(1*R*,3*R*)-1,3-Dimethyl-8-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride – an Enantiomerically Pure Building Block for the Synthesis of Naphthylisoquinoline Alkaloids[a]

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Z. Naturforsch. **50b,** 1137–1139 (1995); received February 17, 1995

Crystal Structure, Naphthylisoquinoline Alkaloids, Stereochemistry

The title compound was prepared by hydrogenolytic deprotection of the corresponding N-benzyl derivative, which had previously been synthesized by a Picted-Spengler condensation of the corresponding arylethylamine. It crystallizes from dichloromethane/methanol in the orthorhombic system, space group $P2_12_12_1$; a = 1305.7(2), b = 1400.3(3), c = 727.4(1) pm. Hydrogen bonds between Cl and OH and NH_2 groups cause a three-dimensional arrangement.

Introduction and Synthesis

Naphthylisoquinoline alkaloids, such as ancistrobrevine C (**1**), constitute a structurally, biosynthetically, and pharmacologically outstanding class of natural products [2]. Especially the strong anti-HIV properties of *dimeric* naphthylisoquinolines, named michellamines [3] and the distinct antimalarial activity of some monomeric naphthylisoquinoline alkaloids [4, 5] makes the total synthesis of authentic and modified representatives of this interesting class of compounds a rewarding goal. Indeed, we have succeeded in elaborating first synthetic pathways to naphthylisoquinolines such as *e.g.* ancistrocladine [6, 7] and very recently, we have even developed a first synthetic access to the michellamines [8, 9]. For the stereoselective synthesis of further related naphthylisoquinolines, the free, *i.e.* still naphthaline-devoid isoquinoline building block **2** has recently been prepared for the first time [10]. For its full structural characterization, especially with respect to its specific OMe,OH oxygenation pattern and the relative *trans* configuration at the two stereocenters, an X-ray structure analysis was highly desirable.

Table I. Positional parameters ($\times 10^4$) and equivalent isotropic displacement parameters ($pm^2 \times 10^{-1}$).

Atom	x	y	z	U_{eq}
N(1)	2509(2)	3733(2)	7665(3)	44(1)
C(2)	3515(2)	3243(2)	7412(4)	43(1)
C(3)	3394(2)	2171(2)	7646(3)	43(1)
C(4)	4282(2)	1614(2)	7817(4)	48(1)
O(4)	5180(1)	2101(1)	7894(4)	66(1)
C(5)	4222(2)	639(2)	7882(4)	55(1)
C(6)	3286(2)	189(2)	7800(4)	52(1)
O(6)	3321(2)	−787(1)	7829(3)	68(1)
C(7)	2393(2)	718(2)	7675(4)	50(1)
C(8)	2456(2)	1714(2)	7589(4)	43(1)
C(9)	1473(2)	2282(2)	7473(4)	52(1)
C(10)	1631(2)	3272(2)	6672(4)	46(1)
C(11)	3968(2)	3513(2)	5553(4)	52(1)
C(12)	2383(2)	−1297(2)	7666(5)	69(1)
C(13)	688(2)	3910(2)	6854(5)	66(1)
Cl(1)	2144(1)	4070(1)	1840(1)	49(1)

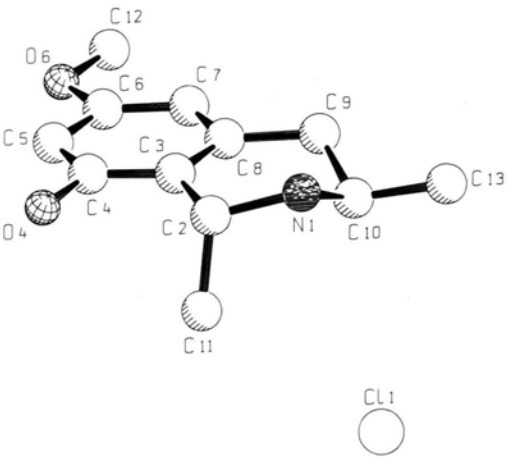

Fig. 1. Perspective drawing of **3** with the labelling of the atoms corresponding to Table I.

[a] "Acetogenic isoquinoline alkaloids", part 72; for part 71, see ref. [1].

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Whereas **2** itself, although spectroscopically and chromatographically pure, did not deliver appropriate crystals, we managed to obtain suited crystals from its N-debenzylation product **3,** as obtained by catalytic hydrogenation over Pd/C and subsequent crystallization as its hydrochloride, giving colorless cubes of melting point 558 K.

X-Ray Investigation

For the crystal structure analysis a crystal of the size 0.23×0.35×0.12 mm was chosen. The determination of the cell parameters from 22 reflections ($8.3° < \theta < 12.5°$) and the measurement of 2340 observed ($F > 3\sigma(F)$) unique reflection intensities ($1.75° < \theta < 27.5°$; $h_{min} = -16$, $h_{max} = 16$, $k_{max} = 18$, $l_{max} = 9$) were carried out on a Siemens R3m/V four-circle diffractometer (MoKα, Wyckoff scan, empirical absorption correction). The structure was solved by direct phase determination (Siemens SHELXTL-PLUS). The parameters of the complete structure could be refined by full-matrix anisotropic least-squares to $R = 0.047$, $R_w = 0.040$; reflection data to parameter ratio = 14.90. The electron density of the largest difference hole was 0.29 eÅ^{-3}.

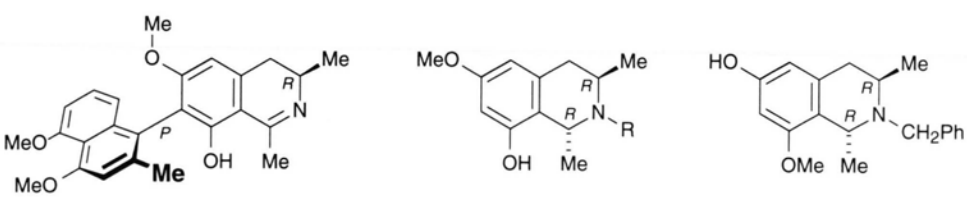
Results and Discussion

$C_{12}H_{18}NO_2Cl$, 207.27 g mol^{-1}, crystallizes in the orthorhombic system, space group $P2_12_12_1$, with $a = 1305.7(2)$, $b = 1400.3(3)$, $c = 727.4(1)$ pm, V = 1329.9(4) pm$^3 \cdot 10^6$ and $Z = 4$. The density was calculated to be 1.217 g cm^{-3}. Atomic parameters are listed in Table I according to the atom labels of Fig. 1*. The crystal structure analysis fully confirms the anticipated constitution of **3** (and thus of **2**) as expected from the synthesis and from the spectroscopic data, *i.e.* with the free phenolic OH group at C(4) and the methyl substituent specifically at C(6). In agreement with structure **3,** the two methyl groups C(11) and C(13) are orientated *trans* to each other. Also in agreement with the spectroscopic data, and as already found for the corresponding regioisomer **4** with the opposite OH/OMe substitution pattern [11], the tetrahydropyrido ring adopts a nearly perfect half-chair, with the methyl group C(11) pseudoaxial, and the other one, C(13), in a pseudoequatorial position. Hydrogen bonds between the chlorine anion and the NH_2 and OH groups of three different cations form a three-dimensional net. The Cl–O (305 pm) and the Cl–N (311 pm) distances show the hydrogen bonds to be in the expected ranges [12]. The crystal structure analysis furthermore shows the compound to be enantiomerically pure, not racemic, which was also expected from its enantioselective synthesis.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 251 "Ökologie, Physiologie und Biochemie pflanzlicher oder tierischer Leistung unter Streß") and by the Fonds der Chemischen Industrie. P. A. K. thanks the Alexander von Humboldt Foundation.

* Further crystal structure data may be obtained from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftliche Information mbH, D-76344 Eggenstein-Leopoldshafen, by quoting the Registry No. CSD 401158, the names of the authors and the journal citation.



1 **2** R = CH_2Ph **4**

3 R = H

Scheme 1.

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