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Endogenous Alkaloids in Man. 28.† (1*R*,3*S*)-1-Trichloromethyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide Methanol Solvate, a Potential Synthetic Precursor to Enantiomerically Pure TaClo

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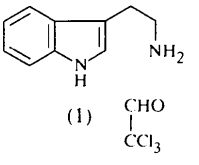
Abstract

The title compound, $C_{13}H_{12}Cl_3N_3O.CH_3OH$, was prepared by amidolysis of the corresponding methyl tetrahydro-β-carboline-3-carboxylate, obtained in turn by condensation of tryptophan methyl ester and chloral. The crystal structure confirms the relative *cis*-array of the substituents at C1 and C3, and thus the absolute *R* configuration at C1.

Comment

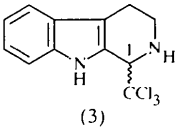
The neurotoxin 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline [TaClo, (3)], the condensation product of the natural compound tryptamine [Ta, (1)] and the synthetic aldehyde and medical drug chloral [Clo, (2)] (Bringmann & Hille, 1990), is believed to be formed spontaneously in man (Bringmann *et al.*, 1995). We have recently been able to show that TaClo, (3), does occur in rats treated chronically with small doses of its putative precursors (Bringmann, Feineis *et al.*, 1996). However, heterocycle (3) is still only known as a racemate. For a thorough investigation of the neurotoxic potential of (3), the availability of the heterocycle in enantiomerically pure form is an important goal. For the stereoselective preparation of *e.g.* (*R*)-(3), the tetrahydro-β-carboline (4) (Bringmann *et al.*, 1991), as prepared from the chiral amino acid L-tryptophan, is a promising precursor. The further transformation of (4) into optically active (*R*)-TaClo still requires the 3-carboxylic ester group to be reductively eliminated, *e.g. via* the corresponding cyano group. For this purpose, the amide precursor, (5), was synthesized by treatment of (4) with saturated methanolic NH_3 for 3 h, giving pure (5) in 86% yield.

From the presence of the 1-CCl_3 group, a chemical, and likewise a configurative, instability at C1 could not be excluded *a priori*. For this reason, and for a confirmation of the stereochemical correlation of C1 [which is important for the ultimate target molecule, (*R*)- or (*S*)-TaClo] with C3 (which is known from the use of L-tryptophan), a crystal structure analysis was highly desirable.

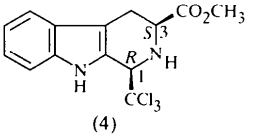


(1)

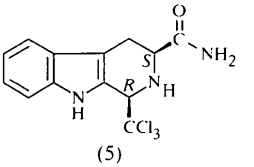
(2)



(3)



(4)



(5)

The crystal structure analysis shows that (5) crystallizes with one equivalent of methanol (Fig. 1). Furthermore, it clearly confirms the successful amidation reaction of the ester, (4), to give the primary amide functionality at C3, with a relative *syn*-orientation at the two nitrogen atoms, N2 and N16, hinting at an intramolecular hydrogen bond. With respect to the goal of preparing (3) in enantiomerically pure form, stereochemical information at C1, as is now available from the X-ray structure analysis, is of particular importance. Indeed, the relative *cis*-configuration of the two substituents at C1 and C3, as already deduced from NMR experiments, is clearly confirmed, and therefore so is the absolute 1*R* configuration of the newly created stereocentre at C1. This reveals the desired chemical and stereochemical stability of these compounds towards the chosen

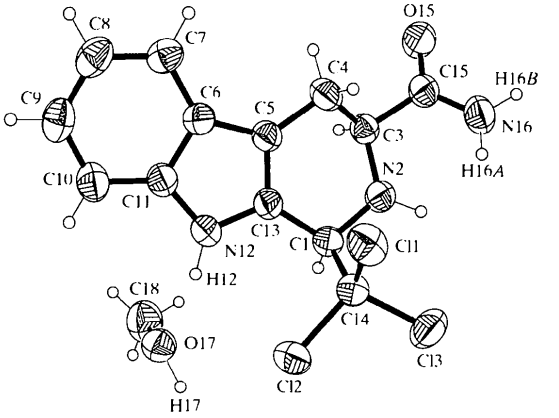


Fig. 1. *SHELXTL-Plus* (Sheldrick, 1990) plot showing the molecular structure of (5) with 50% probability displacement ellipsoids. H atoms have been drawn artificially small.

† Part 27: Bringmann, God & Schäffer (1996).

reaction conditions. The partially saturated tetrahydropyridino ring adopts a partially planarized half-chair conformation, with only C3 being located distinctly out of the ring plane. Thus, only the amido function was observed to be in a pseudo-equatorial orientation, whereas the large lipophilic CCl_3 group adopts a nearly pseudo-axial position. The three chlorine substituents show a perfectly staggered orientation with respect to the C1—C14 bond, thus minimizing their steric interactions with C13 and N2.

The methanol molecules included in the crystal form intermolecular hydrogen bonds (O15···H17 1.82 Å and O17···H12 2.04 Å), thus acting as links between the substrate molecules. This leads to zigzag chains parallel to [001].

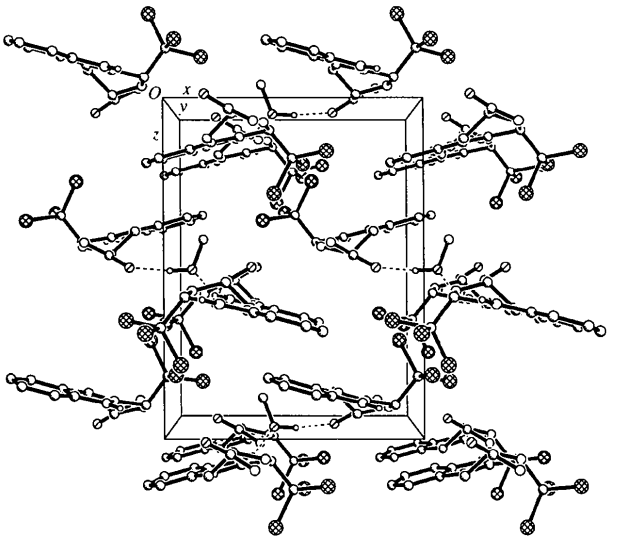


Fig. 2. *SHELXTL-Plus* (Sheldrick, 1990) plot showing the packing diagram viewed approximately parallel to [010]. H atoms, except for H12 and H17, have been omitted.

Experimental

The title compound was prepared by amidolysis of the condensation product of tryptophan methyl ester and chloral. Pale yellow crystals, of appropriate quality for an X-ray structure analysis, were obtained by recrystallization from methanol.

Crystal data

$C_{13}H_{12}Cl_3N_3O.CH_4O$
M_r = 364.65
Orthorhombic
$P2_12_12_1$
a = 10.7523 (6) Å
b = 11.0208 (7) Å
c = 14.0493 (9) Å
V = 1664.8 (2) Å^3
Z = 4
D_x = 1.455 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 60 reflections
θ = 21.1–35.0°
μ = 0.56 mm^{-1}
T = 293 (2) K
Prism
0.75 × 0.75 × 0.55 mm
Pale yellow

Data collection

Siemens $P4$ diffractometer
ω scans
Absorption correction:
ψ scan (*XEMP* in *XSCANS*; Siemens, 1996*b*)
T_{min} = 0.644, T_{max} = 0.735
7726 measured reflections
6018 independent reflections
5592 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 32.50°
h = −1 → 16
k = −1 → 16
l = −21 → 21
3 standard reflections
every 97 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.115
S = 1.058
5633 reflections
200 parameters
H atoms refined by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0778P)^2 + 0.0719P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.007
$\Delta\rho_{max}$ = 0.63 e Å^{-3}
$\Delta\rho_{min}$ = −0.67 e Å^{-3}
Extinction correction: none
Scattering factors from *SHELXTL-Plus* (Sheldrick, 1990)
Absolute structure: Flack (1983)
Flack parameter = 0.06 (5)

Table 1. *Selected geometric parameters (Å, °)*

Cl1—C14	1.776 (2)	N2—C3	1.467 (2)
Cl2—C14	1.775 (2)	C3—C15	1.528 (2)
Cl3—C14	1.778 (2)	C9—C10	1.386 (3)
C1—N2	1.467 (2)	C15—O15	1.235 (2)
C1—C14	1.557 (2)	C15—N16	1.322 (2)
C13—C1—C14	111.1 (1)	C1—C14—Cl3	109.7 (1)
C1—C14—Cl2	109.8 (1)	Cl2—C14—Cl3	107.99 (8)
C1—C14—Cl1	112.0 (1)	Cl1—C14—Cl3	108.96 (9)
Cl2—C14—Cl1	108.30 (8)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O17—H17···O15^i	0.98	1.80	2.763 (2)	167.3
N12—H12···O17	0.91	2.04	2.888 (2)	155.1

Symmetry code: (i) $x - \frac{1}{2}, \frac{1}{2} - y, 1 - z$.

The positions of the H2, H16*A*, H16*B* and H12 atoms, and of the H atom in the methanol OH group, were established by difference synthesis and fixed. All other H-atom positions were calculated and refined using a riding model. Both kinds of H-atom position were assigned a common isotropic displacement parameter of 0.08 Å^2. To establish the absolute configuration, 3383 Friedel pairs were employed.

Data collection: *P4* (Siemens, 1996*a*). Cell refinement: *P4*. Data reduction: *SHELXTL-Plus* (Sheldrick, 1990). Program(s) used to solve structure: *SHELXTL-Plus*. Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL-Plus*. Software used to prepare material for publication: *SHELXL*93.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ1190). Services for accessing these data are described at the back of the journal.

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Calix[4]arene Piperidinium Salt

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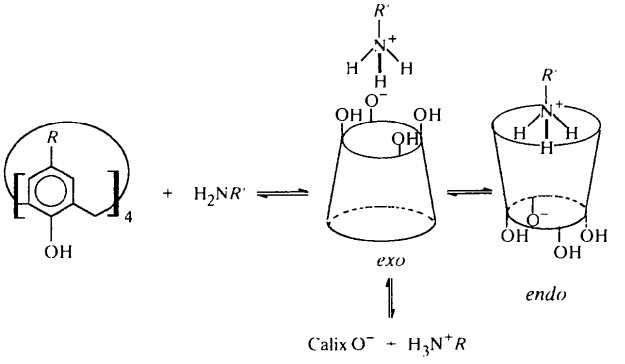
Abstract

In the crystal structure of piperidinium 26,27,28-trihydroxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-25-olate hemiacetonitrile solvate sesquihydrate, $2(C_5H_{12}N^+.C_{28}H_{23}O_4^-).CH_3CN.3H_2O$, two monoanions of calix[4]arene, two piperidinium ions, three molecules of water and one molecule of acetonitrile are observed in the asymmetric unit. They form an intricate network of intra- and intermolecular hydrogen bonds. Each calixarene molecule has a cone conformation. The H atoms of the piperidinium N^+ atom are not directed towards the phenyl rings, indicating that no $(N^+—H)\cdots\pi$ interaction occurs.

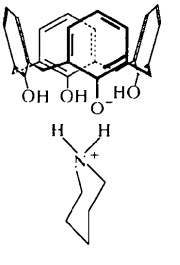
Comment

Calixarenes are a class of synthetic macrocycles having phenolic residues in a cyclic array. They are able to form inclusion compounds with a wide variety of organic guest species, such as toluene (Andreetti *et al.*, 1979), ammonium cations (Harrowfield *et al.*, 1993) and fullurenes (Raston *et al.*, 1996). The simplest representation of these compounds is calix[4]arene (R = H in scheme below), which forms clathrates with several solvents, such as acetone (Ungaro *et al.*, 1984) and acetonitrile (Harrowfield *et al.*, 1993), the crystal structures of which have been determined, revealing 1:3 calixarene–solvent clathrate structures.

The pK_a values of calixarenes are 5–7 pK_a units below those of the corresponding phenols (Shinkai *et al.*, 1991), allowing the formation of salts with amines. The nature of these salts in CH_3CN was studied by Gutsche *et al.* (1987), who proposed the *endo–exo* equilibrium to *p*-alil-calix[4]arene and *tert*-butylamine, based on chemical shifts and relaxation times (T_1) of *tert*-butyl H atoms of the amine. The scheme below shows the equilibria of calix[4]arene and primary amines.



During our attempts to understand the compounds formed by calix[4]arenes and amines, we have determined the structure of the salt formed by calix[4]arene and piperidine, (I).



(I)