THE ABSOLUTE CONFIGURATION OF (+)-CANADALINE

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Abstract—The absolute configuration of natural (+)-canadaline (1) was established to be S-configuration by its biomimetic synthesis from S-(-)-canadine (5).

(+)-Canadaline (1), isolated from Hydrastis canadensis L. is a representative secoberbine alkaloid. Its racemate has been synthesized from 8-benzyltetrahydroberberine through the Hofmann degradation and from tetrahydroberberine through C8-N bond cleavage using ethyl chloroformate. The absolute configuration of (+)-canadaline (1) is still unknown even though its R-configuration (2) has been speculated from the facts that canadalisol (3), reduction product of (+)-canadaline, is dextrorotatory and a related alkaloid (+)-corydalisol (4)
has R-configuration. The configuration of 4 has been confirmed by chemical
correlation with (+)-stylopine (6) of known chirality.\textsuperscript{8} We describe here
determination of the absolute configuration of (+)-canadaline (1) by its
synthesis as an optically active form from S-(-)-canadine (5) according to our
previous method.\textsuperscript{5}

Optical resolution of (+)-tetrahydroberberine using d-camphorsulfonic acid
resulted in (+)-canadine (7) [mp 133-134°C; [\alpha]_D +272° (c 0.912, CHCl\textsubscript{3}) \textsuperscript{9}]
and (−)-canadine (5) [mp 133-135°C; [\alpha]_D -314° (c 0.94, CHCl\textsubscript{3}) \textsuperscript{10}]
as an almost optically pure form. At first we intended to synthesize canadaline
starting from R-(+)-canadine. Reaction of 7 with ethyl chloroformate in
chloroform under reflux for 24 h, followed by treatment with silver nitrate in
aqueous acetone caused C\textsubscript{8}-N bond cleavage and substitution of the resulting
chloride to afford the alcohol (8) in 79% yield from 7. Reduction of 8 with
lithium aluminum hydride in tetrahydrofuran furnished the N-methyl alcohol, (+)-
canadalisol (3) [87%; mp 128-130°C; [\alpha]_D +26° (c 0.1, CHCl\textsubscript{3})]. The product was
oxidized with pyridinium chlorochromate (PCC) in dichloromethane in the presence
of sodium acetate to provide (−)-canadaline (2) [63%; mp 114-116°C; [\alpha]_D -38° (c
0.1, CHCl\textsubscript{3})].

(−)-Canadaline (2) was identical with natural canadaline in $^1$H-nmr spectral
comparison, however the sign of its specific rotation is opposite to that of
natural (+)-canadaline \([\alpha]_D^2 +43^\circ \text{ (c 0.5, CHCl}_3\)).\(^1\) The absolute configuration of
natural (+)-canadaline is therefore S-configuration (1) but not R-configuration
(2) assumed before.

In order to obtain a direct proof of S-configuration of (+)-canadaline, natural
(+)-canadaline was synthesized from S-(-)-canadine (5) through a similar
procedure described above. S-(-)-Canadine (5) was converted via 9 to (-)-
canaldisol (10) \([67\% \text{ from 5; } \text{mp } 130-131^\circ \text{C } [\alpha]_D -37^\circ \text{ (c 0.1, CHCl}_3]\]), which was
oxidized with PCC to afford (+)-canadaline (1) \([58\%, \text{mp } 117-119^\circ \text{C (lit.}^1 \text{ mp 117-}
118^\circ \text{C); } [\alpha]_D^2 +44^\circ \text{ (c 0.1, CHCl}_3\]). Synthetic (+)-canadaline was shown to be
identical with natural canadaline in \(^1\text{H-nmr spectra. Thus, the absolute}
configuration of (+)-canadaline was completely established to be S-configuration.
It was found that canadaline and canadalisol showed opposite sign in their
specific rotation in spite of the same absolute configuration. Usually N-methyl-
tetrahydrobenzylisoquinoline alkaloids with positive or negative specific
rotation have S- or R-configuration, respectively.\(^1\) This rule cannot be applied
to corydalisol and canadalisol possessig an extra hydroxymethyl group at C-10,
however canadaline having an extra formyl group follows this rule, suggesting
that conformation of canadaline has normal anti relationship between the N-methyl
group and the lower aromatic ring whereas corydalisol and canadalisol have
abnormal syn relationship due to a hydrogen bonding.

Recently S-(-)-corydalisol\(^1\) was isolated and considered to be derived from S-+(+)-reticuline (11),\(^1\) which is the main biogenetic source for isoquinoline
alkaloids. The present result suggests that canadaline is also biosynthesized
from S-(-)-reticuline via S-(-)-canadine.

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REFERENCES AND NOTES

7. We could not find any reports described specific rotation of canadalisol derived from natural (+)-canadaline.
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