14
Radiation[a]	Cu-K_α	Cu-K_α
μ/cm^{-1}	10.5	10.6
2θ range (°)	2θ ⩽ 130	2θ ⩽ 130
Recorded reflections	2 975	1 741
Observed reflections[b]	2 541	1 500
g	0.0002	0.0002
R	0.058	0.044
R'	0.063	0.042
F(000)	664.0	664.0

[a] λ (Cu-K_α) = 1.541 78 Å. [b] Only reflections with $F_o^2 \geqslant 2.0\sigma(F_o^2)$ were classified as observed.

Table 2. Positional parameters (× 10^4) for (1b) with estimated standard deviations in parentheses

Atom	x	y	z
Si(1)	5 571(1)	896(1)	1 476(1)
O(1)	3 070(3)	812(1)	979(1)
C(11)	6 455(4)	1 933(2)	1 450(2)
C(12)	8 614(5)	2 159(2)	1 598(2)
C(13)	9 172(6)	2 953(2)	1 594(2)
C(14)	7 678(7)	3 521(2)	1 633(2)
C(15)	5 551(7)	3 316(2)	1 496(3)
C(16)	4 965(5)	2 515(2)	1 503(2)
C(21)	5 716(4)	619(1)	2 568(1)
C(22)	7 939(5)	576(2)	3 100(2)
C(23)	8 086(5)	365(2)	3 982(2)
C(24)	6 558(7)	770(2)	4 361(2)
C(25)	4 367(6)	787(2)	3 846(2)
C(26)	4 190(5)	1015(2)	2 971(2)
C(31)	7 324(5)	249(2)	1 033(2)
C(32)	6 914(5)	−616(2)	1 142(2)
N(33)	8 083(3)	−1 139(1)	706(1)
C(34)	7 626(6)	−1 964(2)	840(2)
C(35)	9 458(6)	−2 404(2)	627(3)
C(36)	11 263(6)	−1 836(2)	745(3)
C(37)	10 425(5)	−1 073(2)	993(2)

cm^3) was stirred under reflux for 10 min. The hot solution was filtered and allowed to cool slowly to room temperature and then kept undisturbed for 24 h at 20 °C. During this time a crystalline solid (41 g) precipitated which was washed with a small amount of ethanol–propan-2-ol (1:3) and then with ether. After being dried *in vacuo* the crystals were treated with ether (1 l) and then with NaOH (1 N aqueous solution, 180 cm^3). After shaking, the organic layer was separated, then washed with water, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give 25 g of a white solid [m.p. 129—132 °C, α(5 g dm^{-3} in $CHCl_3$, 25 °C, 546 nm) = −16°], which was recrystallized carefully seven times from thf–ether (1:1) [the substance was dissolved by heating in thf (7 cm^3 solvent/g substance), followed by addition of ether (7 cm^3); crystallisation by slow cooling to room temperature], yielding 5.0 g pure (2b) [m.p. 146 °C, α(5 g dm^{-3} in $CHCl_3$, 25 °C, 546 nm) = −59°; yield 22%, related to the starting material (1b)]. Melting point and specific rotation are not effected by further recrystallisations. The enantiomeric purity was found to be >97% {^{13}C n.m.r., using tris[3-(perfluorobutyryl)bornan-2-onato]europium(III) as optically active shift reagent}.[3b] Crystals suitable for *X*-ray analysis were obtained by slow cooling of a warm solution of (2b) in hexane to room temperature.

Table 3. Positional parameters (× 10^4) for (2b) with estimated standard deviations in parentheses

Atom	x	y	z
Si(1)	−1 008(1)	−4 097(1)	−7 909(2)
O(1)	−1 620(2)	−4 212(1)	−5 854(4)
C(11)	−1 059(2)	−3 095(2)	−8 742(6)
C(12)	−1 093(3)	−2 867(2)	−10 778(6)
C(13)	−1 136(3)	−2 111(2)	−11 306(7)
C(14)	−1 132(3)	−1 577(2)	−9 769(8)
C(15)	−1 093(3)	−1 792(2)	−7 734(8)
C(16)	−1 062(3)	−2 542(2)	−7 229(7)
C(21)	148(2)	−4 346(2)	−7 161(6)
C(22)	778(2)	−4 238(2)	−8 998(6)
C(23)	1 725(2)	−4 446(2)	−8 440(6)
C(24)	2 040(2)	−4 017(2)	−6 535(6)
C(25)	1 431(3)	−4 148(2)	−4 724(6)
C(26)	490(2)	−3 929(2)	−5 264(6)
C(31)	−1 383(2)	−4 706(2)	−10 080(6)
C(32)	−1 251(2)	−5 533(2)	−9 610(6)
N(33)	−1 590(2)	−6 031(2)	−11 235(5)
C(34)	−1 438(3)	−6 825(2)	−10 702(7)
C(35)	−1 472(3)	−7 238(2)	−12 764(7)
C(36)	−1 395(3)	−6 638(2)	−14 419(7)
C(37)	−1 156(2)	−5 933(2)	−13 240(5)

X-*Ray Structure Analyses of* (1b) *and* (2b).—Intensity data for (1b) and (2b) were collected on a Syntex $P2_1$ four-circle diffractometer in the ω-mode with graphite-monochromated Cu-K_α radiation. The crystal and refinement data are summarized in Table 1. Empirical absorption corrections using azimuthal scan data were applied to the intensity data for both substances. The structures were solved by direct methods and refined in the case of (1b) by full-matrix, and in the case of (2b) by blocked full-matrix least squares with anisotropic thermal parameters for the non-hydrogen atoms. All hydrogen atoms in (1b) were located in a difference synthesis and included in the final least-squares refinement under bond length constraints [d(C–H) = 1.08 ± 0.02, d(O–H) = 0.99 ± 0.02 Å] and with individual isotropic thermal parameters. In the case of (2b), H(1) was located in a difference synthesis and its positional parameters refined. The positions of the remaining hydrogen atoms were calculated geometrically and these atoms were assigned group isotropic thermal parameters. Weights were given by $w = k[\sigma^2(F_o) + g(F_o^2)]^{-1}$ where g was fixed at 0.0002 in both refinements. Atom positional parameters for (1b) and (2b) are listed in Tables 2 and 3. Bond lengths and angles are summarized in Tables 4 and 5. Calculations were carried out with MULTAN (P. Main), SHELX (G. M. Sheldrick), and local programs. The molecular structure of (2b) is shown in Figure 1.

The absolute configuration of (2b) was established on the basis of a Hamilton R-test.[7] Values of R and the generalized R factor $R_G = (\Sigma w\Delta^2/\Sigma wF_o^2)^{\frac{1}{2}}$ ($\Delta = |F_o| - |F_c|$) were 0.047 78 and 0.049 01 respectively for the (*S*)-configuration. For the inverted (*R*)-configuration the respective values were 0.044 19 and 0.045 16. These improvements in the R factors are very strongly significant at the 0.005 level, leading thereby to an unequivocal establishment of the (*R*)-configuration for (2b).

Discussion

The conformations of the molecules in the crystal lattices of the racemate (1b) and the (*R*)-enantiomer (2b) are similar to one

Table 4. Molecular geometry of (**1b**)

Bond lengths (Å)			
O(1)–Si(1)	1.632(2)	C(11)–Si(1)	1.875(3)
C(21)–Si(1)	1.866(3)	C(31)–Si(1)	1.859(3)
C(12)–C(11)	1.408(4)	C(16)–C(11)	1.403(4)
C(13)–C(12)	1.412(4)	C(14)–C(13)	1.382(5)
C(15)–C(14)	1.380(6)	C(16)–C(15)	1.428(5)
C(22)–C(21)	1.496(3)	C(26)–C(21)	1.483(4)
C(23)–C(22)	1.498(4)	C(24)–C(23)	1.467(6)
C(25)–C(24)	1.467(5)	C(26)–C(25)	1.491(4)
C(32)–C(31)	1.529(4)	N(33)–C(32)	1.471(4)
C(34)–N(33)	1.477(3)	C(37)–N(33)	1.474(4)
C(35)–C(34)	1.513(6)	C(36)–C(35)	1.494(5)
C(37)–C(36)	1.514(5)		
Bond angles (°)			
C(11)–Si(1)–O(1)	109.9(1)	C(21)–Si(1)–O(1)	106.7(1)
C(21)–Si(1)–C(11)	108.7(1)	C(31)–Si(1)–O(1)	111.4(1)
C(31)–Si(1)–C(11)	110.0(1)	C(31)–Si(1)–C(21)	110.1(1)
C(12)–C(11)–Si(1)	123.4(2)	C(16)–C(11)–Si(1)	117.4(2)
C(16)–C(11)–C(12)	117.0(2)	C(13)–C(12)–C(11)	120.5(3)
C(14)–C(13)–C(12)	120.1(3)	C(15)–C(14)–C(13)	119.1(3)
C(16)–C(15)–C(14)	119.9(3)	C(15)–C(16)–C(11)	120.0(3)
C(22)–C(21)–Si(1)	114.3(2)	C(26)–C(21)–Si(1)	116.4(2)
C(26)–C(21)–C(22)	113.4(2)	C(23)–C(22)–C(21)	115.0(3)
C(24)–C(23)–C(22)	114.8(3)	C(25)–C(24)–C(23)	114.0(3)
C(26)–C(25)–C(24)	114.7(3)	C(25)–C(26)–C(21)	114.9(3)
C(32)–C(31)–Si(1)	113.3(2)	N(33)–C(32)–C(31)	114.3(2)
C(34)–N(33)–C(32)	111.5(2)	C(37)–N(33)–C(32)	113.4(2)
C(37)–N(33)–C(34)	104.5(2)	C(35)–C(34)–N(33)	104.4(3)
C(36)–C(35)–C(34)	105.6(3)	C(37)–C(36)–C(35)	106.6(3)
C(36)–C(37)–N(33)	104.4(2)		

Table 5. Molecular geometry of (**2b**)

Bond lengths (Å)			
O(1)–Si(1)	1.635(3)	C(11)–Si(1)	1.882(3)
C(21)–Si(1)	1.878(3)	C(31)–Si(1)	1.868(4)
C(12)–C(11)	1.379(5)	C(16)–C(11)	1.394(5)
C(13)–C(12)	1.402(5)	C(14)–C(13)	1.381(6)
C(15)–C(14)	1.372(7)	C(16)–C(15)	1.387(5)
C(22)–C(21)	1.539(5)	C(26)–C(21)	1.528(5)
C(23)–C(22)	1.531(5)	C(24)–C(23)	1.529(6)
C(25)–C(24)	1.512(6)	C(26)–C(25)	1.525(5)
C(32)–C(31)	1.531(4)	N(33)–C(32)	1.473(5)
C(34)–N(33)	1.486(4)	C(37)–N(33)	1.465(4)
C(35)–C(34)	1.526(6)	C(36)–C(35)	1.523(6)
C(37)–C(36)	1.522(5)		
Bond angles (°)			
C(11)–Si(1)–O(1)	109.2(1)	C(21)–Si(1)–O(1)	107.1(1)
C(21)–Si(1)–C(11)	109.8(2)	C(31)–Si(1)–O(1)	111.3(1)
C(31)–Si(1)–C(11)	109.4(2)	C(31)–Si(1)–C(21)	109.9(2)
C(12)–C(11)–Si(1)	124.0(3)	C(16)–C(11)–Si(1)	118.8(3)
C(16)–C(11)–C(12)	117.3(3)	C(13)–C(12)–C(11)	121.4(4)
C(14)–C(13)–C(12)	119.9(4)	C(15)–C(14)–C(13)	119.6(4)
C(16)–C(15)–C(14)	120.0(4)	C(15)–C(16)–C(11)	121.8(4)
C(22)–C(21)–Si(1)	110.8(2)	C(26)–C(21)–Si(1)	114.2(2)
C(26)–C(21)–C(22)	110.2(3)	C(23)–C(22)–C(21)	112.0(3)
C(24)–C(23)–C(22)	111.2(3)	C(25)–C(24)–C(23)	110.6(3)
C(26)–C(25)–C(24)	111.0(3)	C(25)–C(26)–C(21)	112.2(3)
C(32)–C(31)–Si(1)	112.3(3)	N(33)–C(32)–C(31)	113.7(3)
C(34)–N(33)–C(32)	111.3(3)	C(37)–N(33)–C(32)	113.6(3)
C(37)–N(33)–C(34)	104.6(3)	C(35)–C(34)–N(33)	105.0(3)
C(36)–C(35)–C(34)	105.5(3)	C(37)–C(36)–C(35)	104.8(3)
C(36)–C(37)–N(33)	103.5(3)		

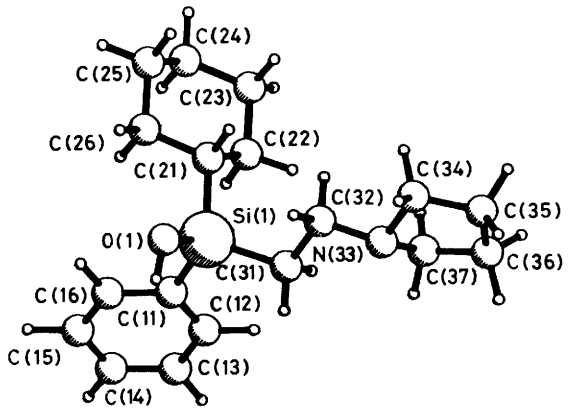


Figure 1. Molecular structure of (**2b**) showing the atomic numbering scheme used for (**1b**) and (**2b**)

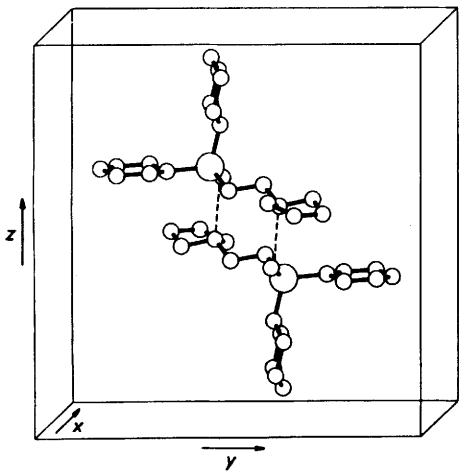


Figure 2. View of the unit cell of (**2b**) with one selected dimer showing the intermolecular O–H ··· N hydrogen bonding between one (*R*)- and one (*S*)-configurated molecule

another. Torsional angles for the Si–C–C–N chain are listed in Table 6. Bond lengths and angles, which are summarized in Tables 4 and 5, are typical.

Intermolecular O(1)–H(1)···N(33) hydrogen bonds of similar O ··· N distance (2.791 and 2.792 Å, respectively) are observed in both crystal structures. However, whereas in (**1b**) one (*R*)- and one (*S*)-configurated molecule are linked together into hydrogen-bonded dimers (Figure 2), (**2b**) contains infinite chains of the (*R*)-configurated molecules parallel to the *c* axis. This chain building allows a more dense molecular packing as evidenced by the respective unit-cell volumes of 1 795.1(8) and 1 766.8(3) Å^3 for (**1b**) and (**2b**). A structure very similar to that of (**1b**) is found for (**4**),[8] in which case O–H ··· N interactions of length 2.758 Å are observed for the hydrogen-bonded dimers.

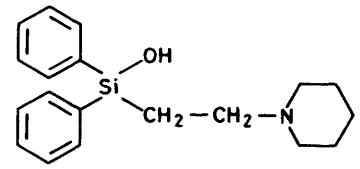
We have also reported chain building similar to that in (**2b**) for compound (**5**).[1] In this case molecules displaced by 1.0 unit parallel to the *a* axis are linked together [*d*(O ··· N) = 2.77 Å]. Similar intra- and inter-molecular O–H ··· N hydrogen bonds have now been reported for a range of aminoalkyl substituted carbinols and silanols related to the title compound.[1,8–11]

With respect to the stereoselectivity of antimuscarinic action the absolute configuration of (**2b**) established in this work is in accordance with stereostructure-activity relationships[6] observed for several chiral antimuscarinic agents structurally

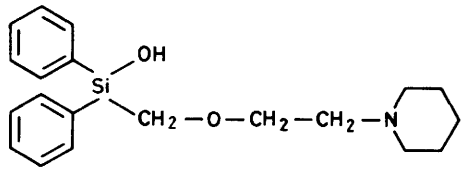
Table 6. Molecular conformations of (**1b**) and (**2b**)

	(**1b**)[a]	(**2b**)
(*a*) Torsional angles (°)		
O(1)–Si(1)–C(31)–C(32)	−66.1(1)	−66.4(2)
Si(1)–C(31)–C(32)–N(33)	172.6(2)	176.4(3)
C(31)–C(32)–N(33)–C(34)	179.7(2)	179.6(3)
C(31)–C(32)–N(33)–C(37)	62.1(2)	65.3(3)
(*b*) Intermolecular hydrogen bonds (Å)[b]		
d[O(1)–H(1) ··· N(33)]	2.791(4)	2.792(5)

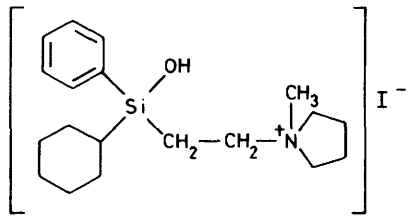
[a] (**1b**) is a racemate: the torsional angles are given for the (*R*)-configurated molecule. [b] Molecules of (**1b**) form centrosymmetric dimers, molecules of (**2b**) participate in infinite chains parallel to the *c* axis.



(**4**)



(**5**)



(**6**)

related to sila-procyclidine. The respective more potent enantiomers of these antimuscarinics have the same absolute configuration as the (*R*)-configurated (**2b**), which exhibits also a greater affinity for ileal and atrial muscarinic receptors of the guinea pig than the (*S*)-configurated (**3b**).[4] The same holds true for the enantiomers of sila-tricyclamol iodide (**6**),[12] which are methiodides of (**2b**) and (**3b**), respectively.

Acknowledgements

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