Absolute Configuration of Cathine

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Cathine, (+)-norpseudoephedrine, is an alkaloid isolated from khat leaves.¹ Khat, the leaves of *Cayha edulis* Forsk., is widely used as a stimulant in eastern Africa and south Arabia. The CNS-effects are generally related to phenylalkylamine as well as cathine or cathinone, which is a phytochemical precursor of cathine.² Cathinone has been transformed into cathine by the drying of the leaves. In recent years, synthetically available cathine is abused as an anorexic.

Cathine contains two asymmetric centers and exists as a pair of enantiomers. We have given some attention to the apparent contradiction regarding the absolute configuration of cathine. Since cathine is referred to as (1*R*,2*R*)- or (1*S*,2*S*)-form in the literature^{2,3}, the absolute configuration has not been determined. Here we present the absolute configuration of cathine based on X-ray crystallographic analysis.

Cathine HCl was recrystallized from ethanol-ether (1:5 v/v). The optical rotation was $[\alpha]_D^{20} = +0.21$ (10 mg samples in 1 ml H₂O). An X-ray analysis was undertaken using a four-circle diffractometer with graphite-monochromated Cu K α radiation. The crystal data and experimental details are given in Table 1. The crystal structure was solved by using SIR92⁴, and refined by the least-squares method. The refined atomic parameters and equivalent isotropic temperature factors are listed in Table 2. The selected bond lengths and angles are given in Table 3. The molecular structure determined to be 2-amino-1-phenyl-1-propanol (Fig. 1), is illustrated in Fig. 2 by ORTEP⁵ drawing.

The absolute configuration was confirmed by the Flack parameter⁶ [0.008(12)]. The configurations of

Fig. 1 Chemical structure of cathine.

Table 1 Crystal and experimental data

Formula: C ₉ H ₁₃ NO·HCl
Formula weight=187.67
Crystal system: monoclinic
Space group: <i>P</i> 2 ₁
<i>Z</i> =2
<i>a</i> =5.443(2) Å
<i>b</i> =8.0708(8) Å
<i>c</i> =11.868(1) Å
β =101.76(2)°
<i>V</i> =510.4(2) Å ³
<i>D</i> _c =1.221 g/cm ³
2 θ _{max} =135.2°
<i>R</i> =0.025
<i>R</i> _w =0.035
(Δ / σ) _{max} =0.06
($\Delta\rho$) _{max} =0.11 e Å ⁻³
($\Delta\rho$) _{min} =-0.11 e Å ⁻³
No. of reflections used=2186
Measurement: RIGAKU AFC-7S
Program system: teXsan ⁷
Structure determination: SIR92
Refinement: full matrix: least-squares

Table 2 Atomic coordinates and *B*_{iso}/*B*_{eq}

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq}
Cl(1)	0.76909(6)	0.5238(8)	0.42039(3)	4.180(7)
O(1)	0.7765(2)	0.1648(8)	0.31701(9)	4.43(2)
N(1)	0.6630(2)	-0.0923(8)	0.44458(9)	3.60(2)
C(1)	0.4169(3)	0.1215(8)	0.1578(1)	3.57(3)
C(2)	0.5399(3)	0.0529(8)	0.0775(1)	4.33(4)
C(3)	0.4315(4)	0.0582(8)	-0.0392(1)	4.81(4)
C(4)	0.2049(3)	0.1335(8)	-0.0762(1)	4.95(4)
C(5)	0.0840(3)	0.2066(8)	0.0028(1)	5.16(4)
C(6)	0.1900(3)	0.1992(8)	0.1193(1)	4.54(3)
C(7)	0.5271(3)	0.1039(8)	0.2858(1)	3.52(3)
C(8)	0.5401(3)	-0.0789(8)	0.3195(1)	3.60(3)
C(9)	0.2876(3)	-0.1630(8)	0.2989(1)	4.86(4)

Table 3 Selected bond lengths (Å) and angles (°)

atom	atom	distance
O(1)	C(7)	1.421(2)
N(1)	C(8)	1.503(2)
C(1)	C(7)	1.522(2)
C(7)	C(8)	1.528(2)
C(8)	C(9)	1.506(3)

atom	atom	atom	angle
O(1)	C(7)	C(1)	112.9(1)
O(1)	C(7)	C(8)	106.0(1)
C(1)	C(7)	C(8)	109.9(1)
N(1)	C(8)	C(7)	108.4(1)
N(1)	C(8)	C(9)	109.7(1)
C(7)	C(8)	C(9)	113.5(2)

the two asymmetric carbons, C(7) and C(8) are definitely determined to be *S*-form. This result indicates the absolute configuration of cathine exhibiting (1*S*,2*S*)-form in the synthetic compound.

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References

1. I. A. A. L. Meshal, A. M. Ageel, N. S. Parmar and M. Tariq, *Fitoterapia*, **LVI**, 131 (1985).
2. R. Brenneisen and S. Geissshudler, *Pharm. Acta. Helv.*, **60**, 290 (1985).
3. Annex to the Annual Statistical Report ("Green List") Eighteenth Edition, 1997.
4. A. Altomar, M. C. Burla, M. Camalli, M. Cascarano, C. Giacovazzo, A. Guagliardi and G. Polidori, *J. Appl. Cryst.*, **27**, 435 (1994).
5. ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA, 1976.
6. H. D. Flack, *Acta Crystallogr.*, **A 39**, 876 (1983).
7. Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

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Fig. 2 ORTEP drawing of cathine.