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TOTAL SYNTHESIS OF *dl*-O-METHYLTILIACORINE*

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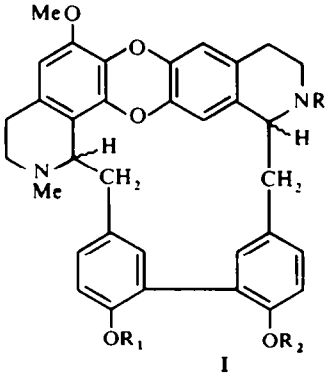
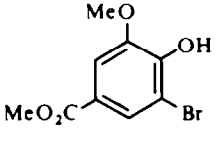
Abstract—The synthesis of *dl*-O-methyltiliacorine (Ic) is described.

TILIACORINE and its diastereoisomer tiliacorinine, which constitute the major alkaloids of *Tiliacora racemosa* Colebr. (Menispermaceae), have been assigned the gross structure Ia on the basis of extensive degradation studies[1]. In the family of bisbenzylisoquinoline alkaloids tiliacorine and its congeners are unique in having a diphenyl unit in place of the usual diphenyl ether. We wish to record here the total synthesis of *dl*-O-methyltiliacorine (Ic).

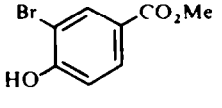


I

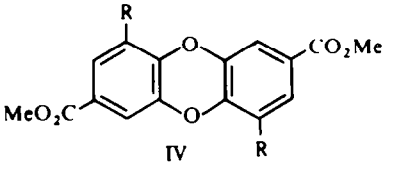
a: R = Me; R_1, R_2 = Me, H
or vice versa
b: R = H; R_1 = R_2 = Me
c: R = R_1 = R_2 = Me



II

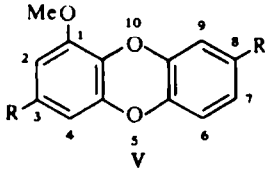


III



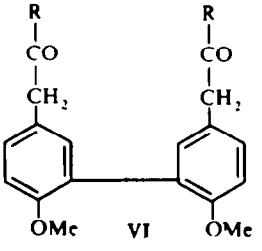
IV

a: R = H
b: R = OMe



V

a: R = CO_2Me
b: R = CH_2OH
c: R = CH_2Cl
d: R = CH_2CN
e: R = $CH_2CH_2NH_2$
f: R = Me



VI

a: R = OH
b: R = Cl

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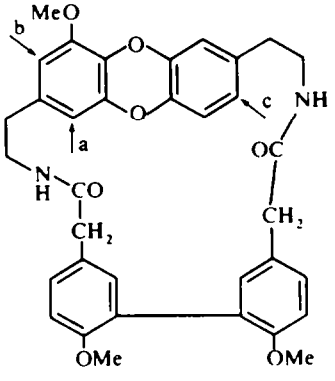
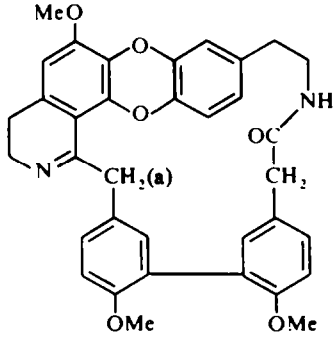
An unsymmetrical Ullman reaction between methyl 5-bromovanillate (II) and methyl 3-bromo-4-hydroxybenzoate (III) yielded all the three possible dicarbomethoxy-dibenzo-*p*-dioxins which were separated by repeated chromatography over silica gel. Of these the symmetrical compounds (IVa[2, 3] and IVb[3, 4]) were found to be identical with authentic samples. The hitherto unknown unsymmetrical product (Va) had an NMR spectrum expected for this structure.

The diester (Va) was reduced with LAH in tetrahydrofuran to the diol (Vb) which was converted by treatment with thionyl chloride to the dichloride (Vc). Confirmatory evidence for the structure of the dichloride was obtained by its catalytic reduction which gave the known 1-methoxy-3,8-dimethyldibenzo-*p*-dioxin (Vf).[1, 5] Treatment of Vc with potassium cyanide yielded the dinitrile (Vd) which was reduced catalytically in presence of Raney mickel to the bisphenylethylamine (Ve).

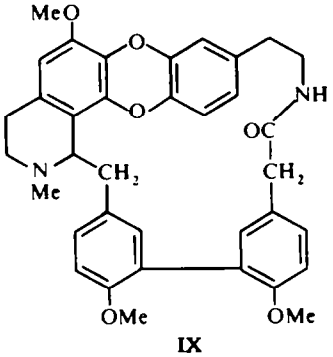
The bisamine (Ve) was condensed with the diacid chloride (VIb)[6] of 2,2′-dimethoxy-diphenyl-5,5′-diacetic acid in chloroform in the presence of alkali under high dilution conditions[7, 8] to yield the bisamide (VII).



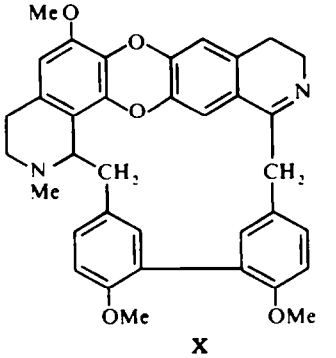
VII



VIII



IX



X

Bischler–Napieralski cyclisation of VII was expected to result in cyclisation at both sides of the molecule simultaneously. Cyclisation on the methoxylbearing benzene ring would result in preferred cyclisation at (a) rather than (b) in alalogy with the amide used for the synthesis of N-methyldihydromenisarine[9] whereas cyclisation on the other benzene ring would take place at position (c). In practice however it was observed that cyclisation with phosphorus oxychloride under a variety of drastic conditions yielded

only traces of the biscyclised product. Conversion of the crude basic product into the dimethiodide and reduction with sodium borohydride yielded O-methyltiliacorine (Ic) in traces which could be recognised on the TLC plate but was insufficient for proper characterisation.

Bischler–Napieralski cyclisation of the bisamide when carried out in nitrogen using phosphorus oxychloride in refluxing benzene gave the monocyclised 3,4-dihydroisoquinoline (VIII). This structure is assigned to the product since cyclisation would be more facile on the methoxylbearing benzene than the other benzene ring. Compound (VIII), m.p. 225–227° (d), showed in its mass spectrum the molecular ion at the expected value (*m/e* 576) but on standing a significant peak appeared at *m/e* 590 due to oxidation of the benzylic methylene (a) (in VIII) to a CO group. In later runs, compound VIII, without purification, was converted to the methiodide and then reduced with sodium borohydride to yield the N-methyltetrahydroisoquinoline (IX), m.p. 190–192° (mol. wt. by mass spectrum 592). The presence of the second amide function was shown by its I.R. spectrum, ν_{max} 3420 (NH), 1665 cm^{-1} (C=O).

In contrast to the 3,4-dihydroisoquinoline (VIII), compound IX could be cyclized with phosphorus oxychloride under forcing conditions to yield X. This difference is due partly to the relative flexibility of the tetrahydroisoquinoline in comparison with the dihydroisoquinoline.

Compound X, without purification, was reduced catalytically in presence of Adams catalyst to yield a mixture of diasteroisomers represented by the formula Ib. Methylation of Ib with formaldehyde and formic acid yielded the diastereoisomeric mixture of racemic O-methyltiliacorine and O-methyltiliacorinine (Ic). Careful chromatography over silica gel yielded *dl*-O-methyltiliacorine, identical in TLC, IR, UV, NMR and mass spectra with the natural sample. The second diastereoisomer was obtained only in trace amounts. Although its TLC corresponded with O-methyltiliacorinine, the amount of synthetic material available was inadequate for proper characterisation.

The mass spectra of synthetic O-methyltiliacorine as well as the natural samples of O-methyltiliacorine and O-methyltiliacorinine showed small peaks (< 1%) at *m/e* 604 and 622 due to the formation of traces of oxidation products.

Of the bisbenzylisoquinoline alkaloids having a dibenzo-*p*-dioxin system, N-methyldihydromenisarine has been synthesized by a similar route.[9] The alkaliod isotrilobine[10] and its antipode* have been partially synthesized from oxyacanthine and epistephanine respectively by demethylative dehydration to get the dibenzo-*p*-dioxin ring system.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined in EtOH on a Beckman DK2 spectrophotometer. IR spectra were taken on a Perkin–Elmer model 337 Infracord instrument. NMR spectra were determined on a Varian A-60 spectrometer, the solvent being $CDCl_3$ unless otherwise specified. Silica gel (70-325 mesh ASTM, Merck) was used for column chromatography.

3,8-*Dicarbomethoxy*-1-*methoxydibenzo*-p-*dioxin* (Va). A soln of methyl 5-bromovanillate[12] (159 g) and methyl 3-bromo-4-hydroxybenzoate[13] (141 g) in MeOH (500 ml) was cooled in ice and treated with a soln of KOH (68 g) in MeOH (400 ml). The solvent was removed *in vacuo*, the residue treated with excess ether, filtered and dried thoroughly at 110°/1 mm for 12 hr. The dry mixture of K salts (200 g) was mixed well with copper bronze (28 g), suspended in diphenyl ether (1 l.) and heated with vigorous stirring at 250–260° for 10 hr. The mixture was filtered and the residue washed with $CHCl_3$. The combined filtrate was passed through a column of Al_2O_3 (2 kg) in $CHCl_3$. The column was eluted thoroughly with $CHCl_3$ and the eluate

* This compound and all the subsequent derivatives containing the dibenzo-*p*-dioxin ring system gave the characteristic blue colour with a mixture of concentrated sulphuric and nitric acids.

evaporated *in vacuo*. The residual diphenyl ether was removed at 5 mm to yield the product as a brownish solid (35 g). This was dissolved in $CHCl_3$, filtered and chromatographed over silica gel (1 kg) suspended in benzene. Elution with benzene removed the residual diphenyl ether. The column was successively eluted with C_6H_6–$CHCl_3$ (1:1), C_6H_6–$CHCl_3$ (1:2), $CHCl_3$ and finally $CHCl_3$–MeOH (99:1). The fractions were examined by TLC and like fractions combined. The C_6H_6–$CHCl_3$ (1:1) eluates yielded IVa (6 g), m.p. 248°, identical with an authentic sample.[2,3] The $CHCl_3$ and $CHCl_3$–MeOH fractions yielded IVb (8 g), m.p. 286°, identical with an authentic sample.[3,4] The intermediate C_6H_6–$CHCl_3$ (1:2) fractions yielded Va (7 g), white needles (from C_6H_6), m.p. 212–214°, ν_{max}^{KBr} 1730 cm^{-1}; NMR (CF_3CO_2H): δ 6·5–7·8 (5H, broad, Ar-H); 3·99 ppm (9H, 3 OMe) (Found: C, 62·17; H, 4·43. $C_{17}H_{14}O_7$ requires C, 61·82; H, 4·27%).

3,8-*Di-hydroxymethyl*-1-*methoxydibenzo*-p-*dioxin* (Vb). A soln of the above diester (6·6 g) in dry THF (600 ml) was added with stirring to a suspension of LAH (3 g) in THF (100 ml). The mixture was refluxed with stirring for 6 hr, allowed to stand overnight and decomposed with water. Filtration and removal of THF gave the diol (5·3 g) which crystallised from a large volume of EtOH, m.p. 187–189°, ν_{max}^{Nujol} 3140–3320 cm^{-1} (broad) (Found: C, 65·70; H, 5·43. $C_{15}H_{14}O_5$ requires: C, 65·69; H, 5·15%).

3,8-*Di-chloromethyl*-1-*methoxydibenzo*-p-*dioxin* (Vc). A suspension of the above diol (5·3 g) in dry C_6H_6 (200 ml) was refluxed with $SOCl_2$ (20 ml) and pyridine (2 drops) for 4 hr. Removal of the solvent gave the dichloride which was dried *in vacuo* and then crystallised from CH_2Cl_2-hexane, m.p. 181–183° (Found: C, 58·10; H, 4·24. $C_{15}H_{12}O_3Cl_2$ requires: C, 57·90; H, 3·86%).

3,8-*Di-cyanomethyl*-1-*methoxydibenzo*-p-*dioxin* (Vd). To a warm soln of Vc (5·3 g) in DMF (150 ml) was added an aq soln of KCN (7 g) and KI (4 g) in H_2O (15 ml) under vigorous stirring. The soln was refluxed with stirring for 5 hr, cooled filtered and the residue washed with warm DMF. The filtrate was evaporated *in vacuo*, diluted with H_2O and extracted with $CHCl_3$ to yield the crude product (3·5 g). This was chromatographed over Al_2O_3 (60 g) in $CHCl_3$ to yield the dinitrile (2·3 g) which was crystallised once from $CHCl_3$–MeOH and then from DMF, m.p. 196–198° (Found: C, 69·97; H, 4·37; N, 9·17. $C_{17}H_{12}N_2O_3$ requires: C, 69·85; H, 4·14; N, 9·59%).

3,8-*Di*-β-*aminoethyl*-1-*methoxydibenzo*-p-*dioxin* (Ve). A suspension of Vd (2 g) in methanolic KOH (5%; 170 ml) was reduced at room temp in presence of Raney nickel catalyst (6 g) in a Parr apparatus at 25 lbs/in^2 for 20 hr. The catalyst was filtered and washed with hot MeOH. The filtrate was evaporated to dryness, the residue diluted with H_2O (100 ml) and acidified dropwise with con HCl. The acid soln was shaken with $CHCl_3$ to remove any neutral matter, basified with con NH_4OH, satd with NaCl and extracted with $CHCl_3$ to yield Ve (1·6 g) which was used as such.

1-*Methoxy*-3,8-*dimethyldibenzo*-p-*dioxin* (Vf). A suspension of Vc (100 mg) in BtOAc (25 ml) was reduced catalytically with Pd-$BaCO_3$ (5%; 200 mg) at room temp and 1 atm for 12 hr and filtered. Evaporation of the filtrate yielded Vf (50 mg), m.p. 118–120°, underpressed by admixture with an authentic sample[1,5]. The two samples were also identical in TLC, IR and NMR spectra.

2,2′-*Dimethoxydiphenyl*-5,5′-*diacetyl chloride* (VIb). The diacid VIa[6] (1·5 g) was treated with $SOCl_2$ (7 ml) and pyridine (1 drop) and the soln allowed to stand overnight at room temp. $SOCl_2$ was removed *in vacuo*, the residue flushed with C_6H_6 and crystallised from C_6H_6 hexane to yield VIb (1·4 g), m.p. 146–148° (d) (Found: C, 59·37; H, 4·48. Calc. for $C_{18}H_{16}Cl_2O_4$: C, 58·88; H, 4·39%). Niimi *et al*[6] have used PCl_5 for preparing the acid chloride.

Bisamide (VII). To a vigorously stirred soln of Ve (1·6 g) in $CHCl_3$ (750 ml) was added, at 0°, a soln of VIb (1·4 g) in $CHCl_3$ (400 ml) over 2 hr. After 2 hr more aq KOH (3%; 35ml) was added and after another 2 hr a second lot of aq KOH (3%; 35 ml) was added. The soon was stirred for 12 hr at room temp, the $CHCl_3$ layer separated, washed with dil HCl, H_2O, dried and evaporated. The crude product (2·4 g) was chromatographed over silica gel in $CHCl_3$. Elution with $CHCl_3$–1% MeOH gave the cisamide (1·2 g), which crystallised from a large volume of C_6H_6; m.p. 265–267°, $\nu_{max}^{CH_2Cl_2}$ 3410, 1665 cm^{-1}; NMR: δ 6·0–7·2 (11H, complex, Ar-H), 5·4 (2H, broad, NH), 3·82 (3H, s, OMe), 3·80 (3H, s, OMe), 3·74 (3H, s, OMe), 3·42 (4H, s, Ar·C<u>H</u>$_2$·CO). (Found: C, 71·09; H, 6·13; N, 4·85. $C_{35}H_{34}N_2O_7$ requires: C, 70·69; H, 5·76; N, 4·71%).

Monoamide (IX). A soln of VII (0·32 g) in C_6H_6 (100 ml) was refluxed with $POCl_3$ (4 ml) for 4 hr in a current of N_2. The separated salt was washed with hexane, basified with NaOH aq (1 g in 10 ml H_2O) under N_2 and extracted with $CHCl_3$. Removal of $CHCl_3$ gave VIII (0·3 g) which became a solid on trituration with MeOH; m.p. 225–227° (d), $\nu_{max}^{CH_2Cl_2}$ 3410, 1665 cm^{-1}; mass spectrum: *m/e* 576 (M^+, 100%), 581 (20%), 545 (12%), 288 (5%), 274 (13%), 202 (17%), 194 (7%). The compound was unstable on exposure and mass spectral samples showed an impurity at *m/e* 590 ($CH_2 \rightarrow CO$) whose intensity increased with greater exposure. In subsequent runs, this compound was without purification converted to the methiodide. A soln

of VIII (0·3 g) in $CHCl_3$ (20 ml) was refluxed with MeI (6 ml) in N_2 for 4 hr. Removal of the solvent yielded the methiodide which was suspended in MeOH (50 ml) and treated at 15–20° under N_2 with $NaBH_4$ (1 g) with vigorous stirring. The soln was stirred overnight at room temp. MeOH removed *in vacuo*, the residue treated with H_2O and extracted with $CHCl_3$ to give crude IX (0·27 g) which crystallised from MeOH as offwhite needles, m.p. 190–192°; $\nu_{max}^{CH_2Cl_2}$ 3420 (NH), 1665 cm^{-1} (C=O); mass spectrum: *m/e* 592 (M^+, 87%), 591 (100%), 577 (17%), 561 (13%), 308 (10%), 295 (42%), 225 (22%), 194 (15%); NMR: δ 6·25–7·5 (complex, Ar-H) 5·6 (1H, NH), 4·1 (1H, Ar-C<u>H</u>-NMe), 3·82 (3H, s, OMe), 3·79 (3H, s, OMe), 3·65 (3H, s, OMe), 3·5 (2H, s, Ar-C<u>H</u>$_2$-CO), 2·62 (3H, s, NMe) Found: C, 72·40; H. 6·48; N, 5·01. $C_{26}H_{36}N_2O_6$ requires C, 72·95; H, 6·12; N, 4·73%). TLC examination of the mother liquors of IX showed one prominent spot corresponding to natural Ic suggesting that biscyclization has also occured with $POCl_3$ to a small extent. The quantity however was insufficient for isolation.

dl-O-*Methyltiliacorine* (Ic). The monoamide IX (0·27 g) was heated with $POCl_3$ (6 ml) at 100° for 4 hr in N_2. $POCl_3$ was removed *in vacuo*, the residue suspended in MeOH (80 ml) and reduced catalytically with H_2 at 1 atm pr in presence of Adams catalyst (0·25 g) for 14 hr. The catalyst was filtered, the filtrate evaporated to dryness, the residue basified with NaOH aq (0·6 g in 15 ml H_2O) and extracted with $CHCl_3$. The crude Ib obtained was refluxed with formic acid (97%; 4 ml) and formaldehyde (37%; 4 ml) for 4 hr in N_2. The soln was evaporated to dryness *in vacuo* the residue basifed with aq NaOH (0·5 g in 20 ml H_2O) and extracted with $CHCl_3$ containing 2% MeOH. The product (0·2 g) was chromatographed over silica gel (5 g) in $CHCl_3$. The column was eluted successively with $CHCl_3$, $CHCl_3$–1% MeOH and $CHCl_3$–2% MeOH. 4 ml fractions were collected, checked by TLC and like fractions combined. Initial fractions of $CHCl_3$–2% MeOH eluates gave an amorphous solid (19 mg), identical in TLC with natural O-methyl-tiliacorinine. The material could not however be crystallised. Later fractions of $CHCl_3$–2% MeOH eluates gave Ic (52 mg) which crystallised from acetone-hexane, m.p. 190–192° (d), λ_{max} 286 mμ (log ε 3·96), λ_{min} 266 mμ (log ε 3·65); mass spectrum: *m/e* 622 (< 1%), 604 (< 1%), 590 (M^+, 53%), 575 (5%), 349 (100%), 335 (61%), 175 (78%). The compound was identical in TLC, UV, IR (CH_2Cl_2) and NMR spectra with natural O-methyltiliacorine. Both samples had also identical mass spectral fragments.

O-*Methyltiliacorinine* (Ic). O-Methyltiliacorinine dimethiodide (1 g) was heated at 165–175° for 1 hr with monoethanolamine (1·1 ml). Working up as in the case of O-methyltiliacorine[1] yielded O-methyltiliacorine (100 mg), crystals (from acetone–ether), m.p. 200–204° (d), λ_{max} 289 mμ (log ε 3·99), λ_{min} 264 mμ (log ε 3·76); mass spectrum: *m/e* 622 (< 1%), 604 (< 1%), 590 (M^+, 57%), 575 (7%), 349 (100%), 335 (61%), 175 (56%). The NMR spectrum of a vigorously dried sample still showed retention of acetone and ether and the sample was hence not analysed. Typical. R_f values of O-methyltiliacorine and O-methyltiliacorinine on silica gel using $CHCl_3$–10% MeOH were 0·5 and 0·65 respectively.

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