1038. *Cularine and Related Compounds. Part XIII.*[1] *Total Syntheses of (+)-Cularimine and (+)-Cularine*[2]

By T. Kametani and S. Shibuya

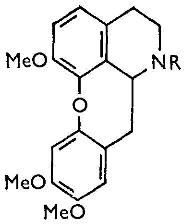
Optical resolution of (±)-cularimine (II) was effected with (+)- and (−)-tartaric acid. Hydrolysis of (+)-cularimine (+)-tartrate gave (+)-cularimine, and Eschweiler–Clarke reaction of (+)-cularimine gave (+)-cularine.

The total syntheses of (±)-cularimine (I) and (±)-cularine (II) have already been described,[3-6] confirming the structures proposed by Manske for the alkaloids. However, the total syntheses of optically active (+)-cularimine (I),[7,8] m. p. 102°, isolated from *Dicentra eximia*, and (+)-cularine (II), isolated from *Corydalis claviculata, Dicentra cucullaria, D. eximia, D. formosa*, and *D. oregana* by Manske [8,9] have not yet been achieved.

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 (+)-cularine.

Optical resolution of (±)-cularimine (II), obtained according to our procedures,[5,6] was effected with (+)- and (−)-tartaric acid in acetone. (+)- Cularimine(+)-tartrate was converted into (+)-cularimine by treatment with potassium carbonate solution. (−)-Cularimine (−)-tartrate was converted into (−)-cularimine by the same procedure.

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



(I: R = H)
(II: R = Me)

Methylation of the (+)-cularimine by the Eschweiler–Clarke reaction afforded (+)-cularine, whose infrared spectrum (in chloroform) was superimposable on that of natural cularine, donated by Dr. Manske. (+)-Cularine was also characterised as its oxalate. Both specimens showed an NMe stretching vibration at 2809 cm.$^{-1}$ (in chloroform), confirming that the total syntheses of (+)-cularimine (I) and (+)-cularine (II) have been accomplished.

Experimental

Infrared spectra were measured on a type EPI-2 Hitachi infrared spectrophotometer. Rotation was determined on a type PO–B (No. 053—4) Hitachi polarimeter. M. p.s were determined on a Kofler hot stage apparatus.

(+)-Cularimine (+)-tartrate and (−)-Cularimine (−)-tartrate.—A solution of (+)-tartaric acid (160 mg.) in acetone (10 ml.) was added to a solution of (±)-cularimine (I) (400 mg.) in acetone (10 ml.). The above mixture became turbid and a small amount of oily precipitate formed. A mixture of acetone (3 ml.) and chloroform (7—10 ml.) was added to the solution, which became clear on warming. After 2—3 days at room temperature the crude tartrate was precipitated and collected by filtration to afford colourless cubes (120 mg.), m. p. 192—195°. After the filtrate had been left for a long time, an additional amount of colourless cubes (107

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[1] Part XII, T. Kametani, S. Shibuya, and I. Noguchi, *J. Pharm. Soc. Japan*, 1965, **85**, 667.

[2] This forms Part CXXX of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.

[3] T. Kametani and K. Fukumoto, *Chem. and Ind.*, 1963, 291.

[4] T. Kametani and K. Fukumoto, *J.*, 1963, 4289.

[5] T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *Tetrahedron Letters*, 1964, 25.

[6] T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *J.*, 1964, 4146.

[7] R. H. F. Manske, *Canad. J. Res.*, 1940, **18**, *B*, 97.

[8] R. H. F. Manske, *J. Amer. Chem. Soc.*, 1950, **72**, 55.

[9] R. H. F. Manske, *Canad. J. Res.*, 1938, **16**, *B*, 88.

mg.), m. p. 185—190°, separated. Recrystallisation of the total product four times from ethanol–chloroform gave (+)-*cularimine* (+)-*tartrate* (110 mg.) as colourless cubes, m. p. 205—206° (Found: C, 57·25; H, 5·8; N, 3·1. $C_{19}H_{21}NO_4,C_4H_6O_6$ requires C, 57·9; H, 5·7; N, 2·9%).

The above filtrate, from which (+)-cularimine (+)-tartrate was filtered off, was concentrated, and the residue was dissolved in chloroform. The solution was basified with potassium carbonate solution. The solvent layer was separated, dried (K_2CO_3), and distilled to give a yellowish-orange syrup (200 mg.), which was dissolved in acetone (3 ml.). To the above clear solution was added (—)-tartaric acid (90 mg.) in acetone (7 ml.) to give a turbid solution, to which was added an additional mixture of acetone (5—7 ml.) and chloroform (10 ml.), and the mixture became clear on warming. After a few days, colourless cubes (90 mg.), m. p. 190—193°, separated. Additional crystals (117 mg.), m. p. 185—188°, were collected after the mother-liquor had stood for a long time. Recrystallisation of the total product from ethanol–chloroform gave (—)-*cularimine* (—)-*tartrate* (107 mg.) as colourless cubes, m. p. 205—207° (Found: C, 58·4; H, 5·5; N, 3·15%).

(+)-*Cularimine* (I).—To a suspension of (+)-cularimine (+)-tartrate (107 mg.) in chloroform was added potassium carbonate solution and the mixture was shaken for a few minutes. The chloroform layer was separated and dried (K_2CO_3). Removal of the solvent and recrystallisation from ether gave (+)-*cularimine* (I) as colourless needles (63 mg.), m. p. 101—102°, $[\alpha]_D$ +259·5° (*c* 0·94 in MeOH) (Found: C, 69·9; H, 6·45; N, 4·1. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·5; N, 4·3%).

(—)-*Cularimine* (I).—An excess of a saturated potassium carbonate solution was added to a suspension of (—)-cularimine (—)-tartrate (100 mg.) in chloroform and the mixture was shaken for a few minutes. The solvent layer was separated, dried (K_2CO_3), and distilled. Recrystallisation of the above residue from ether gave (—)-*cularimine* (55 mg.) as colourless needles, m. p. 101—102°, $[\alpha]_D$ —262·9° (*c* 2·13 in MeOH) (Found: C, 69·6; H, 6·5; N, 4·1%).

(+)-*Cularine* (II).—To a mixture of 98% formic acid (0·4 ml.) and 37% formalin (0·4 ml.) was added (+)-cularimine (60 mg.), and the mixture was heated on a water-bath for 4 hr. After cooling, the mixture was decomposed with water (20 ml.), basified with concentrated ammonium hydroxide on cooling, and extracted with benzene. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave a pale yellow syrup (38 mg.), which was recrystallised from ether to afford (+)-cularine as colourless prisms, m. p. 113—114·5° (lit.,[7,9] 115°), $[\alpha]_D$ +284° (*c* 0·92 in MeOH), which rotation agreed with that of natural cularine, $[\alpha]_D^{25}$ +285° (*c* 0·8 in MeOH), donated by Dr. Manske. The infrared spectrum (in chloroform) of synthetic (+)-cularine was superimposable on that of natural cularine. Recrystallisation of its *oxalate* from methanol gave colourless cubes, m. p. 244—245° (decomp.) (Found: C, 61·0; H, 5·7; N, 3·2. $C_{20}H_{23}NO_4,C_2H_2O_2$ requires C, 61·2; H, 5·8; N, 3·25%).

(—)-*Cularine* (II).—A mixture of (—)-cularimine (50 mg.), 98% formic acid (0·4 ml.), and 37% formalin (0·4 ml.) similarly gave (—)-cularine as colourless prisms, m. p. 113—114·5°, $[\alpha]_D$ —280° (*c* 0·5 in MeOH). The infrared spectrum (in chloroform) of (—)-cularine was superimposable on that of (+)-cularine and of (±)-cularine. Recrystallisation of the *oxalate* of (—)-cularine from methanol gave colourless cubes (Found: C, 60·05; H, 5·8; N, 3·2. $C_{20}H_{23}NO_4,C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 60·0; H, 5·6; N, 3·2%).

We thank Dr. Richard H. F. Manske, Dominion Rubber Company Ltd., Research Laboratories (Guelph, Ontario, Canada), for a gift of natural cularine. We are also grateful to Mrs. F. Seto and Miss N. Nanjo for microanalyses and to Miss T. Oikawa, Pharmaceutical Institute, School of Medicine, Tohoku University, for measurement of infrared spectra.

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[*Received, April 29th*, 1965.]