Tetrahedron Letters No. 1, pp. 25-28, 1964. Pergamon Press Ltd.
Printed in Great Britain.

A TOTAL SYNTHESIS OF (±)-CULARIMINE.

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(Received 4 November 1963)

A total synthesis of cularine has already been described,[1,2] confirming Manske's structure (I)[3,4] for the alkaloid. However, a total synthesis of cularimine[4,5] (II), $C_{19}H_{21}O_4N$, which was isolated from Dicentra eximia, has not yet been elucidated.

The purpose of the present investigation was to study the cyclization of dicarboxylic acid (VII) in order to obtain the corresponding lactone (XI), and lactam (XII and XIII) as possible intermediates for the synthesis of cularimine (II); reductions of lactam (XIV) and thiolactam (XIII) were studied, leading eventually to a synthesis of cularimine that supports the structure (II).

Hydrolysis of the azlactone (VI) of the aldehyde (V),

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1 T. Kametani and K. Fukumoto, Chem & Ind. 1963, 291.

2 T. Kametani and K. Fukumoto, J. Chem. Soc. 1963, 4289.

3 R. H. F. Manske, Canad. J. Res. 18B, 97(1940).

4 R. H. F. Manske, J. Amer. Chem. Soc. 72, 55(1950).

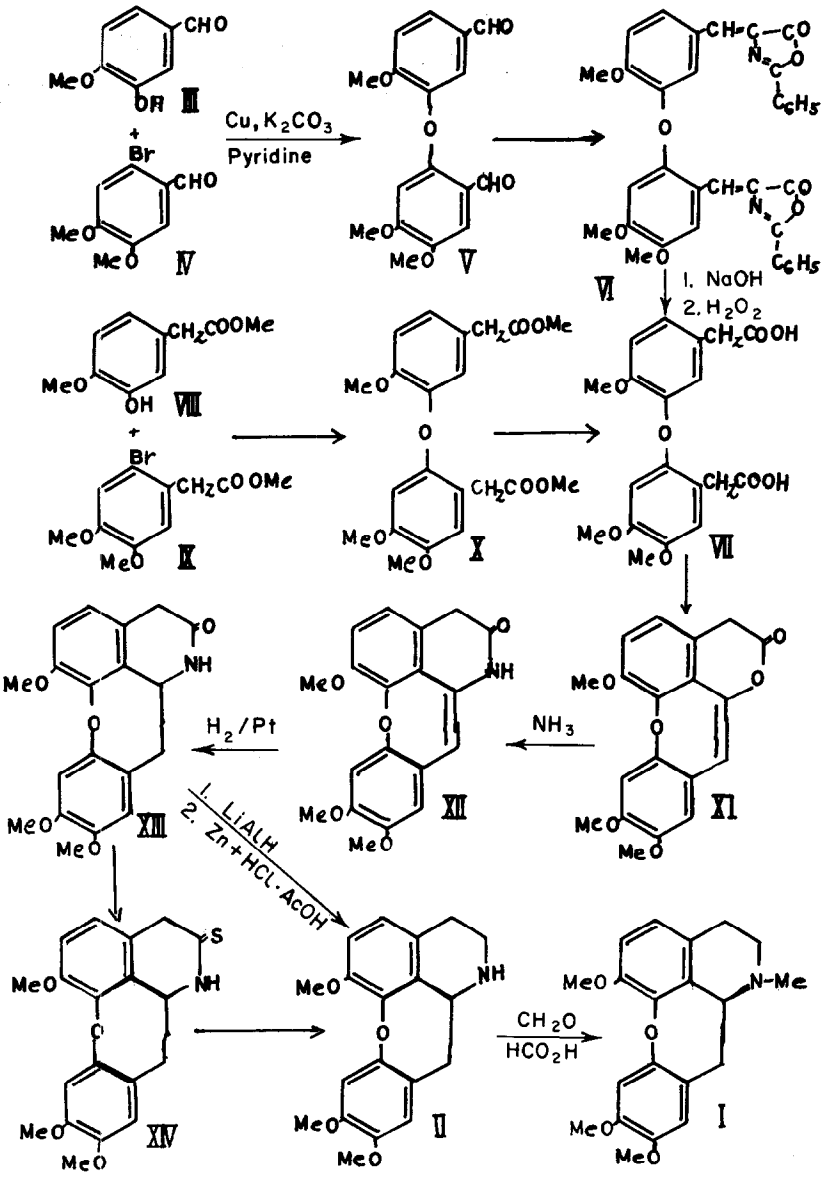
5 R. H. F. Manske, Canad. J. Res. 16B, 88(1938).

which was obtained from isovanillin (III) by the Ullmann reaction, and of the methyl ester (X), obtained from methyl homoisovanillate (VIII) and methyl 2-bromo-4,5-dimethoxyphenylacetate (IX) by the Ullmann reaction, were carried out, giving the corresponding dicarboxylic acid (VII), m.p. 175 ~ 177° (decomp.) (Found: C, 60.42; H, 5.42. $C_{19}H_{20}O_8$ requires C, 60.63; H, 5.36%). Cyclization of the above acid (VII) by polyphosphoric acid gave the lactone of 10-hydroxy-2,3,6-trimethoxy-10,11-dihydrodibenzo[b,f]oxepine-9-acetic acid (XI) as yellowish-white prisms, m.p. 205 ~ 207° (Found: C, 67.30; H, 4.88. $C_{19}H_{16}O_6$ requires C, 67.05; H, 4.75%). Catalytic hydrogenation of the lactam (XII), m.p. 245 ~ 246° (Found: C, 66.12; H, 5.14; N, 4.16. $C_{19}H_{17}O_5N,1/3H_2O$ requires C, 66.07; H, 5.12; N, 4.14%), which was obtained from the lactone (XI) by treating with an alcoholic ammonia solution, afforded 6,9,10-trimethoxy-2keto-1,3,12,12a-tetrahydro-[1]-benzoxepino[2,3,4-ij]isoquinoline (XIII), m.p. 215 ~ 216° (Found: C, 67.90; H, 5.70; N, 4.13. $C_{19}H_{19}O_5N,1/6C_6H_6$ requires C, 67.78; H, 5.69; N, 3.95%). The reduction of the lactam (XIII) with lithium aluminium hydride in tetrahydrofuran during 20 hours gave an oily substance, which was purified by chromatography on alumina. The oily residue showed an infrared ketonic band at 1720 cm^{-1}., probably due to oxidation of the methylene group during chromatography. Clemmensen reduction gave the crystalline (±)-cularimine (II), m.p. 127 ~ 128° (Found: C, 68.79; H, 6.60; N, 4.07. $C_{19}H_{21}O_4N,1/4H_2O$ requires C, 68.75; H, 6.52; N, 4.21%). Furthermore, electrolytic reduction of the thiolactam (XIV), m.p. 195 ~ 197°, which was obtained from the lactam (XIII) by potassium disulphide and phosphorus

pentasulphide in xylene, gave the above cularimine (II), but its yield was very poor.

The natural cularimine (m.p.[5] 102°) was not available for comparison. Accordingly, methylation of the racemic cularimine (II) was investigated. The Eschweiler-Clark reaction of (II) gave a base, (±)-cularine with the correct analysis[2] and an infrared spectrum (in chloroform) superimposable on that of natural cularine (I). Both specimens showed a NMe streching vibration at 2809 cm^{-1}. (in $CHCl_3$) and behaved similarly on paper chromatography. This fact reveals that the total synthesis of cularimine (II) has been accomplished. The resolution of this racemate is under investigation.

We thank Prof. Y. Kitahara, The Chemical Research Institute of Non-Aqueous Solutions, Tohoku University for microanalyses and infrared spectra, and Miss Y. Sato for her helpful experiments.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