

A Synthesis of *O*-Ethylcularidine (Studies on the Syntheses of Heterocyclic Compounds. Part CCCXXXIII(1))

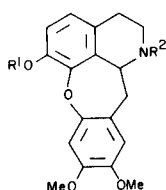
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In order to confirm the structure of cularidine (I), *O*-ethylcularidine (II) was synthesized and shown to be identical with the naturally occurring *O*-ethylcularidine on the basis of NMR spectroscopy and the R_f values.

Cularidine, an alkaloid isolated by Manske from *Dicentra cucullaria* (3) and *Corydalis claviculata* (4), has been assigned the structure I by chemical (5) and spectroscopic methods (6). We are currently investigating the total synthesis of cularidine (I) and wish to report the synthesis of *O*-ethylcularidine (II) by a standard method (7) (8), thus corroborating the structure (I) proposed by Manske (5) and Kametani (6).

CHART 1

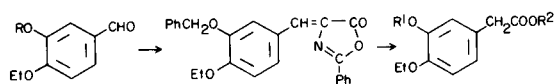


I: $R^1 = H, R^2 = Me$
 II: $R^1 = Et, R^2 = Me$
 XIV: $R^1 = Et, R^2 = H$

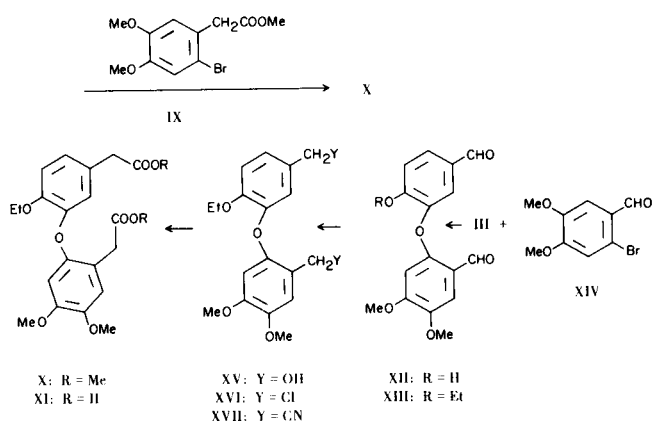
Ethylation of protocatechualdehyde gave III which was benzylated giving 3-benzyloxy-4-ethoxybenzaldehyde (IV). Compound IV was reacted with hippuric acid to give the azalactone (V) which was hydrolysed and then oxidized with hydrogen peroxide to give the phenylacetate derivative (VI). Hydrolysis of VI with hydrochloric acid gave the hydroxycarboxylic acid (VII), whose ester (VIII) was subjected to the Ullmann reaction with methyl 2-bromo-4,5-dimethoxyphenylacetate (IX) in the presence of copper and potassium carbonate in pyridine to afford the diester (X). The diester (X) was converted into the dicarboxylic acid (XI), which was also synthesized by the following route. The hydroxy-dialdehyde (XII) (8) was ethylated with ethyl *p*-toluenesulfonate to give the ethoxydialdehyde (XIII), which was also obtained by direct Ullmann reaction between the hydroxyaldehyde (III) and 6-bromoveratraldehyde (XIV). Reduction of this dialdehyde (XIII) with sodium borohydride, followed by chlorination of the resulting dialcohol (XV) with thionyl chloride, gave the

dichloride (XVI), which was converted into the dinitrile (XVII). Saponification of this dinitrile (XVII) afforded the dicarboxylic acid (XI).

CHART 2



III: $R = H$
 IV: $R = CH_2Ph$
 V:
 VI: $R^1 = CH_2Ph, R^2 = Me$
 VII: $R^1 = R^2 = H$
 VIII: $R^1 = H, R^2 = Me$

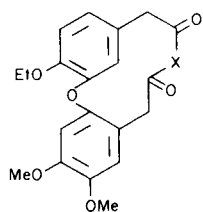


X: $R = Me$
 XI: $R = H$
 XII: $R = H$
 XIII: $R = Et$
 XV: $Y = OH$
 XVI: $Y = Cl$
 XVII: $Y = CN$

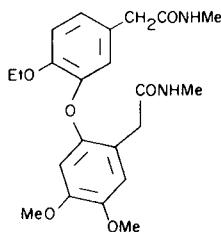
The formation of the acid anhydride (XVIII) and imide (XIX) of the dicarboxylic acid as possible intermediates to *O*-ethylcularidine (II), was attempted unsuccessfully by several methods. In the case of the attempted imide formation, the diamide XX was obtained by treatment with *N*-methylformamide.

Cyclization of the dicarboxylic acid (XI) with polyphosphoric acid gave the lactone (XXI), whose structure was easily confirmed by NMR which showed the olefinic proton at τ 3.43 and the two aromatic protons at 3.13 and 3.04 as a typical AB type quartet ($J_{AB} = 8$ cps.). Ammonolysis of the lactone (XXI) with ammonia in ethanol gave the unsaturated lactam (XXII), which upon

CHART 3



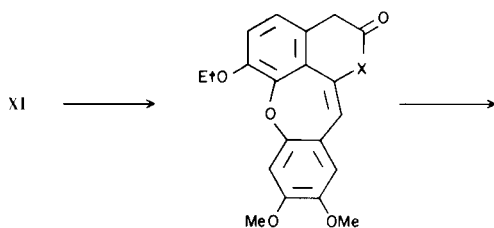
XVIII: X = O
XIX: X = NMe



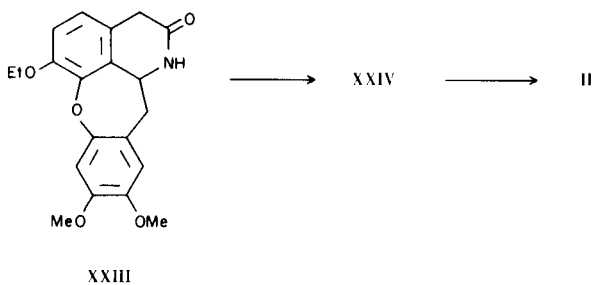
XX

catalytic reduction in the presence of Adams catalyst afforded the saturated lactam (XXIII). Reduction of this lactam (XXIII) with lithium aluminum hydride in tetrahydrofuran or with sodium borohydride in dry pyridine gave the tetrahydroisoquinoline (XXIV), whose structure was proved by mass spectrometry which showed the characteristic pattern (M^+ : 341, M^+-15 : 326) of the cularine type compounds (6,8,9,10). Methylation of XXIV by a modified Eschweiler-Clarke reaction with formalin and sodium borohydride afforded *O*-ethylcularidine (II), which was characterized as its picrate, m.p. 209-210°. The structure of II was also confirmed by its mass spectrum which showed the molecular ion at m/e 355 and *p*-quinolid ion at m/e 340 (M^+-15). The synthetic base was identical with the natural *O*-ethylcularidine (5) in IR and NMR spectra and its R_f value, thus confirming the proposed structure (I) for the cularidine.

CHART 4

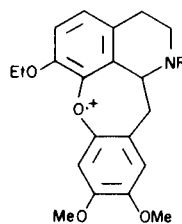


XXI: X = O
XXII: X = NH

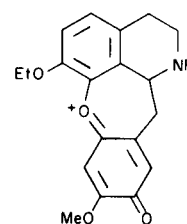


XXIII

CHART 5



M^+
R = H or Me



M^+-15
R = H or Me

In the NMR spectra of both the synthetic and natural *O*-ethylcularidine, two kinds of signals whose resonance centered at τ 5.95 and τ 5.91 corresponding to the methylene group of the ethoxyl group were observed. This phenomena of two different signals corresponding to OCH_2CH_3 may be caused by the hindrance of free rotation of the ethyl group with an oxepine ring.

EXPERIMENTAL

4-Ethoxy-3-hydroxybenzaldehyde (III).

To a stirred suspension of 69 g. of protocatchualdehyde, 300 ml. of dimethylformamide, and 52 g. of anhydrous potassium carbonate was added dropwise 77 g. of ethyl sulfate in a current of nitrogen during 30 minutes while heating at 80°. After the addition heating was continued for an additional 30 minutes. The reaction mixture was poured into 1.5 litres of ice-water and the crystals which separated were collected, washed with water, and recrystallized from 50% aqueous ethanol to give 70 g. (84%) of III as colorless needles, m.p. 127-128° (lit., (11) m.p. 127-128°).

3-Benzyloxy-4-ethoxybenzaldehyde (IV).

A mixture of 83 g. of III, 350 ml. of dimethylformamide, 64 g. of benzyl chloride, and 35 g. of anhydrous potassium carbonate was heated in an oil-bath at 150-160° for 1 hour while stirring and the reaction mixture was poured into 1.5 litres of ice-water. The crystals which separated were collected, dried in air on a filter, and recrystallized from methanol to afford 116 g. (91%) of the aldehyde (IV) as colorless prisms, m.p. 77-78°, ν max (cm^{-1}) (potassium bromide) 1692 (C=O), 751, 699 (monosubstituted benzene).

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.04; H, 6.39.

4-(3-Benzyloxy-4-ethoxybenzal)-2-phenyl-2-oxazoline-5-one (V).

A mixture of 10.4 g. of IV, 7.8 g. of hippuric acid, 12 g. of sodium acetate, and 12 ml. of acetic anhydride was heated in an oil-bath at 110°. After the reaction mixture had become clear and then solidified, the resulting mixture was heated on a water bath at 100° for 1 hour, 20 ml. of ethanol was added after cooling and the mixture was set aside overnight. After the excess of acetic anhydride had been decomposed, the crystals were collected, washed with a small amount of ethanol and then hot water, and dried in air to give 10.5 g. (66%) of IV as yellow crystals, m.p. 137-139°. Recrystallization from benzene afforded yellow needles, m.p. 138-139°, ν max (cm^{-1}) (potassium bromide) 1790, 1766 (sh) (C=O), 1650 (C=N- and C=C).

Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 74.85; H, 5.50; N, 3.44.

Methyl 3-Benzyloxy-4-ethoxyphenylacetate (VI).

A mixture of 10 g. of IV and 50 ml. of 10% sodium hydroxide was heated for 7 hours. After cooling, 5 ml. of 40% sodium hydroxide was added to the reaction mixture followed by a solution of 4 ml. of 30% hydrogen peroxide in 4 ml. of water at $<10^\circ$. After standing at room temperature for 15 hours, the mixture was acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to give the residue, to which was added a solution of 0.7 g. of *p*-toluenesulfonic acid in 70 ml. of methanol. The resultant mixture was refluxed for 7 hours. After removal of the solvent, the residue was extracted with benzene. The extract was washed with water, 10% sodium hydroxide, and water, dried over sodium sulfate and evaporated to give an oil which was distilled *in vacuo* yielding methyl benzoate as the first fraction. Further distillation gave 4.7 g. (63%) of a colorless viscous oil, b.p. 170-175° (0.5 mm Hg), which solidified upon cooling. Recrystallization from methanol gave colorless needles of VI, m.p. 86-87°; ν max (cm^{-1}) (potassium bromide) 1736 (C=O), 754, 702 (mono-substituted benzene).

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.85; H, 6.85.

4-Ethoxy-3-hydroxyphenylacetic Acid (VII).

A mixture of 4.5 g. of VI and 90 ml. of methanol-concentrated hydrochloric acid (1:1) was refluxed in a current of nitrogen for 6 hours. After removal of the solvent, the resulting solid was washed with water, dried and recrystallized from benzene to give 2.5 g. (85%) of VII as colorless prisms, m.p. 120.5-122°, ν max (cm^{-1}) (potassium bromide) 3380 (OH), 2500-3200 (carboxylic OH), 1702 (C=O).

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.08; H, 6.29.

Methyl 4-Ethoxy-3-hydroxyphenylacetate (VIII).

A mixture of 0.3 g. of *p*-toluenesulfonic acid, 2.3 g. of VII and 30 ml. of dry methanol was refluxed in a current of nitrogen for 7 hours and the solvent was distilled off to give the residue, which was extracted with ether. The extract was washed with saturated sodium chloride and sodium bicarbonate, dried over sodium sulfate and evaporated to give an oil which was distilled *in vacuo* to afford 2.1 g. (89%) of VIII as a colorless viscous oil, b.p. 139° (2 mm Hg).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.83; H, 6.84.

6'-Ethoxy-4,5-dimethoxy-2,3'-bis(methoxycarbonylmethyl)phenoxybenzene (X).

A mixture of 2 g. of VIII, 2.8 g. of IX, 4 g. of dry potassium carbonate, 0.4 g. of copper powder, and 40 ml. of dry pyridine was heated in an oil-bath at 170-175° for 15 hours. After removal of an inorganic substance by filtration, the excess pyridine was distilled off to give a syrup, which was extracted with chloroform. The extract was washed with 10% hydrochloric acid, water, and saturated sodium bicarbonate. The alkaline solution was, after extraction with benzene, acidified with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to give a residue, which was recrystallized from ethyl acetate-hexane to afford 0.1 g. of XI as colorless prisms, m.p. 161-163°. This was identical with an authentic sample (XI) described below.

The chloroform layer was washed with 10% sodium hydroxide, water, dried over sodium sulfate and evaporated to give an oil, which was distilled *in vacuo* to afford 0.8 g. (20%) of X as a pale yellow viscous oil, b.p. 125° (0.05 mm Hg), ν max (cm^{-1}) (potassium bromide) 1744, 1731 (C=O).

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 62.83; H, 6.25.

6'-Ethoxy-4,5-dimethoxy-2,3'-bis(hydroxycarbonylmethyl)phenoxybenzene (XI).

A mixture of 0.8 g. of X, 20 ml. of ethanol, 2 g. of potassium hydroxide, and 2 ml. of water was refluxed for 4 hours. After removal of the solvent, the residue was dissolved in water and the solution was washed with benzene. The alkaline solution was acidified with concentrated hydrochloric acid and treated as above to give 0.7 g. of XI as colorless prisms, m.p. 161-163°, ν max (cm^{-1}) (potassium bromide) 3200-2500 (OH); NMR τ (deuteriochloroform) 8.63 (3H, triplet, $J = 7$ cps, CH_2CH_3), 6.82, 6.56 (each 2H, two singlets, 2 x CH_2CO_2H), 6.30, 6.15 (each 3H, two singlets, 2 x OCH_3), 5.92 (2H, quartet, C_6-H), 3.28 - 3.13 (4H, aromatic protons).

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.86; H, 5.63.

6'-Ethoxy-4,5-dimethoxyphenoxybenzene-2,3'-dialdehyde (XIII).

A. Ethylation of XII.

A mixture of 20 g. of XII (8), 100 ml. of dimethylformamide, 13 g. of ethyl *p*-toluenesulfonate, and 5 g. of potassium carbonate was refluxed mildly, and the reaction mixture was poured into an excess of water and extracted with chloroform. The extract was washed with water, 10% potassium hydroxide, and water, dried over magnesium sulfate and evaporated to give the residue, which was recrystallized from benzene-hexane to afford 9.5 g. (44%) of XIII as pale yellow prisms, m.p. 124-125°, ν max (cm^{-1}) (potassium bromide) 1705, 1684 (C=O).

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.32; H, 5.53.

B. Formation of XIII by Ullmann Reaction.

A mixture of 54.5 g. of V, 80 g. of XIV, 45 g. of anhydrous potassium carbonate, 10 g. of copper powder, and 10 ml. of pyridine was heated in an oil-bath at 140-150° for 30 minutes and at 150-155° for 30 minutes while stirring. After the reaction, the reaction mixture was filtered together with 1 litre of benzene. The filtrate was washed with 10% potassium hydroxide, 10% hydrochloric acid, and water, dried over sodium sulfate, evaporated to about 300 ml. and set aside. The crystals which separated were collected and washed with a small amount of methanol to give 64 g. (59%) of XIII as pale yellowish-brown crystals, m.p. 123-125°. Recrystallization from benzene-hexane gave pale yellow prisms, m.p. 124-125°, which were identical with the above sample.

6'-Ethoxy-4,5-dimethoxyphenoxybenzene-2,3'-dimethanol (XV).

To a cooled and stirred suspension of 33 g. of XIII in 500 ml. of methanol was added 10 g. of sodium borohydride. The mixture was stirred at room temperature for 1 hour. After the solvent had been evaporated, the resulting syrup was diluted with water and the mixture was extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and evaporated to give the residue which was recrystallized from benzene-*n*-hexane to afford 30 g. (90%) of XV as colorless plates, m.p. 81-82°, ν max (cm^{-1}) (potassium bromide) 3560-3280 (broad OH).

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.84; H, 6.86.

6'-Ethoxy-4,5-dimethoxy-2,3'-bis(chloromethyl)phenoxybenzene (XVI).

To a suspension of 30 g. of XV in 500 ml. of dry ether was added 30 ml. of thionyl chloride slowly and the resulting clear mixture was allowed to stand at room temperature for 2 hours. After the reaction mixture had been shaken for a while, the precipitate was collected by filtration and recrystallized from benzene-*n*-hexane to give 28 g. (84%) of XVI as colorless prisms, m.p. 136-137.5°, whose Beilstein test was positive; ν max (cm^{-1}) (potassium bromide) 679 (C-Cl).

Anal. Calcd. for $C_{18}H_{20}Cl_2O_4$: C, 58.23; H, 5.43. Found: C, 58.12; H, 5.43.

6'-Ethoxy-4,5-dimethoxy-2,3'-bis(cyanomethyl)phenoxybenzene (XVII).

To a solution of 40 g. of XVI in 600 ml. of ethyl acetate was added a mixture of 80 g. of sodium iodide and 80 g. of sodium cyanide and the mixture was heated under reflux for 12 hours. An excess of water was added to the reaction mixture after cooling. The water layer was extracted with benzene. The extract was added to the above ethyl acetate layer and the combined solvents were washed with 10% potassium hydroxide, water, 10% hydrochloric acid and water, dried over sodium sulfate and evaporated to give a yellow-orange syrup, which solidified on being triturated with methanol. Recrystallization from benzene-*n*-hexane afforded 28 g. (74%) of XVII as colorless needles, m.p. 146-147°, ν max (cm^{-1}) (potassium bromide) 2350 ($C\equiv N$).

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.53; H, 6.03; N, 7.77.

Formation of XI by Hydrolysis of XVII.

To a solution of 60 g. of XVII in 600 ml. of dioxane was added a solution of 120 g. of potassium hydroxide in 600 ml. of methanol and 120 ml. of water and the mixture was refluxed for 15 hours. After the solvent had been evaporated, the resulting residue was dissolved in water. This solution was washed with ether, acidified with concentrated hydrochloric acid, and then extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from ethyl acetate-hexane to give 61 g. (93%) of XI as colorless cubes, m.p. 161-163°, which were identical to an authentic sample of XI described previously.

6'-Ethoxy-4,5-dimethoxy-2,3'-bis(methylaminocarbonylmethyl)phenoxybenzene (XX).

A solution of 1.5 g. of XI in 3 ml. of *N*-methylformamide was heated for 10 hours at 200°. After cooling, the reaction mixture was poured into water and extracted with chloroform. The extract was washed with water, saturated sodium bicarbonate, and water. Evaporation of the solvent gave the residue which was recrystallized from chloroform-*n*-hexane to give 0.9 g. of XX as colorless cubes, m.p. 171-173°; ν max. (cm^{-1}) (potassium bromide), 3285 (NH), 1658 (C=O); NMR, τ (in deuteriochloroform) 8.86 (3H, triplet, $J = 7$ cps, CH_2CH_3), 7.31, 7.26 (each 3H, two singlets, $J = 4$ cps, $2 \times NHCH_3$), 6.59, 6.54 (each 2H, two singlets, $2 \times COCH_2$), 6.25, 6.13 (each 3H, two singlets, $2 \times OCH_3$), 5.89 (2H, quartet, $J = 7$ cps, CH_2CH_3), 3.48 (1H, singlet, C_6-H), 3.28-3.04 (4H, aromatic protons).

Anal. Calcd. for $C_{22}H_{28}N_2O_6$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.75; H, 6.81; N, 6.70.

4-Ethoxy-11-hydroxy-7,8-dimethoxybenz[*b,f*]oxepine-1-ylacetic acid Lactone (XXI).

A mixture of 46 g. of phosphoric acid (which was prepared from 16 g. of 85% phosphoric acid and 30 g. of phosphorous pentoxide) and 2.3 g. of XI was heated for 1 hour at 60° on a water bath. The dark-reddish mixture was poured into ice-water and extracted with ether. The extract was washed with water, saturated sodium bicarbonate, and water, and evaporated to give the residue which was recrystallized from benzene-*n*-hexane to give 0.7 g. of XXI as yellow prisms, m.p. 179-181°; ν max (cm^{-1}) (potassium bromide) 1773 (C=O), 1652 (C=C); NMR, τ (deuteriochloroform) 8.47 (3H, triplet, $J = 7$ cps, CH_2CH_3), 6.28 (2H, singlet, $CH_2C=O$), 6.16, 6.11 (each 3H, two singlets, $2 \times OCH_3$), 5.84 (2H, quartet, $J = 7$ cps, CH_2CH_3), 3.43 (1H, singlet, $C_{10}-H$), 3.37 (1H, singlet, C_6-H), 3.13 (1H, singlet, C_9-H), 3.13 (1H, AB type doublet, $J_{AB} = 8$ cps, C_3-H), 3.04 (1H, AB type doublet, $J_{AB} = 8$ cps, C_2-H).

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.88; H, 5.31.

6-Ethoxy-2,3-dihydro-9,10-dimethoxy-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline-2-one (XXII).

A suspension of 1.7 g. of XXI in 250 ml. of dry ethanol saturated with ammonia gas was heated for 1 hour at 100° on a water bath. After the solvent had been evaporated, the residue was recrystallized from ethanol to give 1.3 g. of XXII as yellow plates, m.p. 222-224°; ν max (cm^{-1}) (potassium bromide) 1665 (C=O), 1631 (C=C); NMR, τ (deuteriochloroform) 8.47 (3H, triplet, $J = 7$ cps, CH_2CH_3), 6.32 (2H, singlet, C_3-H_2), 6.17, 6.12 (each 3H, two singlets, $2 \times OCH_3$), 5.85 (2H, quartet, $J = 7$ cps, CH_2CH_3), 3.73 (1H, broad singlet, $C_{12}-H$), 3.36 (1H, singlet, C_8-H), 3.11 (1H, singlet, $C_{11}-H$), 3.10 (1H, AB type doublet, $J_{AB} = 8$ cps, C_5-H), 2.99 (1H, AB type doublet, $J_{AB} = 8$ cps, C_4-H).

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 68.33; H, 5.91; N, 4.05.

6-Ethoxy-2,3,12,12a-tetrahydro-9,10-dimethoxy-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline-2-one (XXIII).

A solution of 1.5 g. of XXII in 100 ml. of acetic acid-dioxane (1:1) was shaken in the presence of hydrogen over Adams platinum catalyst. After the reaction, the catalyst was filtered off, the organic solvent was evaporated, and the remaining residue was extracted with chloroform. The extract was washed with sodium bicarbonate solution. The organic layer was dried over sodium sulfate and evaporated to give a solid, which was recrystallized from ethyl acetate to afford 1.1 g. of XXIII as colorless prisms, m.p. 197-200°; ν max (cm^{-1}) (potassium bromide) 3300 (NH), 1670 (C=O); NMR, τ (deuteriochloroform) 8.50 (3H, triplet, $J = 7$ cps, CH_2CH_3), 6.78 (2H, doublet $J = 8$ cps, $C_{12}-H_2$), 6.43 (2H, singlet, C_3-H_2), 6.19 (3H, singlet, $C_{10}-OCH_3$), 6.14 (3H, singlet, C_9-OCH_3), 4.73 (1H, broad triplet, $J = 8$ cps, $C_{12a}-H$), 3.41 (1H, singlet, C_8-H), 3.17 (1H, singlet, $C_{11}-H$), 3.15 (2H, singlet, C_4-H and C_5-H).

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.15; H, 5.96; N, 3.94. Found: C, 67.33; H, 6.01; N, 3.96.

6-Ethoxy-2,3,12,12a-tetrahydro-9,10-dimethoxy-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline (XXIV).

A. Reduction of XXIII by Lithium Aluminum Hydride.

To a suspension of 1 g. of lithium aluminum hydride in 10 ml. of dry tetrahydrofuran (THF) was added a solution of 1 g. of XXIII in 40 ml. of THF and the mixture was refluxed for 17 hours. Aqueous THF was then added to the cooled reaction

mixture to decompose the excess lithium aluminum hydride. After removal of an inorganic substance by filtration, the organic solvent was evaporated to give the residue which was dissolved in chloroform. The chloroform layer was washed with water, dried over sodium sulfate and evaporated to give a syrup which was chromatographed on 25 g. of alumina. The benzene eluate gave a pale yellow viscous oil, which was triturated with *n*-hexane to give a solid, whose recrystallization from ether afforded 82 mg. of XXIV as pale yellow prisms, m.p. 141-142°; NMR, τ (deuteriochloroform) 8.55 (3H, triplet, $J = 7$ cps, CH_2CH_3), 7.35 - 6.79 (6H, multiplet, $\text{C}_2\text{-H}_2$, $\text{C}_3\text{-H}_2$, $\text{C}_{12}\text{-H}_2$), 6.22 (3H, singlet, $\text{C}_{10}\text{-OCH}_3$), 6.15 (3H, singlet, $\text{C}_9\text{-OCH}_3$), 5.95, 5.92 (each 1H, two quartet, $J = 7$ cps, CH_2CH_3), 5.20 (1H, triplet, $J = 8$ cps, $\text{C}_{12a}\text{-H}$), 3.45 (1H, singlet, $\text{C}_8\text{-H}$), 3.21 (1H, AB type doublet, $J_{\text{AB}} = 9$ cps, $\text{C}_4\text{-H}$), 3.13 (1H, singlet, $\text{C}_{11}\text{-H}$). Starting material (110 ml.) was recovered from the remaining benzene-chloroform eluate (100:20).

Anal. Calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_4\text{N}$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.41; H, 6.75; N, 3.93.

B. Reduction of XXIII in Pyridine by Sodium Borohydride.

To a solution of 100 mg. of XXIII in 3 ml. of dry pyridine was added 40 mg. of sodium borohydride and, after refluxing for 20 hours mildly, the mixture was evaporated to give the residue which was extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to give a reddish-brown viscous oil, which was chromatographed on 350 mg. of alumina. The benzene eluate was collected, evaporated, and recrystallized from ether to afford 4 mg. of crystals, whose R_f value (0.20) on TLC [silica gel G; acetone-chloroform (1:1); the spot was detected by Dragendorff reagent] was identical with that of an authentic sample of XXIV and no mixed melting point depression was observed.

6-Ethoxy-2,3,12,12a-tetrahydro-9,10-dimethoxy-1-methyl-[1]-benzoxepino[2,3,4-*ij*]isoquinoline (*O*-Ethylcularidine) (II).

To a solution of 38 mg. of XXIV in 3 ml. of methanol-chloroform (1:1) was added 30 mg. of 47% formalin and the mixture was stirred for 30 minutes at room temperature. After 25 mg. of sodium borohydride had been added to the reaction mixture, the stirring was continued for 30 minutes at room temperature. After removal of the solvent, the residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 31 mg. of a pale yellow syrup, whose IR and NMR spectra were superimposable on those of natural *O*-ethylcularidine (5) prepared from natural cularidine; NMR, τ (deuteriochloroform) 8.55 (3H, triplet, $J = 7$ cps, CH_3CH_2), 7.38 (3H, singlet, N-CH_3), 7.22 - 6.54 (6H, multiplet),

6.21 (3H, singlet, $\text{C}_{10}\text{-OCH}_3$), 6.14 (3H, singlet, $\text{C}_9\text{-OCH}_3$), 5.95, 5.91 (each 1H, two quartets, $J = 7$ cps, CH_3CH_2), 5.45 (1H, quartet, $J_{\text{AX}} = 4$ cps, $J_{\text{BX}} = 12$ cps, $\text{C}_{12a}\text{-H}$), 3.46 (1H, singlet, $\text{C}_8\text{-H}$), 3.21 (1H, AB type doublet, $J = 8$ cps, $\text{C}_5\text{-H}$), 3.12 (1H, singlet, $\text{C}_{11}\text{-H}$), 3.10 (1H, AB type doublet, $J = 8$ cps, $\text{C}_4\text{-H}$). Since attempts to crystallize the free base (II) were unsuccessful, the picrate was prepared and recrystallized from acetone-methanol giving yellow crystals, m.p. 209-211°.

Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{NO}_4 \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 55.48; H, 4.83; N, 9.59. Found: C, 55.40; H, 4.73; N, 9.28.

Acknowledgment

We thank Dr. R. H. F. Manske for a gift of natural cularidine. We gratefully thank President Dr. M. Terasaka of Tokyo College of Pharmacy and Dr. Y. Nagase for their encouragement. We also thank Dr. S. Shibuya, Pharmaceutical Institute, Tohoku University, for his helpful discussion from the mass spectral point of view. We are grateful to the Analytical Centre of Tokyo College of Pharmacy for microanalyses and NMR spectral determination.

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Received October 6, 1969

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