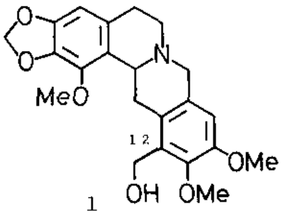
A TRANSFORMATION OF TETRAHYDROBERBERINE TO A RETROPROTOBERBERINE

Miyoji Hanaoka*, Mitsuru Inoue, Shingo Yasuda, and Takeshi Imanishi

Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa, 920, Japan

Abstract—— The retroprotoberberine (8) was synthesized from tetrahydroberberine (4) *via* the urethane (6) and the amino-alcohol (7).

Retroprotoberberine alkaloids,[1,2] *e.g.* mecambridine (1) and orientalidine (2), are characterized by the presence of one extra carbon at C_{12} of the protoberberine skeleton and have been proposed to be biosynthesized from the corresponding protoberberine alkaloid (3) *via* C_8-N bond cleavage.[3,4] The extra carbon, therefore, must originate from C-8 of 3. In previous papers, we reported a regioselective C_8-N bond cleavage of *tetrahydroprotoberberine using ethyl chloroformate* and its application to the syntheses of (±)-canadaline,[5,6] (±)-α-, and (±)-β-hydrastine.[7] This communication deals with the conversion of tetrahydroberberine (4) to the retroprotoberberine (8) according to the above biogenetic assumption.



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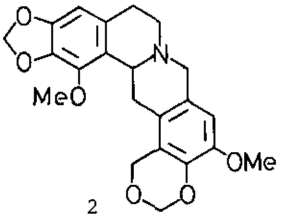

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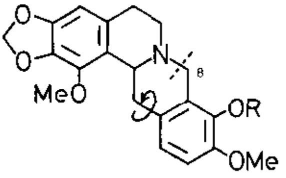

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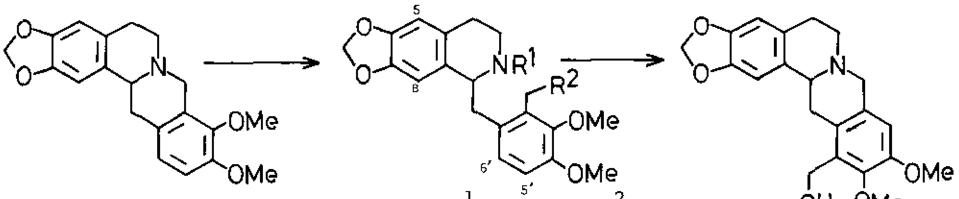
Hydrolysis of the urethane (6),[5] derived from 4 *via* 5, with potassium hydroxide in aqueous ethanol in a sealed tube at 140∿145° for 46 hr gave the amino-alcohol (7) [mp 157∿158°, *m/e* 339 (M^+-18), ν[8] 3300, 3150, δ[8] 7.01 and 6.86 (2H, AB-q, *J*= 8.5, *H*-5′ and *H*-6′), 6.80 (1H, s, H-8), 6.56 (1H, s, H-5), 5.93 (2H, s, OCH_2O), 4.84 and 4.47 (2H, AB-q, *J*= 11.5, $C\underline{H}_2OH$), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3)] in 67% yield (86% yield based on consumed 6). The Mannich reaction of 7 with 37%

aqueous formaldehyde in acetic acid at 100° for 3.5 hr afforded the retroprotoberberine (8) [mp 195∿196°, *m/e* 369 (M^+), ν 3350, δ 6.78, 6.60, and 6.58 (each 1H, s, Ar-H), 5.92 (2H, s, OCH_2O), 4.73 (2H, br-s, $C\underline{H}_2OH$), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3)] as a sole product in 90% yield.



4

5: $R^1 = CO_2Et$, $R^2 = Cl$

6: $R^1 = CO_2Et$, $R^2 = OH$

7: $R^1 = H$, $R^2 = OH$

8

The above biogenetic-type conversion will provide a new general method for the synthesis of the retroprotoberberine alkaloids.

REFERENCES AND FOOTNOTES

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