794. *Cularine and Related Compounds. Part X.*[1] *A Total Synthesis of (±)-Cularimine.*[2]

By T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto.

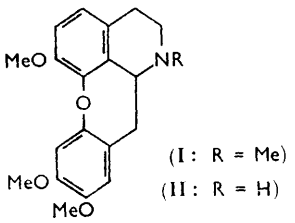
Hydrolysis of the azlactone (VIa) of the aldehyde (V) gave the diketo-di-acid (VIb), which was oxidized to the dicarboxylic acid (VII). The methyl ester (VIII), obtained by an Ullmann reaction, also gave the diacid (VII). Cyclization of this acid gave the lactone (XI). Catalytic hydrogenation of the lactam (XII), which was obtained from the lactone (XI) by ammonolysis with ethanolic ammonia, afforded the lactam (XIV). Reduction of the lactam (XIV) with lithium aluminium hydride, followed by reduction with zinc and hydrochloric acid, gave crystalline (±)-cularimine (II), which was also obtained by electrolytic reduction of the thiolactam (XV). Eschweiler–Clarke reaction of cularimine gave (±)-cularine, whose infrared and mass spectra were identical with those of (+)-cularine.

A total synthesis of cularine has already been described,[3-5] confirming Manske's structure (I)[6,7] for the alkaloid. However, a total synthesis of cularimine[7,8] (II), $C_{19}H_{21}O_4N$, which was isolated from *Dicentra eximia*, has not yet been achieved.

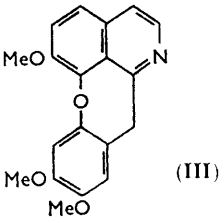
In an earlier Paper,[4] we showed that hydrogenation of the isoquinoline derivative (III) gave a cularimine-like compound, m. p. 106—107°, but in quantities too small for conversion into pure (±)-cularimine.

[1] Part IX, Kametani, Shibuya, Seino, and Fukumoto, *Tetrahedron Letters*, 1964, 25.
[2] This forms Part C of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
[3] Kametani and Fukumoto, *Chem. and Ind.*, 1963, 291.
[4] Kametani and Fukumoto, *J.*, 1963, 4289.
[5] Part VIII, Kametani and Ogasawara, preceding Paper.
[6] Manske, *Canad. J. Res.*, 1940, **18**b, 97.
[7] Manske, *J. Amer. Chem. Soc.*, 1950, **72**, 55.
[8] Manske, *Canad. J. Res.*, 1938, **16**b, 88.

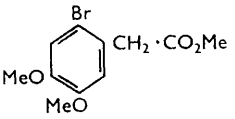
The purpose of the present investigation was to study the cyclization of the dicarboxylic acid (VII) in order to obtain the corresponding lactone (XI), and lactams (XII) and (XIV) as possible intermediates for the synthesis of cularimine (II); the reduction of the lactam



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



(III)

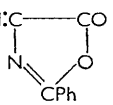


(IV)

(XIV) and the thiolactam (XV) was studied, leading eventually to a synthesis of cularimine which supports structure (II).

Hydrolysis of the azlactone (VIa) of the aldehyde (V), which was obtained from isovanillin by the Ullmann reaction, gave the corresponding diketo-diacid (VIb), which was converted into the dicarboxylic acid (VII) by oxidation with hydrogen peroxide. Saponification of the methyl ester (VIII), prepared by the Ullmann reaction,[9] also afforded the dicarboxylic acid (VII).

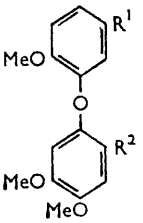
(V) $R^1 = R^2 = CHO$

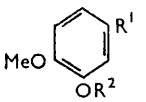
(VIa) $R^1 = R^2 =$ 

(VIb) $R^1 = R^2 = CH_2{\cdot}CO{\cdot}CO_2H$

(VII) $R^1 = R^2 = CH_2{\cdot}CO_2H$

(VIII) $R^1 = R^2 = CH_2{\cdot}CO_2Me$





(IX: $R^1 = CH_2{\cdot}CO_2H$, $R^2 = H$)

(X: $R^1 = CH_2{\cdot}CO_2Me$, $R^2 = H$)

Among various published procedures [10–15] for the preparation of 3-hydroxy-4-methoxyphenylacetic acid (IX) from isovanillin, that of Grundon and Perry [14] was found the most convenient. The Willgerodt–Kindler method was also tried but gave a poor yield.[15]

Cyclization of the above acid (VII) with polyphosphoric acid gave the lactone of 11-hydroxy-4,7,8-trimethoxydibenz[*b*,*f*]oxepin-1-ylacetic acid (XI). Catalytic hydrogenation of the lactam (XII), which was obtained from the lactone (XI) by treatment with ethanolic ammonia, afforded the ketone (XIV). In this case, ammonolysis of the lactone (XIII), which was obtained from (XI) by catalytic hydrogenation, resulted in failure, even when carried out under pressure in a sealed tube, and the starting material was recovered.

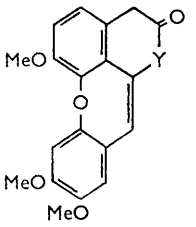
Reduction of the lactam (XIV) with lithium aluminium hydride in tetrahydrofuran for 20 hr. gave an oily substance, which, on attempted purification by recrystallization from ether, yielded a small amount of crystalline (±)-cularimine (II). An absorption band at 1720 cm.$^{-1}$ in the infrared spectrum of the oily residue from the mother-liquor indicated the presence of a keto-group, probably due to oxidation of the methylene group.

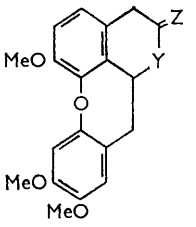
Reduction of the above ketonic compound with zinc in acetic acid–concentrated hydrochloric acid gave crystalline (±)-cularimine (II), m. p. **141—142°**. Furthermore, electrolytic reduction of the thiolactam (XV), which was obtained from the lactam (XIV) by treatment with potassium sulphide and phosphorus pentasulphide in xylene, gave the above cularimine (II), but in very poor yield.

[9] Kametani, Fukumoto, and Nakano, *J. Pharm. Soc. Japan*, 1962, **82**, 1548.
[10] Späth and Lang, *Monatsh.*, 1921, **42**, 273.
[11] Hahn and Schulz, *Ber.*, 1939, **72**, 1302.
[12] Bersch, *Arch. Pharm.*, 1939, **277**, 271.
[13] Fischer and Hibbert, *J. Amer. Chem. Soc.*, 1947, **69**, 1208.
[14] Grundon and Perry, *J.*, 1954, 3531.
[15] Niimi, Sempuku, and Oyasu, *J. Pharm. Soc. Japan*, 1962, **82**, 639.

Natural cularimine (lit.,[8] m. p. 102°) was not available for comparison. Accordingly, methylation of the racemic cularimine (II) was investigated. Eschweiler–Clarke reaction of (II) gave an oily substance, which again showed a weak ketonic band at 1720 cm.$^{-1}$, probably due to oxidation of the methylene group during the reaction. Accordingly,

(XI: Y = O)
(XII: Y = NH)





(XIII: Y = O, Z = O)
(XIV: Y = NH, Z = O)
(XV: Y = NH, Z = S)

purification of the above crude substance by reduction with zinc and acid gave (±)-cularine (I) with an infrared spectrum (in chloroform) superimposable on that of natural cularine. This substance showed no depression of melting point on admixture with authentic (±)-cularine.[4] In this case, reduction of the crude methylated product with sodium borohydride did not remove the ketonic band. Both specimens showed $\nu_{max.}$ (in chloroform) 2809 cm.$^{-1}$ (NMe), and behaved similarly on paper chromatography. Furthermore, the mass spectrum of the racemate was identical with that of (+)-cularine.[16] These facts reveal that the total syntheses of (±)-cularimine (II) and (±)-cularine (I) had been accomplished.

Experimental

4,5,6′-Trimethoxy-2,3′-bis-(5-oxo-2-phenyloxazol-4-yl)phenoxybenzene (VIa).—The aldehyde [5] (V) (0·9 g.), hippuric acid (1·2 g.), sodium acetate (0·47 g.), and acetic anhydride (1·75 g.), were heated at 110° in an oil-bath for a short time. The orange solution which formed quickly solidified. The mixture was heated on a water-bath for 1 hr., cooled, ethanol (20 ml.) was added, and the mixture set aside for 4 hr. The yellowish precipitate was collected, washed with hot water, and recrystallized from benzene–light petroleum, to afford yellowish-brown crystals of the bisazlactone (VIa) (1·3 g.), m. p. 258° (Found: C, 70·0; H, 4·2; N, 4·8. $C_{35}H_{26}N_2O_8$ requires C, 69·8; H, 4·4; N, 4·7%), $\nu_{max.}$ (KBr) 1790 and 1650 cm.$^{-1}$ (lactone C:O and >C=C< or >C=N–).

4,5,6′-Trimethoxy-2,3′-bis(methoxycarbonylmethyl)phenoxybenzene (VIII).—Methyl 3-hydroxy-4-methoxyphenylacetate (X) (6 g.) [prepared from the acid (IX) [14] by treatment with methanol in concentrated sulphuric acid], methyl 2-bromo-4,5-dimethoxyphenylacetate (IV) (9·6 g.), copper powder (0·36 g.), potassium carbonate (5·04 g.), and pyridine (0·6 ml.) were gradually heated, with shaking, in an oil-bath for 1·5 hr. until the temperature of the mixture reached 170—175° (a vigorous gas evolution was observed at this temperature). The mixture was cooled and extracted with chloroform. The extract was washed with 5% sodium hydrogen carbonate, 10% sodium hydroxide, and water, dried (Na_2SO_4), and evaporated to give an oil. Distillation of the product *in vacuo* afforded as the first fraction a viscous oil, b. p. 165—170°/7 mm., which solidified as colourless needles, m. p. 67—68°, of the starting acid (IX). The second fraction gave the ester (VIII) (5 g.) as a yellow oil, b. p. 191—193°/0·01 mm., with a yellowish-green fluorescence (Found: C, 62·3, 62·2; H, 6·1, 6·2. $C_{21}H_{24}O_8$ requires C, 62·4; H, 6·0%).

The above sodium hydrogen carbonate washings were acidified with 10% hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford the acid (IX) (3 g.). The above sodium hydroxide washings, on similar treatment, yielded the diacid (VII) (2 g.) (see below).

4,5,6′-Trimethoxy-2,3′-bis(carboxymethyl)phenoxybenzene (VII).—(*a*) The above azlactone (VI) (5 g.) in 10% sodium hydroxide (40 ml.) was heated under reflux in an oil-bath for 13 hr. (copious evolution of ammonia was observed). The mixture was cooled and filtered. 15% Hydrogen peroxide (20 ml.) was added dropwise to the filtrate at <15°, and the mixture was set

[16] Ohashi, Wilson, Budzikiewicz, Shamma, Slusarchyk, and Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2807.

aside overnight, acidified with 10% hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue was repeatedly extracted with hot light petroleum to remove benzoic acid. Recrystallization of the residual powder from ethyl acetate–hexane gave the *diacid* (VII) (1·2 g.) as colourless cubes, m. p. 175—177° (decomp.) (Found: C, 60·4; H, 5·4. $C_{19}H_{20}O_8$ requires C, 60·6; H, 5·4%), $\nu_{max.}$ (KBr) 3000 (OH) and 1710 cm.$^{-1}$ (C:O), $\delta_{max.}$ (KBr) 1410 cm.$^{-1}$ (active methylene).

(*b*) A solution of the above ester (VIII) (1 g.) in 5% ethanolic potassium hydroxide (40 ml.) was refluxed on a water-bath for 10 hr., and distilled. The residue was taken up in water, filtered, and neutralized with 10% hydrochloric acid. The colourless needles which separated were recrystallized from ethyl acetate–hexane to afford the diacid (VII) (0·8 g.) as colourless cubes, m. p. 175—176°, identical with that obtained in (*a*).

11-*Hydroxy*-4,7,8-*trimethoxydibenz*[b,f]*oxepin*-1-*ylacetic Acid Lactone* (XI).—The above acid (VII) (0·5 g.) was added to polyphosphoric acid [from 85% phosphoric acid (4·2 g.) and phosphorus pentoxide (7·5 g.)]; the temperature rose to 85° and a brownish-black vitreous substance was formed. The mixture was kept at 65° for 2 hr., cooled, decomposed with ice–water, and extracted with ether. Evaporation of the dried extract gave a resinous brown substance. Recrystallization from benzene–hexane gave the *lactone* (XI) as yellow cubes, m. p. 205—207° (Found: C, 67·3; H, 4·9. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·8%), $\nu_{max.}$ (KBr) 1770 and 1710 (lactone) and 1640 cm.$^{-1}$ (C:C).

2,3-*Dihydro*-6,9,10-*trimethoxy*-1H-[1]*benzoxepino*[2,3,4-ij]*isoquinol*-2-*one* (XII).—To a saturated ammonia solution in dry ethanol (50 ml.) was added the above lactone (XI) (0·5 g.), and the mixture was refluxed in an oil-bath at 120° for 40 min. The lactone dissolved within a few minutes, and the yellowish lactam (XII) gradually began to separate. Removal of the solvent gave yellowish crystals which were soluble only in acetic acid or a large amount of dioxan; the solution in dioxan had a yellowish-green fluorescence. Recrystallization from dioxan afforded the *lactam* (XII) as yellow cubes, m. p. 245—246° (Found: C, 66·1; H, 5·1; N, 4·2. $C_{19}H_{17}NO_5,\frac{1}{3}H_2O$ requires C, 66·1; H, 5·1; N, 4·1%), $\nu_{max.}$ (KBr) 3450 [NH and OH (water of crystallization)], 1660 (C:O), and 1635 cm.$^{-1}$ (conjugated >C=C<).

10,11-*Dihydro*-11-*hydroxy*-4,7,8-*trimethoxydibenz*[b,f]*oxepin*-1-*ylacetic Acid Lactone* (XIII).—A suspension of the above lactone (XI) (0·7 g.) in 5% sodium hydroxide (2 ml.), after being heated on a water-bath for a few minutes, formed a solution to which was added methanol (13 ml.), and sodium borohydride (0·5 g.) in small portions with stirring. After the addition of the reagent, the mixture was stirred for 1 hr., acidified with concentrated hydrochloric acid, and the methanol distilled off. The resulting colourless precipitate (0·5 g.), on recrystallization from ethanol, gave the *lactone* as colourless plates, m. p. 188·5—190° (Found: C, 66·2; H, 5·3. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3%), $\nu_{max.}$ (KBr) 1780 cm.$^{-1}$ (C:O).

2,3,12,12a-*Tetrahydro*-6,9,10-*trimethoxy*-1H-[1]-*benzoxepino*[2,3,4-ij]*isoquinol*-2-*one* (XIV).—The lactam (XII) (0·5 g.) in acetic acid (70 ml.) and dioxan (30 ml.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (0·5 g.), giving a yellowish-green, clear solution. Filtration and removal of the solvent *in vacuo* gave a brown oil which was recrystallized from benzene to give the *lactam solvate* (0·4 g.) as yellow prisms, m. p. 215—216° (Found: C, 67·9; H, 5·7; N, 4·1. $C_{19}H_{19}NO_5,\frac{1}{6}C_6H_6$ requires C, 67·8; H, 5·7; N, 4·0%), $\delta_{max.}$ (KBr) 680 cm.$^{-1}$ (unsubstituted benzene). Recrystallization of the crude product from ethyl acetate gave the unsolvated *lactam*, pale yellow cubes, m. p. 215—216° (Found: C, 66·5; H, 5·3; N 4·1. $C_{19}H_9NO_5$ requires C, 66·9; H, 5·6; N, 4·1%).

2,3,12,12a-*Tetrahydro*-6,9,10-*trimethoxy*-1H-[1]*benzoxepino*[2,3,4-ij]*isoquinoline* [(±)-*Cularimine*] (II).—The preceding lactam (XIV) (2 g.) in dry tetrahydrofuran (80 ml.) was gradually added to a stirred suspension of lithium aluminium hydride (2 g.) in tetrahydrofuran (80 ml.) at room temperature. The mixture was refluxed for 15 hr., cooled in an ice-bath, and the excess of reagent decomposed by dropwise addition of wet ether then water. After removal of the solvent, the residue was extracted with 10% hydrochloric acid (2 × 25 ml.), and the extract was washed with benzene. The aqueous layer was basified with concentrated aqueous ammonia and extracted with benzene. Removal of the washed and dried (Na_2SO_4) solvent gave a brown oil (0·9 g.) which was chromatographed on alumina (24 g.). A yellow powder (0·1 g.), m. p. 134—137°, was obtained from the first (benzene) eluate, and colourless needles (0·1 g.) m. p. 190—191°, from the second (chloroform) eluate. The latter compound was not investigated.

The former showed a weak ketonic band at 1720 cm.$^{-1}$ probably due to contamination by the

ketone. Repeated recrystallization weakened this band, but it was not removed completely. A mixture of the above crude product (40 mg.), zinc powder (0·4 g.), aqueous (1 : 2) acetic acid (7·5 ml.), and concentrated hydrochloric acid (2·5 ml.), was heated on a water-bath for 2 hr., filtered from unreacted zinc powder, basified with concentrated sodium hydroxide, and extracted with benzene. The product (30 mg.) resulting from evaporation of the dried (Na_2SO_4) benzene extracts crystallized from ether as *cularimine hydrate*, yellow cubes, m. p. 127·5—128·5° (Found: C, 68·8; H, 6·5; N, 4·2; H_2O, 1·7. $C_{19}H_{21}NO_4,\frac{1}{4}H_2O$ requires C, 68·8; H, 6·6; N, 4·1; H_2O, 1·4%), $\lambda_{max.}$ (KBr) 3455 cm.$^{-1}$ (H_2O of crystallization), but no ketonic absorption. The hydrate, when dried over phosphorus pentoxide at 70°/4 mm. for 30 hr., gave (±)-cularimine, colourless needles, m. p. 141—142° * (Found: C, 69·8; H, 6·6; N, 4·5. Calc. for $C_{19}H_{21}NO_4$: C, 69·7; H, 6·5; N, 4·3%), $\lambda_{max.}$ (KBr) 3333 cm.$^{-1}$ (NH), but no hydroxyl absorption.

2,3,12,12a-*Tetrahydro*-6,9,10-*trimethoxy*-1H-[1]*benzoxepino*[2,3,4-ij]*isoquinoline*-2-*thione* (XV).—A mixture of the preceding lactam (XIV) (1 g.), finely powdered potassium disulphide (0·6 g.), and phosphorus pentasulphide (0·8 g.) in xylene (100 ml.) was stirred and heated at 80° for 3 hr., then filtered hot. The residue was repeatedly extracted with hot xylene (50 ml.). Evaporation of the combined extracts under reduced pressure gave a yellowish-brown powder (0·5 g.). Since its purification by recrystallization was too difficult, the crude thiolactam, $\lambda_{max.}$ (KBr) 3210 (NH) and 1134 cm.$^{-1}$ (C:S), was used in the following reaction.

Electrolytic Reduction of the Thiolactam (XV).—A suspension of the crude thiolactam (1 g.) in 25% sulphuric acid (50 ml.) and ethanol (30 ml.) was reduced electrolytically at 8—10 A, using a lead cathode, with stirring at 25°; evolution of hydrogen sulphide was observed. After 6 hr. the mixture was filtered from insoluble substances and distilled. The residue was basified with 10% sodium hydroxide and extracted with benzene. Removal of the washed and dried (Na_2SO_4) solvent afforded pale brown crystals (20 mg.). Recrystallization from ether gave (±)-cularimine (II) as pale yellow cubes, m. p. 127—128°, whose infrared spectrum was identical with that of the product obtained by reduction of the lactam (XIV) with lithium aluminium hydride.

Eschweiler–Clarke Reaction of (±)-*Cularimine* (II). *A Total Synthesis of* (±)-*Cularine* (I).—To a solution of the above base (II) (40 mg.) in 98% formic acid (0·2 ml.), 37% formalin (0·2 ml.) was added, and the mixture was heated on a water-bath for 4 hr. After cooling, water was added, and the resulting solution was basified with concentrated aqueous ammonia. The mixture was extracted with benzene, and the extract was washed, dried (Na_2SO_4), and evaporated to give a pale yellow oil (30 mg.), which showed a weak ketonic band at 1720 cm.$^{-1}$, probably due to contamination with a small amount of the oxidized product.

The oil was heated with zinc powder (0·1 g.) in 33% acetic acid (1·5 ml.) and concentrated hydrochloric acid (0·5 ml.) on a water-bath for 1·5 hr., and worked up as usual to yield a pale yellow oil (15 mg.). Recrystallization from ether afforded (±)-cularine as pale yellow cubes, m. p. and mixed m. p. 113—114° (lit.,[4] 113—114°). The infrared spectra of synthetic and natural cularine in chloroform were identical, R_F (synthetic) 0·81, (authentic [4]) 0·81 [butanol–acetic acid–water (4 : 1 : 5) as solvent; 1% aqueous potassium permanganate as spray].

Reduction of the above crude product (20 mg.) with sodium borohydride (0·1 g.) in 95% methanol (615 ml.) did not afford pure cularine (I).

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PHARMACEUTICAL INSTITUTE, SCHOOL OF MEDICINE,
TOHOKU UNIVERSITY, JAPAN. [*Received, November 28th*, 1963.]

* The lower m. p. (106—107°) previously reported [4] for (±)-cularimine was due to inadequate purification and we now amend it to 141—142°.