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Protopine hydrochloride

Jiří Dostál,[a] Zdirad Žák,[b] Marek Nečas,[b]* Jiří Slavík[a] and Milan Potáček[c]

[a]Department of Biochemistry, Faculty of Medicine, Masaryk University, 662 43 Brno, Czech Republic, [b]Department of Inorganic Chemistry, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic, and [c]Department of Organic Chemistry, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic
Correspondence e-mail: man@chemi.muni.cz

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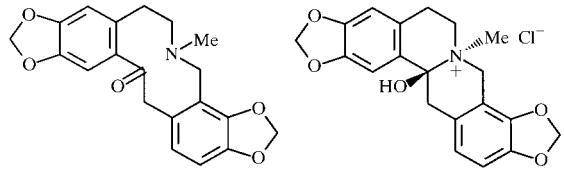
Protopine hydrochloride (5,6,14,14a-tetrahydro-14a-hydroxy-7-methyl-8*H*-bis[1,3]benzodioxolo[5,6-*a*:4,5-*g*]quinolizinium chloride, $C_{20}H_{20}NO_5^+\cdot Cl^-$) is the salt of the isoquinoline alkaloid protopine. It is formed by the action of dilute hydrochloric acid on the protopine free base. The *N*-methyl and hydroxyl groups are in a *trans* configuration in the quinolizine ring and the central quinolizine N—C bond is unusually long [1.579 (2) Å]. The crystal is a racemate.

Comment

Protopine is an isoquinoline alkaloid of the protopine group which is common in the plants of the Papaveraceae, Fumariaceae and other families (Guinaudeau & Shamma, 1982). The free base of protopine, (I), with a ten-membered nitrogen heterocycle, has already been investigated by X-ray analysis (Hall & Ahmed, 1968*a*), as have the free bases of the related alkaloids cryptopine (Hall & Ahmed, 1968*b*), allocryptopine (Sakai *et al.*, 1988; Marek *et al.*, 1998) and corycavine (Kamigauchi *et al.*, 1987). All the cited papers reported a strong electrostatic interaction between the nitrogen and the carbonyl carbon across the ten-membered ring. In an acidic environment, a fundamental alteration of the skeleton occurs and protopines adopt tetracyclic structures corresponding to tetrahydroprotoberberines. Compound (II) has already been described using spectral data (UV, IR and NMR) and has been investigated by diffraction analysis (Luo *et al.*, 1985). However, that report afforded neither complete geometric and crystal data parameters nor packing data. The detailed molecular study of protopine hydrochloride may be of interest with regard to biosynthetic considerations and especially in pharmacological studies. Protopine has been shown to have multiple actions on the cardiovascular system, including antiarrhythmic effects (Song *et al.*, 2000), as well as antithrombotic activity (Saeed *et al.*, 1997). Generally, it is known that the medically active forms of alkaloids are as salts rather than as their free bases (Dostál, 2000).

The title compound, protopine hydrochloride, (II), is the salt of protopine. NMR studies of protopine salts indicated the presence of two (*cis* and *trans*) isomers in solution (Iwasa *et al.*, 1982; Hussain *et al.*, 1983). The crystal of (II) examined in the present paper is a *trans* isomer with respect to the position of the *N*-methyl and hydroxyl groups (Fig. 1). The dihedral angle



(I) (II)

along the C16—N7—C14—O22 junction is −166.31 (15)°. In the tetrahydroprotoberberine alkaloids canadinium camphorsulfonate (Sakai *et al.*, 1987) and tetrahydropalmatine (Ribár *et al.*, 1993), both the central rings were also found to be *trans*-fused. On the other hand, corycavinium camphorsulfonate, structurally close to protopine hydrochloride, is *cis*-configurated (Kamigauchi *et al.*, 1994). The six-membered nitrogen heterocycles in (II) adopt distorted half-chair conformations. The angle between the mean planes of both aromatic rings is 17.10 (5)°.

Selected geometric parameters are given in Table 1. The central N7—C14 bond in the quinolizine ring is unusually long [1.579 (2) Å] and similar to coulteropine hydrobromide, where the length of the central bond was 1.58 Å (Stermitz *et al.*, 1968). This finding implies that this particular bond breaks easily under the action of the hydroxide ion to provide a ten-membered ring of the free base, (I). The mean of the bond angles around the nitrogen is 109.5° (sp^3 hybridization). The molecule bears two chiral centres (C14 and N7) and from the centrosymmetric space group it follows that the crystal is a racemate. From plant extracts, protopines are usually obtained in the form of optically inactive free bases because they are stable and easy to crystallize. However, in plant tissues, protopine alkaloids occur as salts (Kamigauchi *et al.*, 1994). To the best of our knowledge, a natural salt of protopine has probably not yet been isolated from plant material directly without being alkalized. Thus, the *in vitro* prepared protopine hydrochloride, (II), is obviously racemic, whereas the configuration of the protopine salt generated *in vivo* still remains an open question. There are numerous contacts between the chloride ion and H atoms in the range 2.78–2.87 Å, the

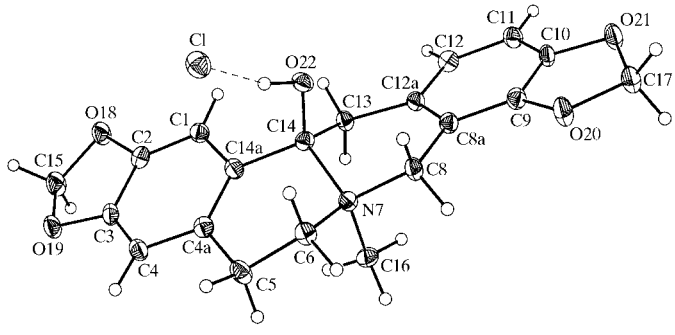


Figure 1
A perspective view of compound (II). Displacement ellipsoids are drawn at the 50% probability level.

shortest one being O22—H22···Cl (2.06 Å) (Table 2). The molecules are packed in a chain-like arrangement with chloride ions between the chains.

Experimental

Protopine, (I), isolated from *Chelidonium majus* L. (Slavík *et al.*, 1965), was dissolved in hot 3% hydrochloric acid and the solution was allowed to stand at ambient temperature. After three weeks, colourless crystals of protopine hydrochloride, (II), were collected, washed and dried [m.p. 534–537 K (decomposition)].

Crystal data

$C_{20}H_{20}NO_5^+\cdot Cl^-$
M_r = 389.82
Monoclinic, $P2_1/n$
a = 6.940 (1) Å
b = 17.755 (1) Å
c = 13.829 (2) Å
β = 104.18 (1)°
V = 1652.1 (3) Å^3
Z = 4
D_x = 1.567 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1967 reflections
θ = 3.3–23.0°
μ = 0.27 mm^{-1}
T = 150 (2) K
Prism, colourless
0.50 × 0.40 × 0.35 mm

Data collection

Kuma KM-4 CCD diffractometer
ω scans
11 498 measured reflections
2900 independent reflections
2546 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 25.0°
$h = -8 \rightarrow 8$
$k = -21 \rightarrow 10$
$l = -16 \rightarrow 16$
Intensity decay: negligible

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.102
S = 1.16
2900 reflections
246 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0382P)^2 + 1.9000P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0064 (9)

Table 1
Selected geometric parameters (Å, °).

C2—O18	1.381 (2)	C9—O20	1.379 (2)
C3—O19	1.372 (2)	C10—O21	1.377 (2)
C4a—C5	1.509 (3)	C12a—C13	1.518 (3)
C4a—C14a	1.397 (3)	C13—C14	1.525 (3)
C5—C6	1.507 (3)	C14—O22	1.394 (2)
N7—C6	1.513 (2)	C14—C14a	1.530 (3)
N7—C8	1.498 (2)	C15—O18	1.437 (3)
N7—C14	1.579 (2)	C15—O19	1.441 (3)
N7—C16	1.510 (2)	C17—O21	1.431 (3)
C8—C8a	1.497 (3)	C17—O20	1.447 (2)
C8a—C12a	1.404 (3)		
C5—C6—N7	110.65 (15)	C14—N7—C16	112.53 (14)
C6—N7—C8	106.93 (14)	C8a—C8—N7	112.41 (16)
C6—N7—C14	108.91 (14)	O22—C14—N7	106.77 (14)
C8—N7—C14	109.11 (14)	C13—C14—N7	105.92 (15)
C6—N7—C16	110.30 (15)	C14a—C14—N7	109.31 (15)
C8—N7—C16	108.90 (15)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O22—H22···Cl	0.97	2.06	2.9962 (15)	162

Data collection: *KM*-4 *Software* (Kuma, 1992); cell refinement: *KM*-4 *Software*; data reduction: *KM*-4 *Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Johnson & Burnett, 1996); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1038). Services for accessing these data are described at the back of the journal.

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