Studies on the Syntheses of Heterocyclic Compounds. Part CCLXXIX (1). Synthesis of *O*-Isobutylcularidine

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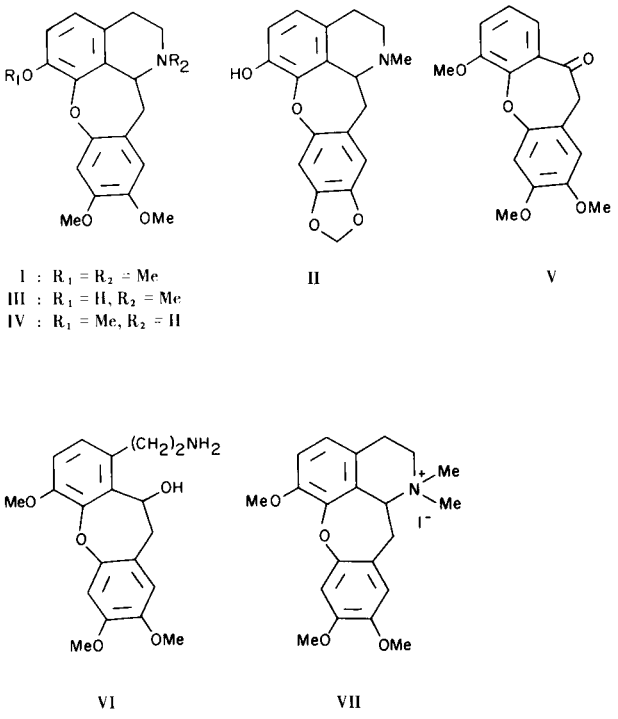
Although various methods of oxepine formation from phenoxybenzene dicarboxylic acids was attempted, only 11-hydroxy-4-isobutoxy-7,8-dimethoxydibenz[*b*,*f*]oxepin-1-ylacetic acid lactone (XXX) was synthesized successfully. Compound XXX gave *O*-isobutylcularidine (XXXVIIb) in a few steps. Our synthetic *O*-isobutylcularidine was identical with that prepared from natural cularidine proving the structure for cularidine proposed by Manske. However, dealkylation of synthetic *O*-isobutylcularidine was unsuccessful.

Cularidine, $C_{19}H_{21}NO_4$, found in very small amounts in *Dicentra cucullaria* (3) with cularicine, forms a hydrochloride that is only sparingly soluble in cold water or methanol. The free base is sparingly soluble in ether and when recrystallized from methanol-ether melts at 157°. It has two methoxyl groups and one phenolic hydroxyl group. Its relation to cularine is shown by the fact that when methylated with diazomethane it yields cularine (I), but the position of the hydroxyl group was only determined recently by the degradation of the *O*-ethyl ether in the following sequence: reaction with sodium liquid ammonia, methylation of the resultant phenolic base followed by two successive Hofmann degradations, and finally oxidation of the unsaturated nitrogen free compound. The main product was 4-ethoxyphthalic acid and therefore cularidine was assigned the structure of compound III (4,5) whose structure has also been confirmed by mass and nmr spectra (6). Since the characteristic structure having an oxepine ring was proposed for cularine (7), Kametani and coworkers have totally synthesized cularine (II) and cularimine (IV) *via* the keto-oxepine (V) as an intermediate (8). Cularine methiodide (VII) was also synthesized *via* the hydroxyoxepine derivative (VI) (9). In addition, an alternative total synthesis of cularine and cularimine was accomplished by cyclization of the dicarboxylic acid (VIII) with polyphosphoric acid to give the lactone (IX) (11) which was treated successively giving cularine and cularimine. However, the total syntheses of cularicine and cularidine have not yet been achieved. We wish now to report an approach to the total synthesis of cularidine, namely, the synthesis of *O*-isobutylcularidine.

CHART 1



I : $R_1 = R_2 = Me$
III : $R_1 = H, R_2 = Me$
IV : $R_1 = Me, R_2 = H$

II V VI VII

In general, the conversion of the dicarboxylic acid to the oxepine ring through the lactone seems to be important in order to synthesize the cularine nucleus. Therefore, if the protecting group at the 6-position is well selected, the formation of the lactone as a key intermediate to cularidine should be successful. Since the benzenesulfonyl

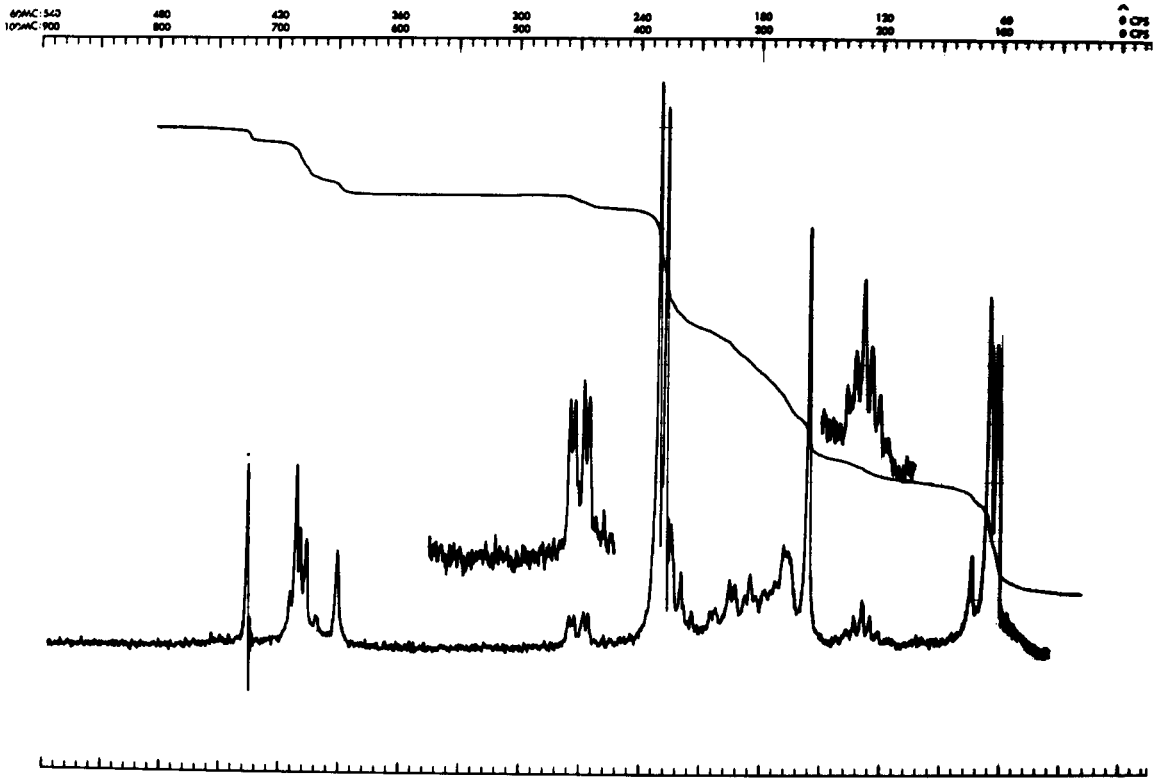


Fig. 1 The nmr spectrum of isobutylcularidine

group of the dicarboxylic acid (X) has been known to be stable in the formation of the lactone (XI) by cyclization with polyphosphoric acid (11), and, our desired lactone could not be obtained when benzyl was the protecting group (11,12), the following synthesis of the lactone (XIII) was attempted.

Ullmann reaction of the 4-benzyloxy-3-hydroxybenzaldehyde (XV) (13) (which was obtained by monobenzylation of protocatechualdehyde (XIV)) with 2-bromo-4,5-dimethoxybenzaldehyde (XVI) in the presence of anhydrous potassium carbonate and copper powder gave the dialdehyde (XVII). Sodium borohydride reduction of XVII afforded the diol (XVIII), whose chlorination with thionyl chloride, followed by cyanation of the resultant dichloride (XIX) with sodium cyanide in ethyl methyl ketone in the presence of sodium iodide, gave the nitrile (XX). Alkaline hydrolysis of XX in methanol-dioxane gave the dicarboxylic acid (XXI), whose catalytic hydrogenation in the presence of 5% palladium-charcoal in methanol afforded the debenzylated dicarboxylic acid (XXIIa).

Tosylation of XXIIa with tosyl chloride in pyridine to give the tosylate (XIIa) was unsuccessful. Furthermore, tosylation of the ester (XXIIb) also gave no oxyester (XIIb). However, after debenzylation of XX by catalytic hydrogenation in methanol-dioxane in the presence of palladium-charcoal, tosylation of the resultant dinitrile (XXIII) with tosyl chloride gave the tosylate (XXIV), which, upon treatment with dry methanol saturated with hydrochloride gas, afforded the diester (XIIb). Acidic hydrolysis of XIIb gave the dicarboxylic acid (XIIa). Attempted cyclization of XIIa with polyphosphoric acid under a variety of conditions gave no lactone (XIII), but gave instead, a resinous substance. Thus, it was found that the protection of the hydroxyl group at the 6′-position with the tosyl group was not suitable for the cyclization with polyphosphoric acid.

Next, the cyclization of the dicarboxylic acid (XXV), whose hydroxyl group at the 6′-position was protected with an isopropyl group, was attempted with polyphosphoric acid. Isopropylation of the preceding dinitrile (XXIII) with isopropyl bromide in methanol in the presence of sodium ethoxide, followed by alkaline hydrolysis of the resultant compound (XXVII), gave the dicarboxylic acid (XXV), whose cyclization with polyphosphoric acid at 40-65° afforded a resinous substance, but no lactone (XXVI).

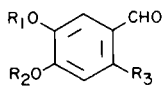
However, hydrolysis of the isobutyl derivative (XXIX) obtained by isobutylation of XXIII gave the dicarboxylic acid (XXVIII), which was cyclized with polyphosphoric

acid at 60° to give our expected lactone (XXX). The i.r. spectrum of XXX showed the absorptions due to the lactone ring at 1774 and 1742 (sh) cm^{-1} and an absorption band attributable to the double bond of C=C appeared at 1647 cm^{-1}. The nmr spectrum (deuteriochloroform) (14) showed an AB type signal (due to aromatic protons at C_2- and C_3-positions) at 2.99 and 3.11 τ, respectively and a singlet due to the C_{10}-olefinic proton at 3.40 τ. These facts support the formation of the lactone (XXX). Thus, protection with an isobutyl group was found to be suitable, but the total yield (3%) of dinitrile (XXIX) from XVIII was so poor that the following modified synthesis of XXIX was investigated. Isobutylation of XXXI, which was obtained by debenzylation with hydrochloric acid in acetic acid, gave the compound (XXXII) with isobutyl iodide or bromide in the presence of sodium ethoxide, but the yield of XXXII was very poor due to chelation between the hydroxyl and aldehyde carbonyl groups indicated by the infrared spectrum which showed the chelated hydroxy band at 2500-3200 cm^{-1}. Further, the nmr spectrum (in trifluoroacetic acid) revealed two singlets due to the aldehyde protons at -0.27 and 0.24 τ, the first of which was observed in an abnormally low field. This low field also indicated that one of the two carbonyl groups was chelated with the hydroxyl group.

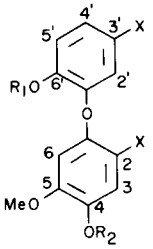
Isobutylation of XXXI with dimethylformamide in the presence of potassium carbonate was carried out to give the isobutyl derivative (XXXII) in good yield. This dialdehyde (XXXII) was converted into the dinitrile (XXIX) in 7.8% yield by way of compounds XXXIII and XXXIV.

Finally, catalytic hydrogenation of the unsaturated lactam (XXXV), which was obtained by ammonolysis of the above lactone (XXX) with ammonia in methanol

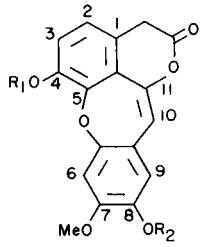
CHART 2



XIV : $R_1 = R_2 = R_3 = H$
XV : $R_1 = R_3 = H$, $R_2 = CH_2Ph$
XVI : $R_1 = R_2 = Me$, $R_3 = Br$



VIII : $R_1 = R_2 = Me$, $X = CH_2COOH$
X : $R_1 = Me$, $R_2 = SO_2Ph$
XIIa : $R_1 =$ Tosyl, $R_2 = Me$, $X = CH_2COOH$
b : $R_1 =$ Tosyl, $R_2 = Me$, $X = CH_2COOMe$
XVII : $R_1 = CH_2Ph$, $R_2 = Me$, $X = CHO$
XVIII : $R_1 = CH_2Ph$, $R_2 = Me$, $X = CH_2OH$
XIX : $R_1 = CH_2Ph$, $R_2 = Me$, $X = CH_2Cl$
XX : $R_1 = CH_2Ph$, $R_2 = Me$, $X = CH_2CN$
XXI : $R_1 = CH_2Ph$, $R_2 = Me$, $X = CH_2COOH$
XXIIa : $R_1 = H$, $R_2 = Me$, $X = CH_2COOH$
b : $R_1 = H$, $R_2 = Me$, $X = CH_2COOMe$
XXIII : $R_1 = H$, $R_2 = Me$, $X = CH_2CN$
XXIV : $R_1 =$ Tosyl, $R_2 = Me$, $X = CH_2CN$
XXV : $R_1 =$ iso-Propyl, $R_2 = Me$, $X = CH_2COOH$
XXVII : $R_1 =$ iso-Propyl, $R_2 = Me$, $X = CH_2CN$
XXVIII : $R_1 =$ iso-Butyl, $R_2 = Me$, $X = CH_2COOH$
XXIX : $R_1 =$ iso-Butyl, $R_2 = Me$, $X = CH_2CN$
XXXI : $R_1 = H$, $R_2 = Me$, $X = CHO$
XXXII : $R_1 =$ iso-Butyl, $R_2 = Me$, $X = CHO$
XXXIII : $R_1 =$ iso-Butyl, $R_2 = Me$, $X = CH_2OH$
XXXIV : $R_1 =$ iso-Butyl, $R_2 = Me$, $X = CH_2Cl$

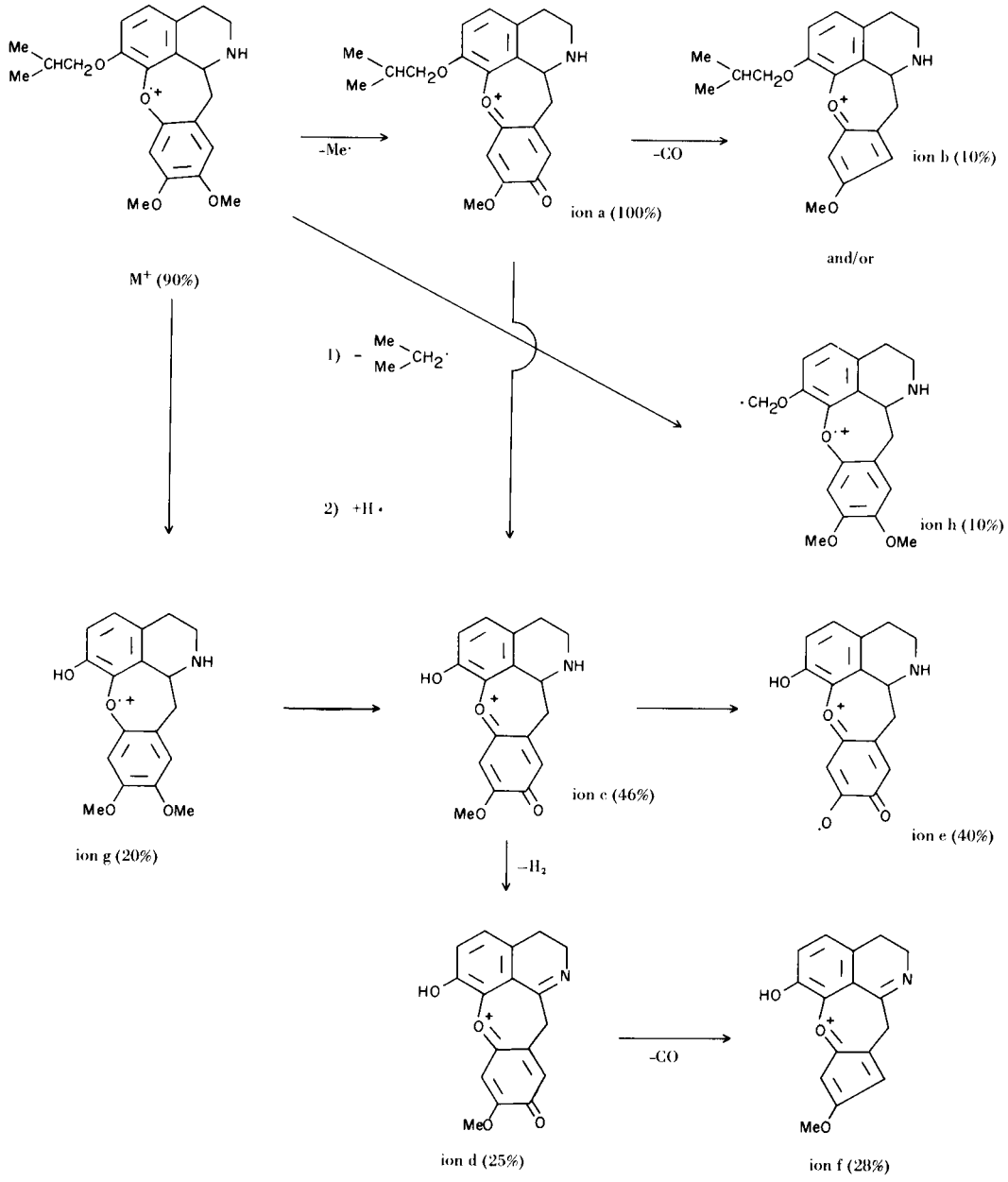


IX : $R_1 = R_2 = Me$
XI : $R_1 = Me$, $R_2 = SO_2Ph$
XIII : $R_1 =$ Tosyl, $R_2 = Me$
XXVI : $R_1 =$ iso-Propyl, $R_2 = Me$
XXX : $R_1 =$ iso-Butyl, $R_2 = Me$

according to our method (10), gave the lactam (XXXVI) in acetic acid in the presence of Adams' platinum. Reduction of XXXVI with lithium aluminum hydride, followed by alumina-chromatography, gave the expected compound (XXXVIIa) by evaporation of the first benzene eluate and the carbinolamine (XXXVIII) as a by-product by removal of the benzene-chloroform (4:1) eluant. The structures of XXXVIIa and XXXVIII were elucidated by the spectroscopic data. The mass spectra (15) especially supported these structures.

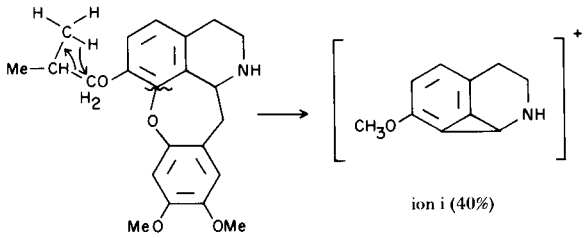
The high resolution mass spectrum of the tetrahydroisoquinoline derivative (XXXVIIa) showed the strong molecular ion at *m/e* 369.194 (calcd. for $C_{22}H_{27}NO_4$: 369.194). The base ion peak at *m/e* 354 is due to the loss of a methyl group from the *para*-orientated methoxy function forming the stable quinoid ion a. Further, loss of CO and isobutyl groups from the ion a would furnish the ion b (M^+ - 43, *m/e* 326) and ion c (M^+ - 73, *m/e* 298), respectively, the latter of which might also come from the molecular ion through the ion g. (M^+ - 56, *m/e* 313). The peak at *m/e* 326 could also be attributed to the ion h which is stabilized by the loss of the isopropyl group from the molecular ion. In addition, loss of a methyl group and two hydrogens from the ion c would furnish the ion e (M^+ - 88, *m/e* 281) and the ion d (M^+ - 75, *m/e* 296), the latter of which would give rise to the ion f (M^+ - 103, *m/e* 266) by the loss of a CO group.

CHART 3



Furthermore, a characteristic peak for cularine-type compounds was observed at *m/e* 161 and attributed to the ion i (15).

CHART 4



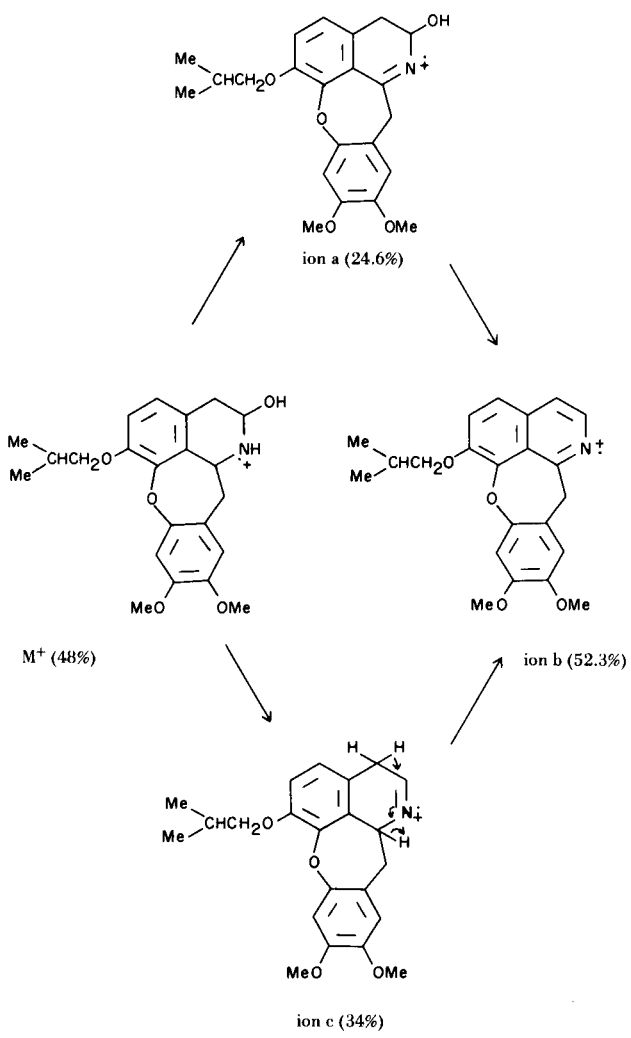
The high resolution mass spectrum of the carbinolamine by-product (XXXVIII) showed the molecular ion peak at *m/e* 385.189 (calcd. for $C_{22}H_{27}NO_5$: 385.189). Loss of two hydrogens from the molecular ion would furnish the ion a (M^+ - 2, *m/e* 383) which might decompose into the ion b. The latter ion would be stabilized by aromatization with loss of water. The ion b could also be derived from the molecular ion through the formation of the ion c (M^+ - 18, *m/e* 367) with direct dehydration, followed by dehydrogenation.

The second fragmentation mode (16) characteristic of dibenzoxepine derivatives having a methoxyl group at the position para to the biphenyl ether linkage involves loss of a methyl radical from the *para*-orientated methoxyl function giving the ion d (M^+ - 15, *m/e* 370). Further, dehydration would furnish the ion e (M^+ - 33, *m/e* 352) which then gives rise to the ion h (M^+ - 88, *m/e* 294) through the ion g (M^+ - 86, *m/e* 296) by stabilization due to aromatization. Loss of carbon monoxide from the ion i (*m/e* 309), the ion j (*m/e* 310) and the ion h would furnish the ion k (*m/e* 281), the ion l (*m/e* 280) and the ion m (*m/e* 266), respectively.

Chlorination of XXXVIII with thionyl chloride in dry ether gave the chloride (XXXIX) whose reduction with lithium aluminum hydride in tetrahydrofuran followed by alumina chromatography afforded a small amount of crystals which were identical with an authentic sample (XXXVIIa) by mixed melting point test and thin layer chromatography. Further, methylation of XXXVIIa with formalin and sodium borohydride in methanol gave the *O*-isobutylcularidine (XXXVIIb), which was shown to be identical with natural *O*-isobutylcularidine (prepared from natural cularidine) on comparison of tlc and uv spectrum. The high resolution mass spectrum also supported the structure of XXXVIIb.

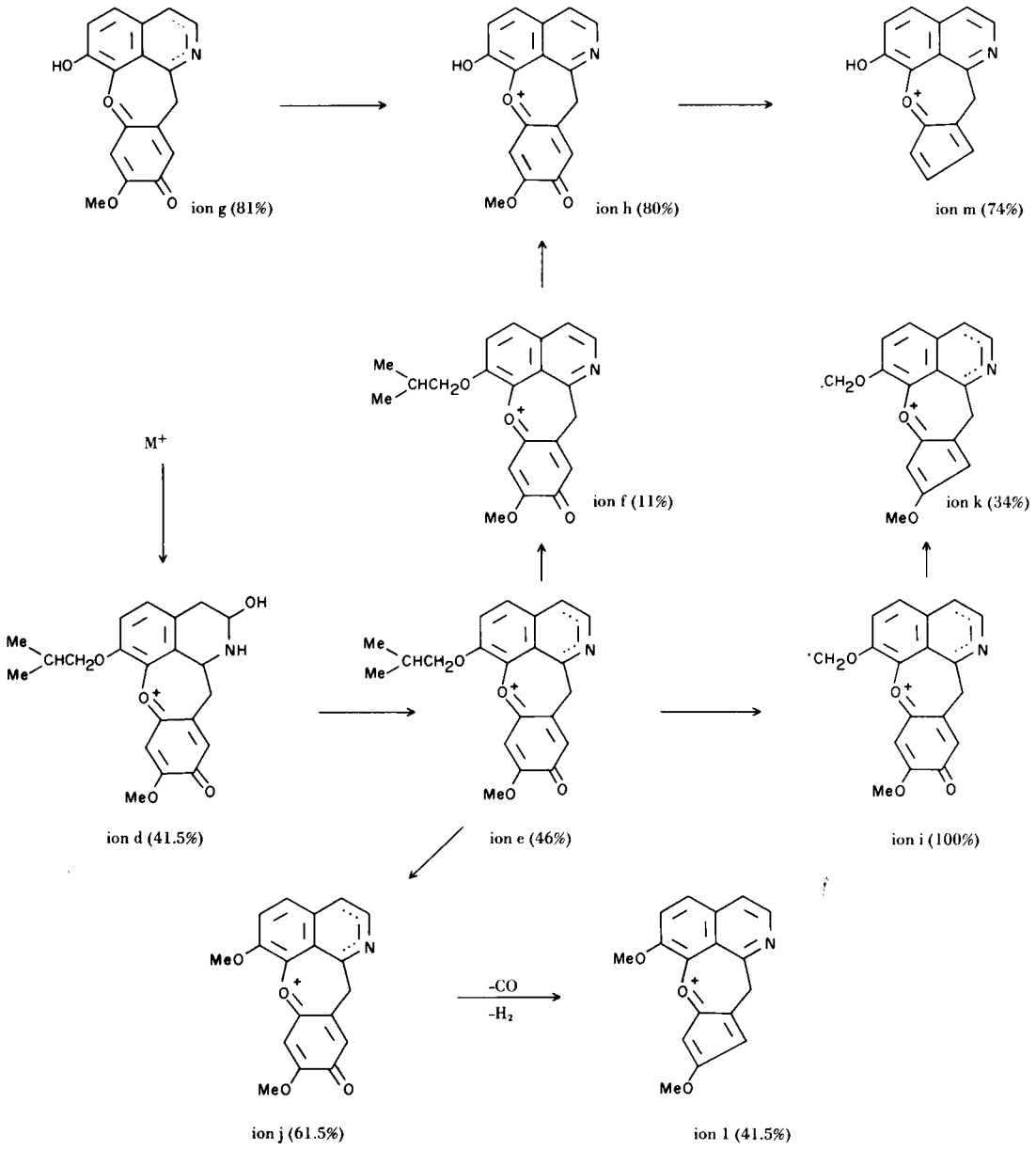
Finally, dealkylation of XXXVIIa with 48% hydrobromic acid in acetic acid at 50° was observed on tlc. The spot due to the starting material (XXXVIIa) disappeared

CHART 5



after 94 hours and that of the demethylated compound (XLa) at the C_{10}-position was observed. The same treatment of XXXVIIb also gave the demethylated compound (XLb) at the C_{10}-position (16). In order to determine the position of the methoxyl group of both specimens (XLa and XLb), the nmr spectra were investigated. With regard to the remaining methoxyl group in the demethylation of cularine (I) and cularimine (IV) with hydrobromic acid in acetic acid, Kametani, *et al.* (17) have reported the formation of compounds XLIa and XLIb monomethylated at the C_9-position by nmr spectral comparison with cularicine (II) and cularidine (III) which are not methylated at the C_6-position. The methyl signals at the C_{10}-position of cularine (I), cularidine (III) and cularimine (IV) was, in general, observed at 6.16, 6.15 and 6.17 τ, respectively, and those of three alkaloids with methyl at the C_{10}-position were at 6.21 τ (6). On the other hand, the methyl

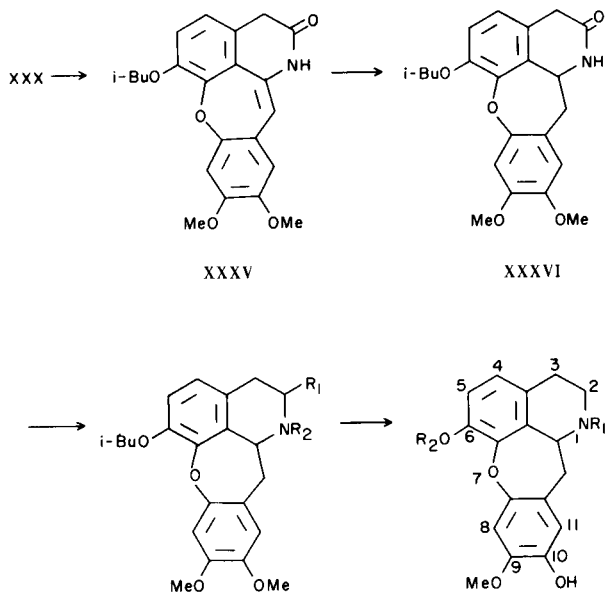
CHART 6



resonances of XXXVIIa at the C_9- and C_{10}-position were observed at 6.16 and 6.21 τ, respectively, whereas the methyl protons of XLa and XLb appeared at 6.16 τ. According to the results above, the remaining methoxyl group should be at the C_9-position.

In conclusion although the total synthesis of cularidine could not be achieved, the structure of cularidine proposed by R. H. F. Manske (4,5) was found to be correct through the synthesis of *O*-isobutylcularidine.

CHART 7



XXXV XXXVI

XXXVIIa : $R_1 = R_2 = H$
XXXVIIb : $R_1 = H$, $R_2 = Me$
XXXVIII : $R_1 = OH$, $R_2 = H$
XXXIX : $R_1 = Cl$, $R_2 = H$

XLa : $R_1 = H$, R_2 = iso-Butyl
XLb : $R_1 = Me$, R_2 = iso-Butyl
XLIa : $R_1 = Me$, $R_2 = H$
XLIb : $R_1 = R_2 = H$

EXPERIMENTAL

6′-Benzyloxy-4,5-dimethoxyphenoxybenzene-2,3′-dialdehyde (XVII).

A mixture of 57 g. of 4-benzyloxy-3-hydroxybenzaldehyde (XV), 61 g. of 2-bromo-4,5-dimethoxybenzaldehyde (XVI), 34.5 g. of anhydrous potassium carbonate, 15 g. of copper powder, and 15 ml. of dry pyridine was heated at 145° in an oil-bath for 30 minutes with stirring and then at 160° for 30 minutes. The warm reaction mixture was extracted with 800 ml. of benzene and the extract was filtered through celite. The filtrate was washed with 10% sodium hydroxide, 10% hydrochloric acid and water, dried over sodium sulfate and concentrated to a volume of ca. 100 ml., which, upon standing, gave 47.5 g. (49%) of pale brown prisms, m.p. 145-147°. Recrystallization from benzene gave the dialdehyde (XVII) as colourless prisms, m.p. 146-147.5°, ν max (potassium bromide) cm^{-1}: 1692, 1672 (C=O), δ max: 742, 700 (monosubstituted benzene).

Anal. Calcd. for $C_{23}H_{20}O_6$: C, 70.40; H, 5.14. Found: C, 70.52; H, 5.39.

6′-Benzyloxy-4,5-dimethoxyphenoxybenzene-2,3′-dimethanol (XVIII).

To a suspension of 60 g. of XVII in 800 ml. of ethanol was added in small portions 15 g. of sodium borohydride at room temperature and the mixture was refluxed for 1 hour. After the solvent had been distilled, an excess of water was added to the residue and the mixture was extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give a residue, which was recrystallized from benzene yielding 55 g. (80%) of XVIII as colorless needles, m.p. 124-124.5°, ν max (potassium bromide) cm^{-1}: 3340-3240 (OH), δ max: 734, 691 (monosubstituted benzene).

Anal. Calcd. for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.50; H, 6.08.

6′-Benzyloxy-4,5-dimethoxy-2,3′-bis(chloromethyl)phenoxybenzene (XIX).

A mixture of 75 g. of XVIII, 75 g. of thionyl chloride, 1 l. of dry ether was allowed to stand at room temperature for 2 hours and then refluxed for 2 hours. After the mixture had been concentrated to a volume of ca. 300 ml., 300 ml. of hexane was added to the resultant residue and, on standing, 69 g. (85%) of XIX, m.p. 102-104.5°, were precipitated and collected. Recrystallization from benzene-hexane gave colorless needles, m.p. 104-105°, δ max (potassium bromide) cm^{-1}: 738, 696 (monosubstituted benzene).

Anal. Calcd. for $C_{23}H_{22}Cl_2O_4$: C, 63.75; H, 5.12. Found: C, 63.30; H, 5.30.

6′-Benzyloxy-4,5-dimethoxy-2,3′-bis(cyanomethyl)phenoxybenzene (XX).

A suspension of 43 g. of XIX, 33 g. of sodium iodide and 34 g. of sodium cyanide, in 500 ml. of ethyl acetate was refluxed for 15 hours. After the reaction, the organic solvent layer was separated from the aqueous solution which was extracted with benzene. The above ethyl acetate layer was combined with the benzene extract, and the solvent was washed with 10% sodium hydroxide and water. After drying on sodium sulfate, evaporation of the extract gave a reddish-orange syrup which was chromatographed on 430 g. of alumina using benzene as an eluant. Removal of the benzene eluate gave a pale yellow viscous syrup, which upon recrystallization from benzene-hexane, gave 18 g. (44%) of XX as colorless needles, m.p. 127-128°, ν max (potassium bromide) cm^{-1}: 2250 (C=N), δ max: 742, 696 (monosubstituted benzene).

Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.92; H, 5.64; N, 6.79.

6′-Benzyloxy-4,5-dimethoxy-bis(hydroxycarbonylmethyl)phenoxybenzene (XXI).

A mixture of 4.0 g. of (XX), 65 ml. of methanol, 50 ml. of dioxane, 16 ml. of water, and 16.0 g. of potassium hydroxide was refluxed for 20 hours. After removal of the solvents, the residue was dissolved in water and the alkaline solution was washed with benzene, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated to give 3.7 g. (83%) of XXI, which upon recrystallization from ethyl acetate-hexane gave colorless needles, m.p. 169-171°. ν max (potassium bromide) cm^{-1}: 1724, 1713 (C=O), δ max 750, 696 (monosubstituted benzene).

Anal. Calcd. for $C_{25}H_{24}O_8$: C, 66.36; H, 5.35. Found: C, 66,24; H, 5.25.

6′-Hydroxy-4,5-dimethoxy-2,3′-bis(hydroxycarbonylmethyl)-phenoxybenzene (XXIIa).

A solution of 500 mg. of XXI in 20 ml. of methanol upon hydrogenation in the presence of 100 mg. of palladium-charcoal at atmospheric pressure and room temperature, absorbed the calculated amount of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to give a syrup, which was recrystallized from ethyl acetate-hexane to give 120 mg. of XXIIa as colorless needles, m.p. 139-141°.

Anal. Calcd. for $C_{18}H_{18}O_8$: C, 59.66; H, 5.01. Found: C, 60.11; H, 5.23.

6′-Hydroxy-4,5-dimethoxy-2,3′-bis(methoxycarbonylmethyl)-phenoxybenzene (XXIIb).

A solution of 250 mg. of XIIa in 3 ml. of dry methanol saturated with hydrogen chloride gas was refluxed for 8 hours, and the solvent was then distilled off, giving a syrup which was extracted with chloroform. The extract was washed with water and saturated sodium bicarbonate and extracted with 10% sodium hydroxide solution. After washing with benzene, the resultant alkaline solution was acidified with concentrated hydrochloric acid and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 130 mg. of XXIIb as a colorless oil, ν max (potassium bromide) cm^{-1}: 3575 (OH), 3359 (OH), 1748 (C=O), 1733 (C=O).

6′-Hydroxy-4,5-dimethoxy-2,3′-bis(cyanomethyl)phenoxybenzene (XXIII).

A solution of 7.0 g. of XX in 50 ml. of methanol and 140 ml. of dioxane was hydrogenated at room temperature in the presence of 2.0 g. of 10% palladium-charcoal. After the calculated amount of hydrogen had been absorbed, the catalyst was removed, the solvent was distilled off and a chloroform solution of the resultant residue was extracted with 10% sodium hydroxide solution. The alkaline solution was washed with benzene, acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate and evaporated to give a pale yellow syrup, which solidified on being triturated with hexane. Recrystallization of 4.9 g. (89%) of XXIII from ethyl acetate-hexane gave colorless needles, m.p. 130-131°. ν max (potassium bromide) cm^{-1}: 3555 (OH), 2250 (C=O).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.51; H, 5.14; N, 9.02.

4,5-Dimethoxy-6′-tosyloxy-2,3′-bis(cyanomethyl)phenoxybenzene (XXIV).

To a solution of 10.0 g. of XXIII in 35 ml. of 1 *N* sodium hydroxide solution was added dropwise with stirring a solution of 6.2 g. of tosyl chloride in 50 ml. of dry chloroform (< 10°, 30 minutes) and the stirring was continued for 1 hour. After completion of the reaction, the chloroform layer was separated, washed with 5% sodium hydroxide solution and water, dried over sodium sulfate, and evaporated to give a syrup, which upon trituration gave 8.5 g. of solid (XXIV). Recrystallization from benzene-hexane afforded colorless prisms, m.p. 146-147.5°. The test for sulfur with sodium nitroprusside was positive.

Anal. Calcd. for $C_{25}H_{22}N_2O_6S$: C, 62.76; H, 4.63; N, 5.85. Found: C, 62.81; H, 4.48; N, 6.12.

4,5-Dimethoxy-6′-tosyloxy-2,3′-bis(hydroxycarbonylmethyl)-phenoxybenzene (XIIa).

A mixture of 3.0 g. of XIIb, 20 ml. of acetone, 10 ml. of acetic acid, 25 ml. of concentrated hydrochloric acid, and 5 ml. of water was refluxed for 20 hours. The solvent was removed by distillation and the residue was extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution and extracted with saturated sodium bicarbonate solution. The resultant alkaline solution was washed with benzene, filtered, and acidified with concentrated hydrochloric acid. The pale yellow oil which separated, solidified upon standing in a refrigerator. Collection by filtration, followed by drying on a filter, gave 1.8 g. of XIIa. Recrystallization from ethyl acetate-hexane gave 1.5 g. of XIIa as colorless prisms, m.p. 161-163°. ν max (potassium bromide) cm^{-1}: 1727 (C=O), 1717 (C=O), 1376 (as SO_2), 1174 (s SO_2); nmr τ (deuteriochloroform): 7.58 (3H, singlet, C-CH_3), 6.53, 6.55 (4H, two singlets, -CH_2COOH), 6.26, 6.12 (6H, two singlets, 2 x OCH_3), 3.63 (1H, singlet, C_6-H), 3.00-3.37 (4H, multiplet, C_1′-H, C_2′-H, C_3-H), 2.15 (4H, quartet, $CH_3C_6H_4SO_2$).

Anal. Calcd. for $C_{25}H_{24}O_{10}S$: C, 58.13; H, 4.68. Found: C, 58.09; H, 4.79.

4,5-Dimethoxy-6′-tosyloxy-2,3′-bis(methoxycarbonylmethyl)-phenoxybenzene (XIIb).

A suspension of 2.5 g. of XXIV in 150 ml. of dry methanol containing dry hydrochloride gas was refluxed for 20 hours and the solvent was distilled off *in vacuo* to give a syrup which was extracted with chloroform. The extract was washed with water, 5% sodium hydroxide solution and water, dried over sodium sulfate, and evaporated to give a yellowish-orange oil. This oil was chromatographed on silica gel using chloroform as an eluant to give 2.1 g. of XIIb as a pale yellow oil, b.p. 270° (0.02 mm), ν max (chloroform) cm^{-1}: 1740 (C=O).

6′-Isopropoxy-4,5-dimethoxy-2,3′-bis(hydroxycarbonylmethyl)-phenoxybenzene (XXV).

A mixture of 1.5 g. of XXVII, 30 ml. of methanol, 25 ml. of dioxane, 6.0 g. of potassium hydroxide, and 6 ml. of water was refluxed for 20 hours and the solvent was removed by distillation. The residue was dissolved in water, the alkaline solution was washed with benzene, acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to give a syrup, which solidified on being triturated with hexane. Recrystallization of 1.3 g. of XXV from ethyl acetate-hexane gave 1.1 g. of colorless prisms, m.p. 132-134°. ν max (potassium bromide) cm^{-1}: 1730 (C=O), 1718 (C=O), 1385, 1376 (isopropyl CH).

Anal. Calcd. for $C_{21}H_{24}O_8$: C, 52.37; H, 5.98. Found: C, 62.40; H, 6.29.

6′-Isopropoxy-4,5-dimethoxy-2,3′-bis(cyanomethyl)phenoxy-benzene (XXVII).

To a solution of 0.23 g. of sodium in 80 ml. of dry ethanol was added 3.24 g. of XXIII and 1.32 g. of isopropyl bromide, and the mixture was refluxed for 15 hours. After removal of the solvent by distillation, a solution of the resultant residue in chloroform was washed with 5% sodium hydroxide solution and water, dried over sodium sulfate, and evaporated to give a reddish-brown oil, which upon recrystallization from benzene-hexane afforded 1.14 g. of XXVII as pale yellow prisms, m.p. 87-88.5°, ν max (potassium bromide) cm^{-1}: 2250 (C=N), 1389, 1379 (isopropyl CH); nmr τ deuteriochloroform): 8.75 (6H, doublet, J = 6 cps, -CH(CH_3)$_2$, 6.21, 6.32 (4H, two singlets, 2 x CH_2CN), 6.06, 6.23 (6H, two singlets, 2 x OCH_3), 5.43 (1H, sextet, J = 6 cps, -CH(CH_3)$_2$, 3.56 (1H, singlet C_6-H), 3.08 (1H, doublet, J = 2 cps, C_2′-H), 2.99 (1H, singlet, C_3-H), 2.88-2.93 (2H, multiplet, C_4′-H, C_5′-H).

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.83; H, 6.05; N, 7.65. Found: C, 69.24; H, 6.09; N, 7.70.

6′-Isobutoxy-4,5-dimethoxy-2,3′-bis(hydroxycarbonylmethyl)-phenoxybenzene (XXVIII).

A mixture of 8.0 g. of XXIX, 120 ml. of methanol, 100 ml. of dioxane, 30.0 g. of potassium hydroxide and 30 ml. of water was refluxed for 20 hours. After treatment as usual, extraction with ethyl acetate, followed by evaporation, gave 7.5 g. of XXVIII. Recrystallization from ethyl acetate-hexane gave colorless needles, m.p. 138.5-139.5°.

Anal. Calcd. for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 62.23; H, 6.32.

6′-Isobutoxy-4,5-dimethoxy-2,3′-bis(cyanomethyl)phenoxybenzene (XXIX).

(a)

To a mixture of 2.7 g. of XXIII, 0.17 g. of sodium, and 70 ml. of dry ethanol was added 1.2 g. of isobutyl bromide and the mixture was refluxed for 15 hours. After removal of the solvent, a solution of the resultant oil in chloroform was washed with 5% sodium hydroxide solution and water, dried over sodium sulfate, and evaporated to give a solid, which upon recrystallization from benzene-hexane afforded 1.1 g. of XXIX as colorless needles, m.p. 91-92°, ν max (potassium bromide) cm^{-1}: 2250 (C=N), 1379, 1367 (isopropyl CH); nmr τ (deuteriochloroform): 9.13 (6H, doublet, J = 7 cps, $CH(CH_3)_2$, 8.02 (1H, multiplet, $>CHCH_2$), 6.23, 6.34 (4H, two singlets, 2 x CH_2CN), 6.10, 6.23 (6H, two singlets, 2 x OCH_3), 6.28 (2H, doublet, J = 6 cps), 3.63 (1H, singlet, C_6-H), 3.09 (1H, doublet, J = 2 cps), 3.05 (1H, doublet, J = 7 cps, C_5′-H), 3.01 (1H, singlet, C_3-H), 2.94 (1H, quartet, J = 2 cps, J = 7 cps, C_4′-H).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.30; H, 6.29; N, 7.49.

(b)

A mixture of 40.0 g. of XXXV, 500 ml. of ethyl methyl ketone, 33.0 g. of sodium iodide, and 34.3 g. of sodium cyanide was refluxed for 15 hours, and water was then added in order to dissolve an inorganic substance. The ethyl methyl ketone and aqueous layers were separated, and the aqueous layer was extracted with benzene. The organic solvent layers were combined, washed with 10% sodium hydroxide solution, water, 10% hydrochloric acid and water, dried over sodium sulfate, and evaporated to give a reddish-orange oil, which was chromatographed on 400 g. of alumina using benzene as an eluant. Removal of the benzene eluate gave a pale yellow viscous oil, which was recrystallized from benzene-hexane to afford 16.5 g. (43%) of XXIX as colorless needles, m.p. 91-92°. This was identical with the above authentic sample.

6′-Hydroxy-4,5-dimethoxyphenoxybenzene-2,3′-dialdehyde (XXXI).

A mixture of 80 g. of XVII, 800 ml. of acetic acid and 400 ml. of concentrated hydrochloric acid was refluxed at 150° for 1.5 hours and the solvent was then distilled *in vacuo* to give crystals which were washed with hot water followed by benzene and dried to give 57 g. (93%) of XXXI. Recrystallization from acetone-water gave colorless scales, m.p. 180-181.5°, ν max (potassium bromide) cm^{-1}: 3200-2500 (chelated OH), 1684, 1664 (m) (C=O); nmr τ (deuteriochloroform): 6.08 (3H, singlet, C_4-OCH_3), 5.91 (3H, singlet, C_5-H), 3.32 (1H, singlet, C_6-H), 2.62 (1H, doublet, J = 9 cps, C_5′-H), 2.32 (1H, doublet, J = 2 cps, C_2′-H), 2.31 (1H, singlet, C_3-H), 2.10 (1H, quartet, J = 2 cps, J = 9 cps, C_4′-H), 0.24 (1H, singlet, C_3′-CHO), -0.27 (1H, singlet, C_2-CHO).

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 64.08; H, 4.66.

6′-Isobutoxy-4,5-dimethoxyphenoxybenzene-2,3′-dialdehyde (XXXII).

A mixture of 30.0 g. of the dialdehyde (XXXI), 150 ml. of dimethylformamide, 23.0 g. of isobutyl tosylate, and 7.0 g. of anhydrous potassium carbonate was refluxed at 170° for 30 minutes. The mixture was poured into an excess of water and extracted with ether. The extract was washed with water, 10% sodium hydroxide solution and water, dried over sodium sulfate, and evaporated to give a syrup, which upon trituration with 50 ml. of hexane gave 21.5 g. (61%) of XXXIII. Recrystallization from methanol-water gave colorless scales, m.p. 90-91.5°, ν max (potassium bromide) cm^{-1}: 1690 (C=O), 1683 (C=O).

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.26; H, 6.50.

6′-Isobutoxy-4,5-dimethoxyphenoxybenzene-2,3′-dimethanol (XXXIII).

To a solution of 25.0 g. of XXXII in 300 ml. of methanol was added in small portions 6.0 g. of sodium borohydride and the mixture was refluxed for 1 hour. After removal of the solvent, the residue was extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to give a syrup, which was recrystallized from benzene to afford 21.7 g. (79%) of XXXIII as colorless scales, m.p. 90-91°, ν max (chloroform) cm^{-1}: 3600 (OH), 3380 (OH).

Anal. Calcd. for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.28; H, 7.25.

6′-Isobutoxy-4,5-dimethoxy-2,3′-bis(chloromethyl)phenoxybenzene (XXXIV).

A mixture of 25.0 g. of XXXIII, 25 ml. of thionyl chloride, and 300 ml. of dry ether was refluxed for 3 hours. The mixture was concentrated to a volume of 100 ml. and an excess of hexane was added. The crystals which precipitated were collected by filtration, washed with hexane, and dried to give 22.8 g. (83%) of XXXIV. Recrystallization from hexane afforded colorless needles, m.p. 79-80°.

Anal. Calcd. for $C_{20}H_{24}Cl_2O_4$: C, 60.16; H, 6.06. Found: C, 59.95; H, 5.89.

11-Hydroxy-4-isobutoxy-7,8-dimethoxydibenz[*b,f*]oxepin-1-ylacetic Acid Lactone (XXX).

A mixture of 1.0 g. of XXVIII and polyphosphoric acid (PPA) [prepared from 8 g. of 85% phosphoric acid and 15 g. of phosphorous pentoxide] was heated at 60° in a water-bath for 30 minutes, and the reaction mixture was then poured into 200 ml. of ice-water and extracted with ether. The extract was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated to give a syrup, which upon recrystallization from benzene-hexane afforded 0.3 g. of XXX as pale yellow prisms, m.p. 196-198°, ν max (potassium bromide) cm^{-1}: 1774, 1742 (s) (C=O), 1647 (C=C); nmr τ (deuteriochloroform): 8.87 (6H, doublet, J = 6 cps, $-CH(CH_3)_2$ 7.76 (1H, multiplet, $CH(CH_3)_2$, (2H, singlet, $-CH_2CO$), 6.17 (2H, doublet, J = 6 cps, $-CH_2O-$), 6.14, 6.15 (6H, two singlets, 2 x OCH_3), 3.40 (1H, singlet, C_{10}-H), 3.34 (1H, singlet, C_9-H), 3.08 (1H, singlet, C_6-H), 3.11 (1H, doublet, J = 6 cps, C_3-H), 2.99 (1H, doublet, J = 6 cps, C_2-H).

Anal. Calcd. for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.43; H, 5.83.

2,3-Dihydro-6-isobutoxy-9,10-dimethoxy-1*H*-[1]benzoxepino-[2,3,4-*i,j*]isoquinol-2-one (XXXV).

A suspension of 1.3 g. of the lactone (XXX) and 130 ml. of dry ethanol saturated with ammonia gas was refluxed at 110° in an oil-bath for 1 hour and the solvent was removed by distillation. Recrystallization from chloroform-hexane gave 1.1 g. of XXXV as yellow scales, m.p. 239-242°, ν max (potassium bromide) cm^{-1}: 3220 (NH), 1660 (C=O), 1635 (C=C).

Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.35; H, 6.26; N, 3.88.

2,3,12,12a-Tetrahydro-6-isobutoxy-9,10-dimethoxy-1*H*-[1]benzoxepino[2,3,4-*i,j*]isoquinol-2-one (XXXVI).

A solution of 1.1 g. of XXXV in 65 ml. of acetic acid was hydrogenated at room temperature in the presence of 0.3 g. of Adams' platinum, a calculated amount of hydrogen being absorbed. After removal of the catalyst by filtration, the filtrate was evaporated to give a syrup which was dissolved in chloroform. The chloroform layer was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated to give a solid, which was recrystallized from ethyl acetate to afford 0.65 g. of XXXVI as pale yellow prisms, m.p. 206-207°, ν max (potassium bromide) cm^{-1}: 3200 (NH), 1684 (C=O); nmr τ (deuteriochloroform): 8.88 (6H, doublet, J = 7 cps, $CH(CH_3)_2$, 7.80 (1H, multiplet, $CH(CH_3)_2$, 6.93 (2H, singlet, C_3-H_2), 6.77 (2H, doublet, J = 8 cps, C_{12}-H_2), 6.19 (3H, singlet, C_{10}-OCH_3), 6.16 (3H, singlet, C_9-OCH_3), 6.20 (2H, OCH_2CH), 4.81 (1H, triplet, J = 8 cps, C_{12a}-H), 3.42 (1H, singlet, C_8-H), 3.17 (3H, singlet, C_4-H, C_5-H), C_{11}-H), 2.43 (1H, broad, NH).

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.78; H, 6.30; N, 3.80.

Lithium Aluminum Hydride Reduction of XXXVI.

To a stirred suspension of 750 mg. of lithium aluminum hydride in 75 ml. of tetrahydrofuran was added dropwise a solution of 750 mg. of XXXVI in 25 ml. of tetrahydrofuran and the mixture was refluxed for 17 hours. After the reaction mixture had been decomposed with a small amount of water and filtered, the filtrate was evaporated to give a syrup which was extracted with benzene. The extract was washed with water, dried over sodium sulfate and evaporated to give a syrup, which was chromatographed on alumina using benzene as an eluant. Removal of the benzene eluate, followed by recrystallization from ether, afforded 29 mg. of 2,3,12,12a-tetrahydro-6-isobutoxy-9,10-dimethoxy-1*H*-[1]benzoxepino[2,3,4-*i,j*]isoquinoline (*O*-isobutylcularimine) (XXXVIIa) as colorless plates, m.p. 149-151°, R_f 0.08 (19), ν max (potassium bromide) cm^{-1}: 3200 (NH), nmr τ (deuteriochloroform): 8.90, 8.92 (6H, a pair of doublets, J = 7 cps, $CH(CH_3)_2$, 7.73 (1H, multiplet, $CH(CH_3)_2$, 6.67-7.33 (6H, multiplet, C_2-H_2, C_3-H_2, C_{12}-H_2), 5.20 (1H, multiplet, C_{12a}-H), 3.42 (1H, singlet, C_8-H), 3.26 (1H, doublet, J = 8 cps, C_5-H), 3.17 (1H, doublet, J = 8 cps, C_4-H), 3.16 (1H, singlet, C_{11}-H).

Anal. Calcd. for $C_{22}H_{27}NO_4 \cdot 1/5H_2O$: C, 70.83; H, 7.40. Found: C, 70.75; H, 7.29.

Removal of the second benzene-chloroform (8:2) eluate gave a syrup, which was recrystallized from chloroform-hexane to afford 25 mg. of 2-hydroxy-2,3,12,12a-tetrahydro-6-isobutoxy-9,10-dimethoxy-1*H*-[1]benzoxepino[2,3,4-*i,j*]isoquinoline (XXXVIII) as colorless scales, m.p. 140-142°, ν max (potassium bromide) cm^{-1}: 3550-3100 (broad, OH and NH), nmr τ (deuteriochloroform): 8.91 (6H, doublet, J = 6 cps, $CH(CH_3)_2$, 6.68-6.97 (4H, multiplet, C_3-H_2 and C_{12}-H_2), 6.21 (3H, singlet, C_{10}-OCH_3), 6.16 (3H, singlet, C_9-OCH_3), 5.92 (1H, C_2-H), 5.22 (1H, multiplet, C_{12a}-H), 3.50 (1H, singlet, C_8-H), 3.17 (1H, singlet, C_{11}-H), 3.14 (1H, doublet, J = 8 cps, C_5-H), 2.84 (1H, doublet, J = 8 cps, C_8-H).

Anal. Calcd. for $C_{22}H_{27}NO_5 \cdot 1/2H_2O$: C, 66.98; H, 7.16. Found: C, 66.81; H, 7.09.

An Alternative Synthesis of XXXVIIa.

A mixture of 4.5 mg. of carbinolamine (XXXVIII), 10 mg. of thionyl chloride, and 6 ml. of dry ether was refluxed for 8 hours. After addition of dry benzene to the above reaction mixture, the solvent was removed by distillation to give a syrup (XXXIX) which was dissolved in 10 ml. of dry tetrahydrofuran. To a suspension of 10 mg. of lithium aluminum hydride in 10 ml. of tetrahydrofuran was added the above solution of XXXIX, and the mixture was refluxed for 17 hours. After decomposition with water and filtration, the filtrate was evaporated to give a syrup, whose chloroform solution was washed with water and 5% sodium hydroxide solution and dried over sodium sulfate. Removal of the solvent, followed by alumina chromatography, afforded *O*-isobutylcularimine (XXXVIIa), m.p. 149-151.5°, which was identical with the above sample on mixed m.p. test.

2,3,12,12a-Tetrahydro-6-isobutoxy-9,10-dimethoxy-1-methylbenzoxepino[2,3,4-*i,j*]isoquinoline (*O*-Isobutylculariddine) (XXXVIIb).

To a stirred mixture of 30 mg. of XXXVIIa, 1.51 ml. of methanol, 0.5 ml. of chloroform, and 25 ml. of 37% formalin was added 20 mg. of sodium borohydride and the stirring was continued for 1 hour. After removal of the solvent, the residue was mixed with water, dried over sodium sulfate, and evaporated to give a pale yellow syrup, which was chromatographed on 1 g. of alumina. Removal of the benzene eluate gave 21 mg. of XXXVIIb as a pale yellow syrup, R_f 0.38 (19); nmr τ (deuteriochloroform): 8.92, 8.93 (6H, two doublets, J = 6 cps, $CH(CH_3)_2$, 7.42 (3H, singlet, NCH_3), 6.58-7.26 (6H, multiplet), 6.23 (3H, singlet, C_{10}-OCH_3), 6.17 (3H, singlet, C_9-OCH_3), 5.15 (1H, quartet, J_{AX} = 4.0 cps, J_{BX} = 11 cps, C_{12a}-H), 3.49 (1H, singlet, aromatic), 3.26 (1H, doublet, J = 8 cps, aromatic), 3.16 (1H, singlet, aromatic), 3.15 (1H, doublet, J = 8 cps, aromatic) (see Fig. 1). Mass (high resolution): M^+, 383.207 (Calcd. for $C_{23}H_{29}NO_4$:383.209); M^+ -15, 368.187 (Calcd. for $C_{22}H_{26}NO_4$: 368.186), λ max (dioxane); 285.5mμ.

Natural *O*-Isobutylcularidine.

A mixture of 10 mg. of natural cularidine (III), 1.5 mg. of 50% sodium hydride, and 4 ml. of dry benzene was heated with stirring at 50° for 2 hours and the sodium salt of III began to separate as a paste. A solution of 5.6 mg. of isobutyl iodide in 4 ml. of dry benzene was added and the stirring was continued at 80° for 15 hours, but no change was observed on tlc. Therefore, 10 ml. of dimethylformamide was added to the above mixture and the mixture was heated at 130° for 1 hour. The solvent was distilled off to give a residue which was extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and evaporated to give a syrup, which was positive for Dragendorf reagent. R_f-value (0.38) (19) of this natural sample was identical with that of our synthetic one. λ max (dioxane):285.5 mμ.

Dealkylation of XXXVIIa.

A mixture of 15 mg. of XXXVIIa, 4 ml. of acetic acid, and 3 ml. of 48% hydrobromic acid was stirred at room temperature for 72 hours, but no change was observed on its thin layer chromatogram (tlc). Therefore, the above mixture was heated at 50° and after 20 hours of heating, the other spot showing a blue color against Gibbs reagent appeared besides the spot of starting material colored with Dragendorf reagent. The latter spot disappeared completely after 94 hours. The reaction mixture was basified with concentrated ammonia and then extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The resultant residue was chromatographed on 350 mg. of alumina. After removal of the first chloroform eluate, evaporation of the second chloroform-methanol (100:4) eluate gave a colorless solid, which was triturated with a small amount of ether-methanol (1:1) to give 0.3 mg. of XLa, m.p. 196-200°, R_f 0.08 (19); nmr τ (deuteriochloroform): 8.91,8.93 (6H, two doublets, J = 7 cps, $CH(CH_3)_2$),6.82-7.37 (6H, multiplet)-

6.21 (2H, doublet, > $CHCH_2O$), 6.17 (3H, singlet, C_9-OCH_3), 5.21 (1H, C_{12a}-H), 3.40 (1H, singlet, C_8-H), 3.26 (1H, doublet, J = 9 cps, C_5-H), 3.17 (1H, doublet, J = 9 cps, C_4-H), 3.17 (1H, singlet, C_{11}-H). Further investigation could not be done because of its shortage.

Dealkylation of XXXVIIb.

A mixture of 21 mg. of XXXVIIb, 3 ml. of acetic acid, and 3 ml. of 48% hydrobromic acid was heated with stirring at 55° under a current of nitrogen for 65 hours, after which time the spot of starting material disappeared on its tlc. After the same treatment, chromatography on 0.7 g. of alumina was carried out, using chloroform-benzene (1:1) followed by chloroform. Removal of the third chloroform-methanol (50:2) eluate gave a yellowish-orange syrup, which was triturated with ether to give a powder. Washing with ether-methanol (1:1) gave 0.9 mg. of XLb as colorless plates, m.p. 153-155°, R_f 0.34 (19); nmr τ (deuteriochloroform): 8.93 (6H, doublet, J = 7 cps, -$CH(CH_3)_2$), 7.84 (1H, multiplet, > $CHCH_2O$), 7.42 (3H, singlet, NCH_3), 6.55-7.31 (6H, multiplet), 6.23 (2H, doublet, J = 6 cps, > $CHCH_2O$), 6.17 (3H, singlet, C_9-OCH_3), 5.12 (1H, quartet, J = 6 cps, C_{12a}-H), 3.42 (1H, singlet, C_8-H), 3.25 (1H, doublet, J = 10 cps, C_5-H), 3.19 (1H, singlet, C_{11}-H), 3.17 (1H, doublet, J = 10 cps, C_4-H). Recrystallization of its perchlorate from methanol afforded colorless prisms, m.p. 267-269°, which could not be examined because of its shortage.

Acknowledgments.

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 assistance. We also thank Dr. H. Yagi, Pharmaceutical Institute, Tohoku University School of Medicine, for this helpful discussion from the mass spectral point of view. We are grateful to the Analytical Center of Tokyo College of Pharmacy for microanalyses and Pharmaceutical Institute, Tohoku University for microanalyses and nmr spectral determinations. We also thank Hitachi, Ltd. Japan for high-resolution mass (Hitachi RMU-7 type) spectral determination.

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Received November 22, 1968 Sendai, Japan