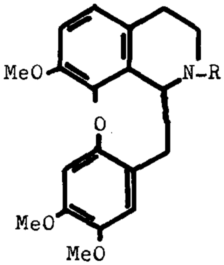
Tetrahedron Letters No.24, pp. 1897-1899, 1965. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESES OF (+)-CULARIMINE AND (+)-CULARINE

Tetsuji Kametani and Shiroshi Shibuya
Pharmaceutical Institute, School of Medicine,
Tohoku University
No. 85, Kitayobancho, Sendai, Japan

(Received 30 March 1965; in revised form 23 April 1965)

The total syntheses of (±)-cularimine (I) and (±)-cularine (II) have already been described (1,2,3,4,5), confirming the structures proposed by Manske for the alkaloids. However, the total syntheses of optically active (+)-cularimine (I) (6,7), m.p. 102°, isolated from <u>Dicentra eximia</u>, and (+)-cularine (II), isolated from <u>Corydalis claviculata</u>, <u>Dicentra cucullaria</u>, <u>D. eximia</u>, <u>D. formosa</u>, and <u>D. oregana</u> by Manske (7,8), have not yet been achieved.



I : R=H
II : R=Me

The purpose of the present investigation was to study the resolution of (±)-cularimine in order to obtain the (+)-cularimine-(+)-tartrate and (+)-cularimine as possible intermediates for the synthesis of (+)-cularine. The Eschweiler-Clarke reaction of (+)-cularimine was studied, leading eventually to a synthesis of natural (+)-cularine.

Optical resolution of (±)-cularimine (II) obtained according to our procedures (1,2,5) was effected with (+)- and (-)-tartaric acid in acetone.

Recrystallization of (+)-cularimine-(+)-tartrate from chloroform-methanol gave colourless cubes, m.p. 205 - 206° (Found: C, 57.25; H, 5.79; N, 3.06. $C_{19}H_{21}O_4N\cdot C_4H_6O_6$ requires C, 57.86; H, 5.70; N, 2.93%), which were converted into (+)-cularimine (lit. m.p. 102°) (8), $[\alpha]_D= +259.5^\circ$ (C=0.94 in MeOH) (Found: C, 69.90; H, 6.45; N, 4.13. $C_{19}H_{21}O_4N$ requires C, 69.70; H, 6.47; N, 4.28%) by treatment with potassium carbonate solution.

Recrystallization of (-)-cularimine-(-)-tartrate from chloroform-methanol gave colourless cubes, m.p. 205 - 206° (Found: C, 58.35; H, 5.50; N, 3.15. $C_{19}H_{21}O_4N\cdot C_4H_6O_6$ requires C, 57.86; H, 5.70; N, 2.93%), which were converted into (-)-cularimine, $[\alpha]_D= -262.9^\circ$ (C=2.13 in MeOH) (Found: C, 69.56; H, 6.48; N, 4.14. $C_{19}H_{21}O_4N$ requires C, 69.70; H, 6.47; N, 4.28%) by the same procedure as above.

Each of the optically active compounds (I) so obtained melted at 100 - 101°, after recrystallization from ether, and a mixture of the two optical isomers in acetone gave the racemic cularimine (I) which melted at 141 - 142°.

Methylation of the (+)-cularimine by the Eschweiler-Clarke reaction afforded (+)-cularine, $[\alpha]_D= +284^\circ$ (C=0.92 in MeOH), whose infrared spectra (in chloroform) were superimposable on those of natural cularine, $[\alpha]^{25}_{D}$= +285° (C=0.8 in MeOH), donated by Dr. Manske. (+)-Cularine was also characterized as its oxalate, m.p. 244 - 245° (decomp.) (Found: C, 61.04; H, 5.69; N, 3.19. $C_{20}H_{23}O_4N\cdot C_2H_2O_4$ requires C, 61.24; H, 5.84; N, 3.25%). Both specimens showed a NMe stretching vibration at 2809 $cm.^{-1}$ (in $CHCl_3$). This fact reveals that the total syntheses of (+)-cularimine (I) and (+)-cularine (II) have been accomplished.

We express our deep gratitude to Dr. R. H. F. Manske for a gift of natural cularine.

REFERENCES

1. T. Kametani and K. Fukumoto, Chem. & Ind., 1963, 291.
2. T. Kametani and K. Fukumoto, J. Chem. Soc., 1963, 4289.
3. T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, Tetrahedron Letters, 1964, 25.
4. T. Kametani, S. Shibuya, S. Seino and K. Fukumoto, J. Chem. Soc., 1964, 4146.
5. T. Kametani, S. Shibuya, and I. Noguchi, J. Pharm. Soc. Japan (Yakugaku Zasshi), 85, in press.
6. R. H. F. Manske, Canad. J. Res., 18B, 97 (1940).
7. R. H. F. Manske, J. Amer. Chem. Soc., 72, 55 (1950).
8. R. H. F. Manske, Canad. J. Res., 16B, 88 (1938).