HETEROCYCLES, Vol 12, No 4, 1979

# A NEW SYNTHESIS OF (±)-CANADALINE

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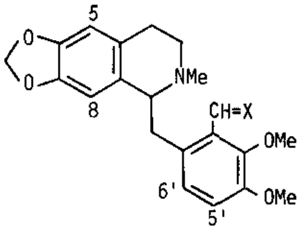
Abstract —— (±)-Canadaline was synthesized using a regioselective N-$C_8$ bond cleavage of tetrahydroberberine with ethyl chloroformate.

Canadaline (1),[1] an alkaloid isolated from Hydrastis canadensis L, is representative of a new group of isoquinoline alkaloids, the secoberbines.[2] In 1978, Shamma et al.[2] reported the first synthesis of its racemate from the Hofmann degradation product (2)[3] of 8-benzyltetrahydroberberine. We now wish to report an alternative and convenient synthesis of (±)-canadaline via a regioselective N-$C_8$ bond cleavage of tetrahydroberberine itself.

In boiling ethyl chloroformate, tetrahydroberberine (3) gave the urethane (4) in 81% yield as a sole product,[4] while the Hofmann degradation[5] or the von Braun reaction[6] of tetrahydroberberine has been found to result in the N-$C_6$ and/or N-$C_{14}$ bond fission. Structure of 4 was confirmed by its conversion to 5 [with $LiAlH_4$, 66%, $\delta$ 2.02 (3H, s), 2.46 (3H, s)]. Treatment of 4 with silver nitrate in aqueous acetone afforded 6 in 66% yield and subsequent lithium aluminum hydride reduction of 6 gave the amino alcohol (8) in 80% yield. The alcohol (8) was also obtained by solvolysis of 4 with acetic acid-sodium acetate followed by lithium aluminum hydride reduction (via 7) in a rather low yield (overall 31%). PCC oxidation[7] of 8 furnished (±)-canadaline (1) [68%, mp 143-143.5°, m/e 369 ($M^+$), $\nu$ ($CHCl_3$) 1680 $cm^{-1}$, $\delta$ ($CDCl_3$) 10.20 (1H, s, CHO), 6.86 and 6.68 (2H, AB-q, J=8, $C_{5'}$- and $C_{6'}$-H), 6.40 (2H, s, $C_5$- and $C_8$-H), 5.76 (2H, s, $OCH_2O$), 3.86 (3H, s, $OCH_3$), 3.82 (3H, s, $OCH_3$), 2.32 (3H, s, $NCH_3$), $\lambda_{max}^{MeOH}$ 288 nm (log $\varepsilon$=3.85)].

The synthetic (±)-canadaline was proved to be completely identical with natural canadaline[1] by $^1H$-NMR spectral comparison.

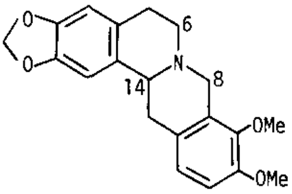


**1** ; X=O

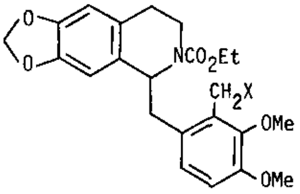
**2** ; $X=CHC_6H_5$

**5** ; $X=H_2$

**8** ; X=OH,H



**3**



**4** ; X=Cl

**6** ; X=OH

**7** ; X=OAc

ACKNOWLEDGEMENT

The authors wish to thank Prof. E. Stanislas, U.E.R. des Sciences Pharmaceutiques, for sending the spectra of canadaline.

REFERENCES AND FOOTNOTES

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2. M. Shamma, A.S. Rothenberg, and G.S. Jayatilake, *Tetrahedron*, 1978, **34**, 635.
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4. The product showed two spots on TLC and exhibited a complex $^1$H-NMR spectrum. This phenomenon could be attributed to the presence of two rotamers, because both isolated components gave the same reduction product (**5**) in excellent yields.
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Received, 16th January, 1979