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ALKALOIDS OF *TILIACORA RACEMOSA* COLEBR*.

B. ANJANEYULU, T. R. GOVINDACHARI, S. S. SATHE and N. VISWANATHAN
CIBA Research Centre, Goregaon, Bombay 63, India

and

K. W. GOPINATH† and B. R. PAI
Department of Chemistry, Presidency College, Madras 5, India

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Abstract—The isolation of tiliacorine, tiliacorinine, nortiliacorinine A and nortiliacorinine B is described. Tiliacorine and tiliacorinine are shown to be diastereoisomers having the structure XIa or XIb.

TILIACORA RACEMOSA Colebr. (Menispermaceae), synonymous with *Tiliacora acuminata* (Lam.) Miers, is a woody climber regarded as an antidote to snake bite.[1] Various workers[2–4] have reported the isolation of an alkaloid tiliacorine. Rao and Row[5] later reported the isolation of a second alkaloid tiliarine. Degradative work[6–9] revealed tiliacorine to be a novel bisbenzylisoquinoline alkaloid. Parts of our work have been published in the form of preliminary communications.[6–8] We wish to present here details as well as the isolation of three other closely related alkaloids.

Using a combination of chromatography and counter-current distribution we isolated tiliacorine and three other alkaloids. The most abundant of these has been named tiliacorinine. The two minor alkaloids have been shown to be isomeric N-demethyl derivatives of the latter and have been named nortiliacorinine A and nortiliacorinine B.

Analytical values for tiliacorine were unsatisfactory due to the tenacious retention of solvents of crystallization and led at first[6] to the assignment of the wrong molecular formula $C_{37}H_{38}N_2O_6$. On the basis of the NMR spectra of tiliacorine and its O-methyl ether the formula was later revised[8] to $C_{36}H_{36}N_2O_5$.

Tiliacorine, m.p. 262–264° (d), $C_{36}H_{36}N_2O_5$, has two OMe, one hinered OH group and two N-Me groups. Its UV spectrum, λ_{max} 295 mμ (log ε 3·91), λ_{min} 265 mμ (log ε 3·48), is very similar to that of trilobine and menisarine. With a mixture of concentrated sulphuric and nitric acids, the alkaloid gives a blue colour indicating the presence of a dibenzo-*p*-dioxin system.[10] The NMR spectrum‡ of tiliacorine shows the presence of two N-Me groups (δ 2·30 and 2·66), two OMe (δ 3·83 and 3·93) and nine aromatic protons.

The OH group in tiliacorine is not methylated by diazomethane. With methyl iodide in the cold the alkaloid yielded a dimethiodide but in the presence of sodium methoxide in boiling methanol, O-methyltiliacorine dimethiodide was formed. Tiliacorine dimethiodide when refluxed with ethyl iodide and sodium ethoxide yielded O-ethyltiliacorine dimethiodide.

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† Present address: Regional Research Laboratory, Jorhat, Assam.

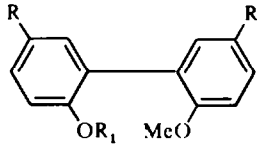
‡ NMR spectra were determined in $CDCl_3$ at 60 mc using a Varian A-60 instrument. Chemical shifts are expressed in ppm.

On heating O-methyltiliacorine dimethiodide with monoethanolamine,[11] the tertiary base, O-methyltiliacorine, $C_{37}H_{38}N_2O_5$, m.p. 210–212°, was obtained. Its NMR spectrum showed the presence of two N-Me groups (δ 2·41, 2·63), three OMe groups (δ 3·76, 3·85 and 3·86) and nine aromatic protons. O-Ethyltiliacorine dimethiodide similarly yielded O-ethyltiliacorine, m.p. 192–194°.

Confirmatory evidence for the revised molecular formula for tiliacorine was obtained from the mass spectrum of O-acetyltiliacorine, m.p. 238–240° (d), $C_{38}H_{38}N_2O_6$, which showed the molecular ion peak at *m/e* 618.

Oxidation of O-methyltiliacorine dimethiodide with alkaline permanganate followed by methylation of the acidic products yielded a dicarbomethoxy ester, m.p. 172–173°, and a tetracarbomethoxy ester, m.p. 180–181°.

The diester, $C_{18}H_{18}O_6$, on hydrolysis, gave a diacid, $C_{16}H_{14}O_6$, m.p. 340–342° (d), which on decarboxylation yielded 2,2′-dimethoxydiphenyl[12] (Ia), m.p. 155–156°. The diester was identified as 5,5′-dicarbomethoxy 2,2′-dimethoxydiphenyl (Ib). This has been prepared previously[13] by the Ullmann reaction of methyl 3-bromo-4-methoxybenzoate. In the present work an authentic sample of Ib was synthesized from the diphenyl (Ia) by Friedel–Crafts reaction to the diacetyl compound (Id) followed by oxidation with sodium hypobromite to the acid (Ic) and esterification of the latter with diazomethane.



I

a: R = H; R_1 = Me
b: R = CO_2Me; R_1 = Me
c: R = CO_2H; R_1 = Me
d: R = $COCH_3$; R_1 = Me
e: R = H; R_1 = Et
f: R = CO_2Me; R_1 = Et
g: R = CO_2H; R_1 = Et
h: R = $COCH_3$; R_1 = Et

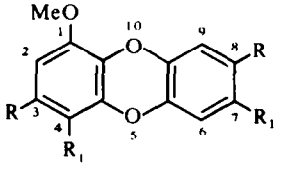
Oxidation of tiliacorine dimethiodide with alkaline permanganate resulted in cleavage of the ring containing the phenolic OH and yielded 4-methoxyisophthalic acid, identified as its dimethyl ester, m.p. 95°, besides the tetracarboxylic acid obtained from O-methyltiliacorine dimethiodide. The formation of 4-methoxyisophthalic acid indicated that the OH was located in the diphenyl portion of the molecule.

This was confirmed by oxidation of O-ethyltiliacorine dimethiodide with permanganate. The acidic product on esterification yielded a diester, $C_{19}H_{20}O_6$, m.p 129–130°, identified as 5,5′-dicarbomethoxy-2-ethoxy-2′-methoxy-diphenyl (If) by comparison with a sample synthesized for the purpose. The synthesis was based on a method used by Hill and Hale[14] several years ago for the synthesis of *p*-nitrophenol derivatives. Condensation of 2-methoxyphenylacetone with sodium nitromalonaldehyde gave 2-hydroxy-2′-methoxy-5-nitrodiphenyl. Ethylation followed by reduction gave the amine which was deaminated to give 2-ethoxy-2′-methoxydiphenyl

(Ie). Friedel-Crafts acylation of this yielded the diacetyl compound (Ih) which was oxidized by sodium hypobromite to the acid (Ig). Esterification of the latter gave the diester (If), identical with the degradation product.

The formation of the dicarboxydiphenyls in the oxidation showed that in tiliacorine the two isoquinoline moieties are linked by a diphenyl system instead of a diphenyl-ether system as in other bisbenzylisoquinoline alkaloids. The diphenyl unit arises by the oxidative removal of two H atoms adjacent to the phenolic OH groups of two coclaurine units, a reaction which finds a parallel in the biogenesis of aporphines from 1-benzylisoquinolines.

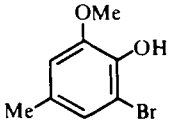
The tetracarbomethoxy ester, m.p. 180–181°, obtained in the oxidation of O-methyltiliacorine dimethiodide and tiliacorine dimethiodide, has the molecular formula $C_{21}H_{18}O_{11}$ (mol. wt. by mass spectrum 446) and on hydrolysis yields a tetracarboxylic acid, $C_{17}H_{10}O_{11}$, m.p. 326–328° (d). The NMR spectrum of the ester shows the presence of five OMe groups and three aromatic proton singlets at δ 7·18, 7·20 and 7·27 ppm. The ester gave a blue colour with a mixture of conc sulphuric and nitric acids and was identified as IIa by comparison with a sample synthesized for the purpose.



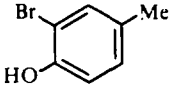
II

a: R = R_1 = CO_2Me
b: R = R_1 = CO_2H
c: R = Me; R_1 = H
d: R = Me; R_1 = $COCH_3$
e: R = Me; R_1 = CO_2H

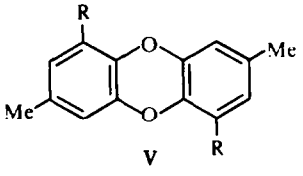
The unsymmetrical Ullmann reaction[15] between 5-bromocreosol (III) and *m*-bromo-*p*-cresol (IV) has been reported to give the unsymmetrical dibenzo-*p*-dioxin (IIc), besides both the symmetrical products (Va and Vb) in very poor yield. We have modified the reaction conditions and obtained reasonable yields of all three products.



III



IV

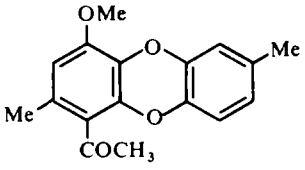


V

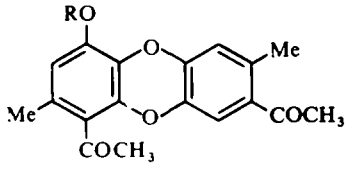
a: R = H
b: R = OMe

Acylation of IIc with acetyl chloride in carbon disulphide in presence of aluminium chloride gave a mixture of the monoacetyl compound (VI), m.p. 136–138°, the acetoxydiacetyl compound (VIIa), m.p. 141–143°, and the desired methoxydiacetyl compound (IId), m.p. 240–242°. Use of milder conditions resulted in a larger proportion of VI

whereas vigorous conditions led to more of VIIa. Hydrolysis of the acetoxy compound (VIIa) gave the hydroxy compound (VIIb), m.p. 213–215°, which with diazomethane



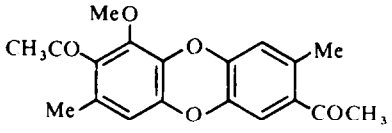
VI



VII

a: R = Ac
b: R = H

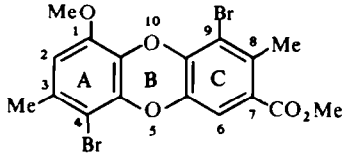
yielded the methoxy compound (IId). Structure IId is assigned to the methoxy-diacetyl compound in preference to the less likely VIII since the IR spectrum of the hydroxy compound shows the lack of H-bonding between the OH and COMe groups. In all three compounds (IId, VIIa and VIIb), the absorption due to the COMe group appeared in the IR spectrum at 1680–1685 cm^{-1}.



VIII

Oxidation of IId with sodium hypochlorite gave the diacid (IIe), m.p. 325° (d). Oxidation of the latter with alkaline permanganate at 70–75° followed by esterification gave the tetracarbomethoxy ester (IIa), m.p. 180–181°, identical with the degradation product.

Oxidation of IId with sodium hypobromite proceeded in an unexpected manner. Esterification of the acidic product gave a dibromoester, $C_{17}H_{14}O_5Br_2$, having only one carbomethoxy group. The NMR spectrum of the ester, assigned structure IX,

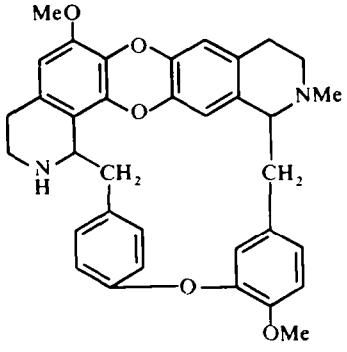


IX

shows the presence of two C—Me groups as a 6-proton singlet at δ 2·50, two OMe groups at δ 3·85 and 3·90 and two aromatic proton singlets at δ 6·80 (H-2) and 7·58 (H-6). The hypobromite reaction evidently leads to oxidation of the two acetyl groups followed by bromination of ring C and displacement of the carboxyl in ring A by bromine.

We wish to point out here an anomaly in the reported m.ps of the tetracarbomethoxy ester (IIa) and the tetracarboxylic acid (IIb) obtained from the alkaloid/trilobine (X).

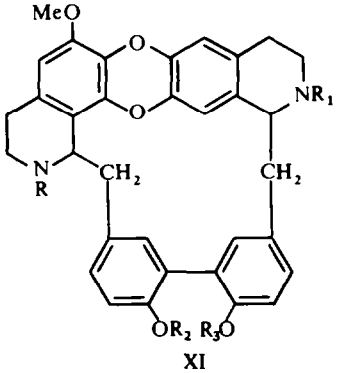
Kondo and Tomita[16] reported m.p. 85° for the ester and m.p. 192–197° (d) for the acid obtained by oxidation of the alkaloid. Samples of the ester and acid were no longer available with the Japanese workers but in view of the present synthetic work



X

and the correctness of the trilobine formula,[17] the m.ps reported by Kondo and Tomita must be in error.

The identification of the tetracarbomethoxy ester obtained from tiliacorine as IIa establishes the gross structure of tiliacorine as XIa or XIb, incorporating a monomethoxydibenzo-*p*-dioxin unit as in trilobine.

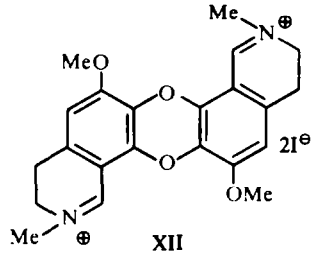


XI

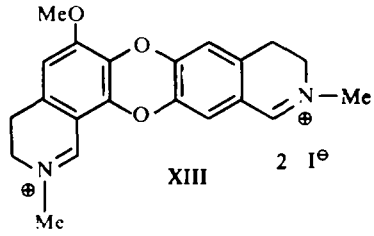
a: $R = R_1 = R_2 = Me; R_3 = H$
b: $R = R_1 = R_3 = Me; R_2 = H$
c: R, R_1 = Me, H or vice versa;
R_2, R_3 = Me, H or vice versa

Oxidation of tiliacorine with manganese dioxide and sulphuric acid was earlier reported[18] to give a dimethiodide, m.p. 270° (d), assigned structure XII on the basis of the wrong molecular formula for tiliacorine. Ueda[19] synthesized the dimethiodide (XII) and although no direct comparison was made, it has been suggested[20] incorrectly that the synthetic iodide was identical with the manganese dioxide oxidation product. We have repeated the oxidation several times and find the results are not reproducible.

The diiodide obtained in the earlier experiment is most likely the monomethoxy compound XIII.



XII

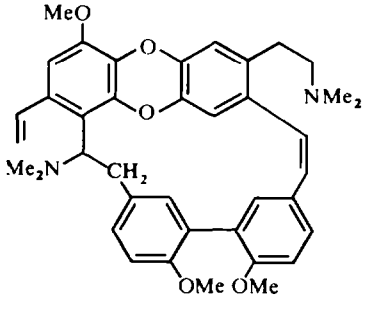


XIII

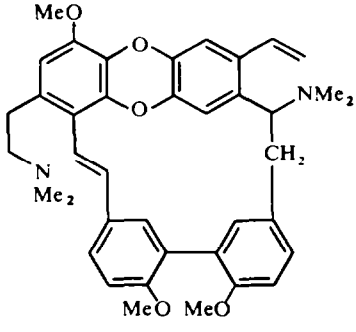
Tiliacorinine, m.p. 195° (d), the second most abundant alkaloid in *T. racemosa*, has the molecular formula $C_{36}H_{36}N_2O_5$ and is isomeric with tiliacorine. Its UV spectrum, λ_{max} 290 mμ (log ε 3·95), λ_{min} 264 mμ (log ε 3·55) is very similar to that of tiliacorine. The alkaloid gives a blue colour with a mixture of conc sulphuric and nitric acids and has two OMe groups, a hindered phenolic OH and two N-Me groups. Its NMR spectrum shows the presence of two N-Me groups at δ 2·28 and 2·62, two OMe's at δ 3·82 and 3·95 and nine aromatic protons. It forms an O-acetyl derivative, m.p. 170–172° (d), $C_{38}H_{38}N_2O_6$ (mol. wt. by mass spectrum 618).

Tiliacorinine forms a dimethiodide in the cold which can be converted to O-methyltiliacorinine dimethiodide or O-ethyltiliacorinine dimethiodide. Oxidation of the O-methyl dimethiodide with permanganate gave, as in the case of tiliacorine, 5,5′-dicarboxy-2,2′-dimethoxydiphenyl and 3,4,7,8-tetracarboxy-1-methoxydibenzo-*p*-dioxin. Oxidation of the O-ethyl dimethiodide gave 5,5′-dicarboxy-2-ethoxy-2′-methoxydiphenyl. This showed that the phenolic OH was located in the diphenyl unit as in the case of tiliacorine.

Direct correlation between tiliacorine and tiliacorinine was achieved by Hofmann degradation of the alkaloids. Both O-methyltiliacorine dimethiodide and O-methyltiliacorinine dimethiodide on Hofmann degradation gave a mixture of two methines. Chromatographic separation yielded methine A, $[\alpha]_D$ −42·60°, and methine B, $[\alpha]_D$ −64·80°. The NMR spectrum of methine A showed the N-Me groups as a singlet at δ 2·28, three OMe's at δ 3·57, 3·72 and 3·90 ppm and the aromatic and olefinic protons as a complex set of bands at δ 5·1 to 8·1 ppm. Methine B showed the N-Me's as a singlet at δ 2·30, three OMe's at δ 3·58, 3·70 and 3·90 ppm and the aromatic



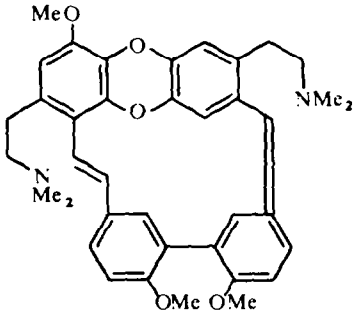
XIV



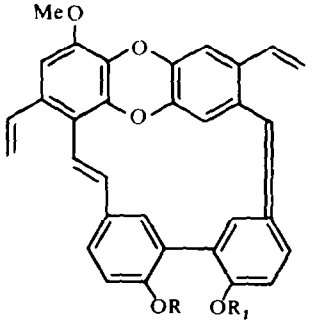
XV

and olefinic protons as complex signals from δ 5·2 to 7·3 ppm. Methines A and B are both optically active and can be assigned structures XIV and XV or *vice versa*.

In contrast with the findings in other bisbenzylisoquinoline alkaloids, the bis-stilbene (XVI) which would be optically inactive, was not formed in any significant amount in the Hofmann degradation. Both methines A and B on a second Hofmann degradation yielded the same optically inactive N-free compound (XVIIa), m.p.



XVI



XVII

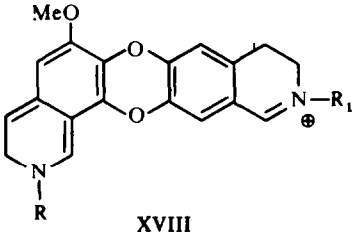
a: R = R_1 = Me
b: R = Me; R_1 = Et
c: R = Et; R_1 = Me

194–196° (d), $C_{35}H_{28}O_5$ (mol. wt. by mass spectrum 528). Its NMR spectrum shows the OMe's at δ 3·83, 3·86 and 3·92 and the unsaturated hydrogens at δ 5·2 to 8·2 ppm. Ozonolysis of XVIIa followed by oxidation with permanganate gave the acids (Ic and IIb) in excellent yield.

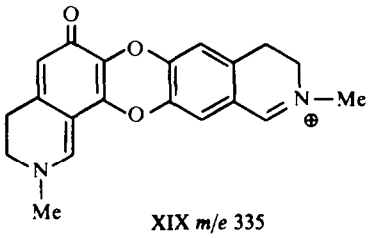
Two-stage Hofmann degradation of O-ethyltiliacorine dimethiodide as well as O-ethyltiliacorinine dimethiodide yielded an identical N-free optically inactive product, m.p. 158–160° (d), which is either XVIIb or XVIIc. This correlation establishes that the phenolic OH group in both alkaloids is in the same relative position with respect to the isoquinoline moieties and that the two alkaloids are diastereoisomers of either XIa or XIb.

The two minor alkaloids, nortiliacorinine A, m.p. 262–268° (d), and nortiliacorinine B, m.p. 218–220° (d), are isomers with the molecular formula $C_{35}H_{34}N_2O_5$. They form O,N-diacetyl derivatives, m.p. 306–308° (d) and m.p. 208° (d) respectively, with the formula $C_{39}H_{38}N_2O_7$ (mol. wt. in both cases by mass spectrum 646). The NMR spectrum of nortiliacorinine A shows the presence of one N-Me group at δ 2·30, two OMe's at δ 3·83 and 3·95 and nine aromatic protons at δ6·28–8·08. The NMR spectrum of nortiliacorinine B shows the N-Me signal at δ 2·23, two OMe's at δ 3·75 and nine aromatic protons at δ 6·38–8·20. Both alkaloids on N-methylation yield tiliacorinine. They are therefore isomeric N-demethyl tiliacorinines having structure XIc.

The mass spectra of bisbenzylisoquinoline alkaloids possessing the dibenzo-*p*-dioxin system have recently been studied.[21] The mass spectra of O-acetyltiliacorine and O-acetyltiliacorinine show prominent peaks at *m/e* 349, 335 and 175 which can be assigned to the fragments XVIIIa, XIX and XXa.

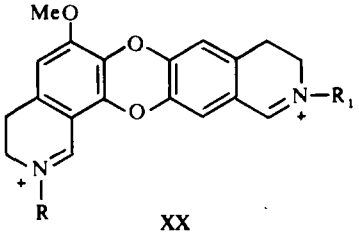


XVIII



XIX *m/e* 335

a: R = R_1 = Me; *m/e* 349
b: R = H; R_1 = Me or vice versa; *m/e* 335

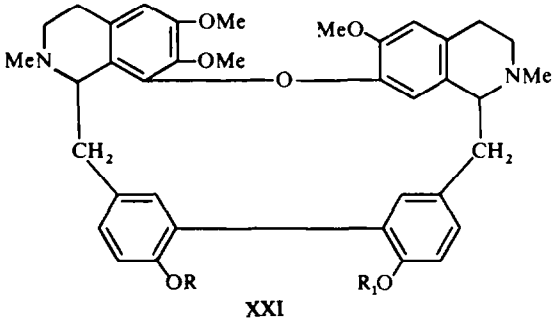


XX

a: R = R_1 = Me; *m/e* 175
b: R = H; R_1 = Me or vice versa; *m/e* 168

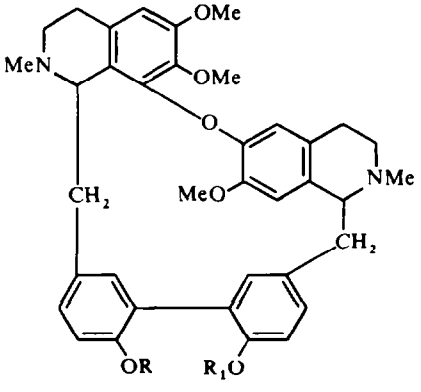
The mass spectra of O,N-diacetylnortiliacorinine A and B show significant peaks at *m/e* 335 and 168 ascribed to the fragments XVIIIb and XXb.

In the family of bisbenzylisoquinoline alkaloids tiliacorine and its congeners are unique in having a diphenyl unit. Recently[22] rodiasine, an alkaloid isolated from the greenheart tree, *Nectandra rodiei* R. Schomb, has been assigned structure XXI, with structure XXII being mentioned as a less likely possibility.



XXI

R = Me; R'_1 = H or *vice versa*



XXII

Structure XXI bears an obvious similarity to that of tiliacorine (XIa) since demethylation and ring closure could lead from XXI to the tiliacorine skeleton.

EXPERIMENTAL

Extraction of Tiliacora racemosa *and isolation of the alkaloids.* The air-dried powdered roots (25 kg) were extracted 3 times in the cold with EtOH containing 1% HOAc. The extract was concentrated *in vacuo* and the viscous residue extracted with cold 1% aq HOAc until the extracts no longer gave a positive Meyer's test. The acid soln was extracted with ether to remove non-basic materials, cooled and basified with ammonia. The brown gelatinous solid that separated was filtered. The solid and the filtrate were extracted with $CHCl_3$, the extract washed with water, dried (Na_2SO_4) and evaporated to yield the total alkaloids (370 g) as a brown gum.

The crude base (50 g) was chromatographed in $CHCl_3$ over neutral Al_2O_3. Evaporation of the eluates yielded a pale brown glass which was dissolved in acetone and left overnight at 0°. The colourless crystals of tiliacorine (4 g) that separated had m.p. 256–262° (d). Two crystallizations from $CHCl_3$–acetone gave tiliacorine, m.p. 262–264° (d), $[\alpha]_D$ +71·2° (Py, *c* 1·5), λ_{max} 295 mμ (log ε 3·91), λ_{min} 265 mμ (log ε 3·48). (Found: C, 73·61; H, 6·62; N, 4·48; OMe 9·6]. $C_{36}H_{36}N_2O_5$. MeCOMe requires: C, 73·79; H, 6·67; N, 4·41; 2 OMe, 9·81%).

The mother liquors after separation of tiliacorine were evaporated to give a brown amorphous solid. 30 g of this was subjected to a 30-transfer counter-current distribution between $CHCl_3$ and pH 5 buffer (prepared by dissolving 42 g of citric acid and 85 g Na_2HPO_4 in 4·4 l. water). Each tube had a capacity of 300 ml. Individual tubes were worked up for the alkaloids, examined by TLC and like tubes combined. Tubes 1–6 gave 22 g of a mixture of tiliacorine and tiliacorinine. Tubes 7–19 yielded 6·8 g of a mixture of nortiliacorinines A and B and tubes 20–30 yielded about 1 g of a polar amorphous material.

The alkaloid mixture (69 g) from tubes 1–6 was chromatographed over Al_2O_3 (1·5 kg) activated at 120° for 18 hr. The column was eluted with $CHCl_3$, $CHCl_3$–EtOAc (2%) and finally $CHCl_3$–MeOH (5%). The fractions were examined by TLC and like fractions combined. The earlier fractions gave *tiliacorinine* (12 g), colourless crystals (from acetone), m.p. 195° (d), shrinking over 172°, $[\alpha]_D$ +310° (Py, *c* 2·6), λ_{max} 290 mμ (log ε 3·95), λ_{min} 264 mμ (log ε 3·55). (Found: C, 73·82; H, 6·82; N, 4·26 $C_{26}H_{36}N_2O_5$. MeCO Me requires: C, 73·79; H, 6·67; N, 4·41%) The later fractions in the chromatography gave a mixture of tiliacorine and tiliacorinine. The two alkaloids could also be separated by chromatography over silica gel in $CHCl_3$ and eluting with $CHCl_3$–MeOH (0·5%).

The alkaloid mixture (6·8 g) from tubes 7–19 in the counter-current distribution was resubjected to a 30-stage counter-current distribution between EtOAc and pH 6·5 buffer prepared from 0·1M solns of KH_2PO_4 and K_2HPO_4. Tubes 10–20 gave a light brown solid (5 g). This was chromatographed over silica in $CHCl_3$. Elution with $CHCl_3$–MeOH (2%) gave *nortiliacorinine A* (4 g), m.p. 262–268° (d) (from acetone), $[\alpha]_D$ +268·8° (Py, *c* 1·5). (Found: C, 72·67; H, 6·21; N, 4·73. $C_{35}H_{34}N_2O_5 \cdot H_2O$ requires: C, 72·39; H, 6·25; N, 4·82%). The more polar fractions in the chromatography yielded *nortiliacorinine B* (0·3 g), m.p. 218–220° (d) (from acetone-MeOH), $[\alpha]_D$ +356·2° (Py, *c* 1·25). (Found: C, 71·99; H, 6·39; N, 4·70. $C_{35}H_{34}N_2O_5 \cdot H_2O$ requires: C, 72·39; H, 6·25; N, 4·82%).

In a typical run in TLC using silica gel and $CHCl_3$–MeOH (10%), tiliacorinine, tiliacorine, nortiliacorinine A and nortiliacorinine B had R_f values 5·6, 4·4, 2·8 and 2·1 respectively.

Acetyl derivatives. The following general procedure was used: A mixture of the alkaloid (0·5 g), Ac_2O (3 ml) and pyridine (0·5 ml) was left overnight at 30°. The soln was poured on water, basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4) and evaporated to yield the acetyl derivatives.

O-*Acetyltiliacorine* crystallized from $CHCl_3$-acetone as plates, m.p. 238–240° (d), ν_{max}^{Nujol} 1770 cm^{-1} (OCOMe). (Found: C, 72·54; H, 6·43. $C_{38}H_{38}N_2O_6 \cdot$MeCOMe requires: C, 72·76; H, 6·55%); Mass spectrum: *m/e* 618, 603, 350, 349, 335, 175; NMR: δ 2·13 (3H, s, OCOMe), 2·38 (3H, s, NMe), 2·63 (3H, s, NMe), 3·73 (3H, s, OMe), 3·80 (3H, s, OMe), 6·27–7·75 (aromatic protons).

O-*Acetyltiliacorinine*, crystallized from CH_2Cl_2–hexane, had m.p. 170–172° (d), $[\alpha]_D$ +363·8° (Py, *c* 2·5), $\nu_{max}^{CH_2Cl_2}$ 1765 cm^{-1} (OCOMe). (Found: C, 73·78; H, 6·27. $C_{38}H_{38}N_2O_6$ requires: C, 73·76; H, 6·19%); mass spectrum: *m/e* 618, 603, 350, 349, 335, 175; NMR: δ 2·13 (3H, s, OCOMe), 2·30 (3H, s, NMe), 2·62 (3H, s, NMe), 3·83 (3H, s, OMe), 3·87 (3H, s, OMe).

O,N-*Diacetylnortiliacorinine A*, crystallized from CH_2Cl_2–acetone had m.p. 306–308° (d), $[\alpha]_D$ +560° (Py, *c* 2·5), $\nu_{max}^{CH_2Cl_2}$ 1760 (OCOMe) and 1635 (NCOMe) cm^{-1}. (Foupd: C, 72·22; H, 5·56. $C_{39}H_{38}O_7N_2$ requires: C, 72·43; H, 5·92%); mass spectrum: *m/e* 646, 631, 604, 603, 378, 335, 281; NMR: δ 2·10 (3H, s, NCOMe), 2·20 (6H, s, 1 OCOMe, 1NMe), 3·78 (6H, s, 2 OMe), 6·25–8·00 (9H, aromatic protons).

O,N-*Diacetylnortiliacorinine B*, crystallized from acetone, had m.p. 208°, shrinking over 198°, $[\alpha]_D$ +500° ($CHCl_3$, *c* 2), ν_{max}^{KBr} 1765 (OCOMe) and 1645 (NCOMe) cm^{-1}. (Found: C, 71·03; H, 6·22; N, 3·90.

$C_{39}H_{38}O_7N_2 \cdot MeCOMe$ requires: C, 71·57; H, 6·29; N, 3·98%); mass spectrum: *m/e* 646, 631, 604, 603, 377, 335, 333); NMR: δ 2·17 (3H, s, NCOMe), 2·23 (6H, s, 1 OCOMe, 1 NMe), 3·78 (6H, s, 2 OMe), 6·28–7·92 (9H, aromatic protons).

N-Methylation of nortiliacorinines A and B

Nortiliacorinine A (0·5 g) was refluxed for 6 hr with formic acid (100%; 6 ml) and formaldehyde (38%; 3 ml). The soln was cooled, basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4) and evaporated to yield the N-Me base, identical (m.m.p., TLC, IR spectra) with tiliacorinine.

Nortiliacorinine B on similar treatment also furnished tiliacorinine.

O-Methyltiliacorine dimethiodide. Tiliacorine (5·5 g) suspended in MeOH (1 l.) was heated with NaOMe (1 g Na in 40 ml MeOH) and MeI (20 ml). The mixture was refluxed for 24 hr, similar additions of NaOMe and MeI being made every 6 hr. The solvent was removed *in vacuo*, the residue taken up in hot water and cooled. The yellow ppt that separated was filtered off, dissolved in hot water and refluxed for 10 min with precipitated Cu powder (2 g). The soln was filtered hot and the colourless solid that separated on cooling was recrystallized from MeOH to yield *O-methyltiliacorine dimethiodide* (6·1 g), colourless needles, m.p. above 360°. (Found: C, 51·02; H, 5·79; N, 2·84. $C_{39}H_{44}N_2O_5I_2 \cdot 3H_2O$ requires: C, 50·44; H, 5·39; N, 3·02%).

O-Methyltiliacorinine dimethiodide. Similar treatment of tiliacorinine or nortiliacorinines A and B yielded *O-methyltiliacorinine dimethiodide*, m.p. 270–275° (d) from MeOH. (Found: C, 51·78; H, 6·04. $C_{39}H_{44}N_2O_5I_2$. 3 MeOH requires: C, 51·95; H, 5·82%).

Tiliacorine dimethiodide. A soln of tiliacorine (2 g) in $CHCl_3$ (30 ml) was treated with MeI (6 ml) and left overnight at 30°. The solid that separated was filtered off and crystallized from acetone–MeOH to yield the *dimethiodide* (2·3 g), needles, m.p. 294–295° (d), $[\alpha]_D$ + 136·7° (H_2O, *c* 0·3). (Found: C, 51·15; H, 5·36; N, 2·94. $C_{38}H_{42}N_2O_5I_2 \cdot 2H_2O$ requires: C, 50·91; H, 5·13; N, 3·13%).

Tiliacorinine dimethiodide, prepared similarly from tiliacorinine, crystallized from MeOH as needles, m.p. above 300°, $[\alpha]_D$ +194·7° (H_2O, *c* 0·3). (Found: C, 52·87; H, 5·53; N, 3·32. $C_{38}H_{42}N_2O_5I_2$ requires C, 53·03; H, 4·92; N, 3·26%).

O-Ethyltiliacorine dimethiodide. A suspension of tiliacorine dimethiodide (3·1 g) in EtOH (500 ml) was treated with EtI (10 ml) and NaOEt (0·5 g Na in 20 ml EtOH). The mixture was refluxed for 24 hr, three more additions of EtI and NaOEt being made every 6 hr. The solvent was removed *in vacuo* and water added to the residue. The solid that separated was filtered, washed with water and dried to yield O-ethyltiliacorine dimethiodide (2·2 g). The product was used as such for the subsequent reactions.

Similar treatment of tiliacorinine dimethiodide yielded *O-ethyltiliacorinine dimethiodide* which crystallized from MeOH as needles, m.p. above 260°. (Found: C, 52·72; H, 5·82. $C_{40}H_{46}N_2O_5I_2 \cdot H_2O$ requires: C, 52·99; H, 5·34%).

O-Methyltiliacorine. A mixture of O-methyltiliacorine dimethiodide (1·1 g) and freshly distilled monoethanolamine (1·1 ml) was heated at 165–175° for 1 hr. Addition of water and extraction with $CHCl_3$ gave an oily product which was repeatedly extracted with ether. The ether soln was evaporated to give the crude product (0·32 g). Chromatography of this over Al_2O_3 in $CHCl_3$ and crystallization of the product from a large volume of ether yielded *O-methyltiliacorine* (0·15 g), m.p. 210–212°. (Found: C, 75·29; H, 6·66; N, 4·65; OMe, 15·20. $C_{37}H_{38}N_2O_5$ requires: C, 75·23; H, 6·48; N, N, 4·74; 3 OMe 15·76%).

O-Ethyltiliacorine. A mixture of O-ethyltiliacorine dimethiodide (1 g) and monoethanolamine (1·5 ml) was heated at 175–180° for 45 min and worked up as above. The crude product (0·6 g) was chromatographed over Al_2O_3 and eluted with benzene containing 0·5% EtOH. The product crystallized from a large volume of ether to give *O-ethyltiliacorine* (0·4 g), m.p. 192–194°. (Found: C, 75·30; H, 6·75. $C_{38}H_{40}N_2O_5$ requires: C, 75·47; H, 6·67%).

$KMnO_4$ oxidation of O-methyltiliacorine dimethiodide

Aqueous $KMnO_4$ (4%; 240 ml) was added dropwise to a stirred soln of O-methyltiliacorine dimethiodide (2 g) in water (100 ml). After 5 hr at 70–75°, the contents were filtered and the MnO_2 residue washed well with water. The combined filtrates were concentrated to 50 ml *in vacuo* and acidified with conc HCl. The ppt (0·6 g) was filtered off, washed with water, dried, suspended in MeOH and treated with excess ethereal CH_2N_2. The ester obtained was chromatographed over Al_2O_3 in benzene and crystallized from MeOH to yield plates of Ib (0·4 g), m.p. 172–173°, identical (m.m.p., IR spectra) with a synthetic specimen (*vide infra*). (Found: C, 65·24; H, 5·51; OMe, 36·61. Calc. for $C_{18}H_{18}O_6$: C, 65·44; H, 5·49; 4 OMe, 37·57%).

The filtrate and water-washings from the dicarboxydiphenyl were combined and evaporated to dryness *in vacuo*. The residual solid containing inorganic salts was dried well, suspended in MeOH and treated with excess ethereal CH_2N_2. The solvents were removed from the product and the residue extracted with hot benzene. Evaporation of benzene gave a gummy product (0·39 g) which was chromatographed in benzene over Al_2O_3. Fractions which gave a positive dibenzo-*p*-dioxin test (blue colour with a mixture of conc H_2SO_4 and HNO_3 acids) were combined and the product crystallized from benzene–hexane to yield 3,4,7,8-*tetracarbomethoxy*-1-*methoxydibenzo*-p-*dioxin* (IIa; 40 mg), m.p. 180–181°, λ_{max} 242, 300 mμ (log ε 4·42, 3·74), λ_{min} 290 mμ (log ε 3·72) ν_{max}^{KBr} 1720 cm^{-1}, identical (m.m.p., IR spectra) with a synthetic specimen (*vide infra*). (Found: C, 56·62; H, 4·42; O, 38·90; OMe, 34·37. $C_{21}H_{18}O_{11}$ requires: C, 56·50; H, 4·06; O, 39·43; 5 OMe, 34·77%). Mass spectrum: *m/e* 446, 415.

Oxidation of O-methyltiliacorinine dimethiodide (4 g) with $KMnO_4$ under similar conditions yielded Ib (1·1 g) and IIa (0·1 g) identical with the respective synthetic samples.

$KMnO_4$ *Oxidation of tiliacorine dimethiodide*

Tiliacorine dimethiodide (2 g) in water (100 ml) was treated with stirring at 75–80° with $KMnO_4$aq (4%; 250 ml). After 6 hr, the mixture was filtered and the MnO_2 residue washed with water. The filtrate and washings were concentrated to 50 ml *in vacuo* and acidified with conc HCl. The solid that separated was filtered, washed with water, dried and treated with excess ethereal CH_2N_2. Chromatography of the product in benzene over Al_2O_3 followed by crystallization from benzene–hexane gave dimethyl 4-methoxyisophthalate (0·5 g), m.p. 95°, identical (m.m.p., IR spectra) with a synthetic specimen. (Found: C, 58·64; H, 5·56. Calc. for $C_{11}H_{12}O_5$: C, 58·92; H, 5·40%).

The aqueous filtrate and water-washings of 4-methoxyisophthalic acid were combined, evaporated *in vacuo* and esterified with CH_2N_2 to yield IIa (0·15 g) identical with the ester obtained in the oxidation of O-methyltiliacorine dimethiodide.

Hydrolysis of the dicarbomethoxy ester, m.p. 172–173° (Ib)

The ester, m.p. 172–173° (0·5 g), was refluxed with alcoholic KOH (10%; 5 ml) for 3 hr. The solvent was removed *in vacuo*, the residue dissolved in water and acidified with conc HCl. The precipitated solid was filtered and crystallized from DMF-MeOH to yield Ic, m.p. 340–342° (d), undepressed by admixture with a synthetic sample (*vide infra*). (Found: C, 63·85; H, 4·78. Calc. for $C_{16}H_{14}O_6$: C, 63·57; H, 4·67%).

Decarboxylation of the diacid (Ic)

A mixture of the above diacid (0·2 g), Cu powder (0·1 g), $CuSO_4$ (0·1 g) and quinoline (3 ml) was refluxed for 4 hr. The mixture was diluted with benzene and filtered. The benzene soln was washed successively with dil HCl, H_2O, dil NaOHaq, H_2O, dried (Na_2SO_4) and evaporated. Chromatography of the product in benzene over Al_2O_3 followed by crystallization from MeOH yielded Ia, m.p. 155–156°, identical (m.m.p., IR spectra) with a synthetic specimen (*vide infra*). (Found: C, 78·86; H, 6·85. Calc for $C_{14}H_{14}O_2$: C, 78·48; H, 6·59%).

Hydrolysis of the tetracarbomethoxy ester, m.p. 180–181° (IIa)

The ester (0·25 g) in dioxan (25 ml) was refluxed with KOH (1 g) in water (2 ml) for 3 hr. The soln was evaporated to dryness *in vacuo*, water (20 ml) added and acidified with conc HCl. The soln was cooled in ice and the solid that separated was filtered off, washed with water and crystallized from MeOHaq to yield IIb (80 mg), m.p. 326–328° (d), sintering over 240°, ν_{max}^{KBr} 1695 cm^{-1}. (Found: C, 50·06; 50·07; H, 2·85, 2·75. $C_{17}H_{10}O_{11} \cdot H_2O$ requires: C, 50·00; H, 2·97%). Mass spectrum: *m/e* 354 (M-2 H_2O, corresponding to the formation of the dianhydride), 310, 282, 210.

$KMnO_4$ *Oxidation of* O-*ethyltiliacorine dimethiodide*

The dimethiodide (1·5 g) in water (50 ml) was oxidized with $KMnO_4$aq (4%; 200 ml) as in the case of O-methyltiliacorine dimethiodide. The water-insoluble acid obtained was esterified with excess CH_2N_2. Chromatography of the ester in benzene over Al_2O_3 followed by crystallization of the product from aq MeOH yielded 5,5′-*dicarbomethoxy*-2-*ethoxy*-2′-*methoxydiphenyl* (If) (0·2 g) as plates, m.p. 129–130°, identical (m.m.p., IR spectra) with a synthetic sample (*vide infra*). (Found: C, 66·55; H, 6·30. $C_{19}H_{20}O_6$ requires: C, 66·27; H, 5·85%).

Oxidation of O-ethyltiliacorinine dimethiodide (2 g) under similar conditions also yielded If (0·2 g) identical with the above sample.

Hofmann degradation of O-methyltiliacorine dimethiodide

The dimethiodide (2·2 g) in water (300 ml) was shaken for 6 hr with freshly precipitated Ag_2O (from 4 g of $AgNO_3$). The mixture was filtered and the residue washed well with water. The combined filtrate and washings were concentrated to 20 ml *in vacuo*. KOH aq (50%; 50 ml) was added and the mixture heated at 100° for 15 min. The solid that separated was extracted with ether and the aqueous soln heated again, the separated solid being extracted from time to time. The heating was continued until the aqueous layer no longer became cloudy on heating. The combined ether extracts were washed with water, dried (Na_2SO_4) and evaporated. The amorphous white solid obtained (1 g) was shown by TLC to consist mainly of two compounds, methine A and methine B, in the approximate ratio 2 : 1. Chromatography over silica in $CHCl_3$ yielded the pure methines A (0·7 g) and B (0·2 g). Both methines could be obtained only as amorphous solids. Methine A had m.p. 132–145°, $[\alpha]_D$ −42·67° ($CHCl_3$, *c* 2·5), λ_{max}^{EtOH} 272 mμ (log ε 4·39) and methine B had m.p. 112–126°, $[\alpha]_D$ −64·80° ($CHCl_3$, *c* 2·5) λ_{max}^{EtOH} 270 mμ (log ε 4·31).

Hofmann degradation of O-methyltiliacorinine dimethiodide

The dimethiodide (2·2 g) was subjected to Hofmann degradation as in the case of O-methyltiliacorine dimethiodide to yield the crude methine (0·8 g). Chromatography over silica in $CHCl_3$ gave methine A (0·13 g) and methine B (0·35 g) which were identical (TLC, IR spectra, optical rotation) with methine A and methine B respectively obtained from O-methyltiliacorine dimethiodide.

Second stage Hofmann degradation of O-methyltiliacorine methines A and B

The above methine A (0·7 g) in $CHCl_3$ (5 ml) was refluxed with MeI (5 ml) for 12 hr and then evaporated to dryness *in vacuo*. The residue was stirred with Ag_2O (from 1·6 g $AgNO_3$) and water (150 ml) for 3 hr, filtered and the filtrate concentrated below 50° *in vacuo* to 10 ml. The soln was treated with KOH aq (50%; 20 ml) and heated for 15 min at 100°. The solid that separated was extracted with CH_2Cl_2, the CH_2Cl_2 extract washed with water, dried (Na_2SO_4) and evaporated to yield the N-free *methine* (0·2 g). Chromatography in benzene over silica followed by crystallization from benzene–hexane gave crystals, m.p. 194–196° (d), $[\alpha]_D$ 0°. (Found: C, 77·42; H, 5·29. $C_{35}H_{28}O_5 \cdot H_2O$ requires: C, 76·90; H, 5·53%); mass spectrum: *m/e* 528.

Methine B (0·2 g) was converted into the dimethiodide and subjected to Hofmann degradation as above to yield the N-free *methine* (30 mg), m.p. 194–196° (d), identical (m.m.p., TLC, IR spectra) with the sample from methine A.

Two stage Hofmann degradation of O-ethyltiliacorine dimethiodide and O-ethyltiliacorinine dimethiodide

(a) O-Ethyltiliacorine dimethiodide (4 g) was stirred with Ag_2O (from 7 g $AgNO_3$) and water (500 ml) for 12 hr, filtered, concentrated to about 20 ml *in vacuo* and heated for 10 min at 100° with KOH (100 g) in water (100 ml). The soln was extracted with ether, the aqueous soln heated again and re-extracted with ether. The combined ether extracts gave the methine (1·9 g) as an amorphous solid which was used as such for the second stage Hofmann degradation. The methine in $CHCl_3$ (20 ml) was refluxed for 12 hr with MeI (5 ml) to yield the dimethiodide (2·5 g). This was treated with Ag_2O and subjected to Hofmann degradation as usual. Extraction with CH_2Cl_2 yielded the N-free methine. Chromatography in benzene over silica followed by crystallization from CH_2Cl_2–hexane yielded the *methine* (0·3 g), m.p. 158–160° (d), $[\alpha]_D$ 0°. (Found: C, 78·37; H, 5·73). $C_{36}H_{30}O_5 \cdot \frac{1}{2}H_2O$ requires: C, 78·38; H, 5·67%).

(b) O-Ethyltiliacorinine dimethiodide (3·3 g) on Hofmann degradation as above yielded the methine (1·4 g) which on a second Hofmann degradation gave the N-free methine (0·15 g), m.p. 158–160° (d), $[\alpha]_D$ 0°, identical (m.m.p., TLC, UV, IR and NMR spectra) with the sample from O-ethyltiliacorine dimethiodide.

Ozonolysis and oxidation of the nitrogen-free methine from O-methyltiliacorine dimethiodide

The methine (1·3 g) in $CHCl_3$ (50 ml) was ozonized for 3 hr. at 0–5°. The soln was shaken with 5% Pd–C catalyst (0·2 g) in presence of H_2 at atm press for 1 hr, filtered and evaporated. The residue was suspended in KOH aq (1 g in 30 ml water) and treated with $KMnO_4$ aq (3%; 150 ml) at 40° for 3 hr. The MnO_2 residue was filtered and washed with water. The filtrate was concentrated *in vacuo* to 40 ml and acidified. The solid was filtered, dried and esterified with CH_2N_2 to yield Ib (0·5 g), m.p. and m.m.p. with an authentic sample 172–173°. The aqueous filtrate from the dicarboxydiphenyl was evaporated *in vacuo* to dryness and treated with CH_2N_2. Working up as usual gave IIa (0·4 g), m.p. 180–181°, identical with the synthetic sample.

Synthesis of the Degradation Products

1. *Synthesis of 5,5'-dicarbomethoxy-2,2'-dimethoxydiphenyl* (Ib)

(a) *5,5'-Diacetyl-2,2'-dimethoxydiphenyl* Id. To a well-stirred suspension of anhyd $AlCl_3$ (4·5 g) in dry CS_2 (30 ml) was added dropwise a soln of 2,2'-dimethoxydiphenyl (2·3 g)[12] and acetyl chloride (3 ml) in CS_2 (30 ml). The reaction mixture was refluxed with stirring for 2½ hr, the solvent removed and the residue decomposed with ice and HCl. The solid was filtered off, washed with water, dried and crystallized from EtOH to give the *diacetyl derivative* (2 g), m.p. 162–164°. (Found: C, 72·34; H, 6·01. $C_{18}H_{18}O_4$ requires: C, 72·46; H, 6·08%).

(b) *5,5'-Dicarboxy-2,2'-dimethoxydiphenyl* (Ic). NaOH aq (2·5 g in 20 ml water) was treated at 0° with Br_2 (1·4 ml) dropwise with vigorous stirring. After 5–10 min, the foregoing Id (0·7 g) in dioxan (15 ml) was added, the soln stirred at 30° for ½ hr and diluted with water (30 ml). The filtered soln was acidified with HCl, the ppt filtered off, washed with water and dried to yield the diacid (0·5 g), m.p. 340° (d) [lit.[23] m.p. 340° (d)].

(c) *5,5'-Dicarbomethoxy-2,2'-dimethoxydiphenyl* (Ib). The above diacid (0·2 g) in MeOH (5 ml) was treated with excess ethereal CH_2N_2. The ester crystallized from benzene-hexane as needles (0·15 g), m.p. 172–173°. (Found: C, 65·75; H, 5·87. Calc for $C_{18}H_{18}O_6$: C, 65·44; H, 5·49% [lit.[13] m.p. 172°].

2. *Synthesis of 5,5'-dicarbomethoxy-2-ethoxy-2'-methoxydiphenyl* (If):

(a) *2-Hydroxy-2'-methoxy-5-nitrodiphenyl.* To a soln of sodium nitromalonaldehyde (5 g) in water (30 ml) was added NaOH aq (2 g in 50 ml water) followed by *o*-methoxyphenylacetone[24] (6·5 g) in EtOH (70 ml). The clear soln was allowed to stand for 12 hr at 30°. The EtOH was removed *in vacuo*, the residual aqueous alkaline soln extracted with ether and then acidified with dil HCl. The oil that separated was extracted with ether, the ether extract washed with water, dried (Na_2SO_4) and evaporated. The residue crystallized from EtOH aq as yellow *plates* (5·5 g), m.p. 133–135°. (Found: C, 63·70; H, 4·41. $C_{13}H_{11}NO_4$ requires: C, 63·67; H, 4·52%).

(b) *2-Ethoxy-2'-methoxy-5-nitro-diphenyl* (Ie). The foregoing nitrophenol (2·5 g) was refluxed for 3 hr with EtI (5 ml) and NaOEt (0·3 g Na in 10 ml EtOH). A second lot of NaOEt (from 0·3 g Na and 10 ml EtOH) was then added and refluxing continued for 3 hr more. The EtOH was removed *in vacuo*, water added and the oil that separated extracted with ether. The product was chromatographed in benzene over Al_2O_3 and crystallized from benzene–hexane to yield *needles* (1·6 g), m.p. 79–80°. (Found: C, 65·74; H, 5·75. $C_{15}H_{15}NO_4$ requires: C, 65·92; H, 5·53%).

(c) *5-Amino-2-ethoxy-2'-methoxydiphenyl.* The above nitrodiphenyl (1·4 g) in EtOH (35 ml) was reduced with H_2 (60 lb/in^2) in presence of Adams catalyst (0·2 g). After 45 min, the catalyst was filtered off, the filtrate evaporated *in vacuo* and the residue crystallized from benzene–hexane to give the *amine* (1·2 g) as colourless needles, m.p. 76–77°. (Found: C, 73·84; H, 7·21; $C_{15}H_{17}NO_2$ requires: C, 74·05; H, 7·04%).

(d) *2-Ethoxy-2'-methoxydiphenyl* (Ie). To a suspension of the above amine (2 g) in dil H_2SO_4 (12 ml conc H_2SO_4 in 40 ml water) was added dropwise, with stirring, at 0–5°, an aqueous soln of $NaNO_2$ (2 g in 15 ml water). The solid slowly went into soln. The yellow soln was stirred at 0° for 1½ hr. A further quantity of $NaNO_2$ (1 g in 5 ml water) was added and stirring continued for ½ hr more. The resultant soln was treated at 0° with a 50% soln of hypophosphorous acid (20 ml) in small lots. The stirred soln was allowed to come to room temp. The temp was slowly raised to 70–80° with stirring and maintained for 45 min. The soln was left overnight at 30° and the oil that separated extracted with ether. The reddish product was chromatographed in benzene over Al_2O_3 and then crystallized from MeOH aq to yield the *diphenyl* (1·5 g) as plates, m.p. 56–58°. (Found: C, 78·74; H, 7·12. $C_{15}H_{16}O_2$ requires: C, 78·92; H, 7·06%).

(e) *5,5'-Diacetyl-2-ethoxy-2'-methoxydiphenyl* (Ih). A soln of the above diphenyl (1·2 g) and acetyl chloride (2 ml) in dry CS_2 (15 ml) was added dropwise with vigorous stirring to a suspension of anhyd $AlCl_3$ (2 g) in CS_2 (15 ml). After refluxing for 2 hr the solvent was distilled, the residue decomposed with ice and dil HCl and extracted with $CHCl_3$. The product crystallized from EtOH aq as *needles* (1·2 g), m.p. 104–105°. (Found: C, 72·83; H, 6·51. $C_{19}H_{20}O_4$ requires: C, 73·06; H, 6·45%).

(f) *5,5'-Dicarboxy-2-ethoxy-2'-methoxydiphenyl* (Ig). The above diacetyldiphenyl (0·5 g) in dioxan (15 ml was added to NaOBr prepared from Br_2 (4·2 g) and NaOH (2·5 g in 20 ml water). After stirring for 1 hr at 30°, the mixture was diluted with water and acidified. The solid that separated was crystallized from DMF–EtOH to yield the *dicarboxylic acid* (0·3 g), m.p. 330° (d). (Found: C, 64·14; H, 5·35. $C_{17}H_{16}O_6$ requires: C, 64·55; H, 5·10%).

(g) *5,5'-Dicarbomethoxy-2-ethoxy-2'-methoxydiphenyl* (If). The above acid (0·2 g) in MeOH (10 ml) was treated with excess CH_2N_2. The product was chromatographed in benzene over Al_2O_3 and then crystallized

from MeOH aq to yield the *diester* (0·15 g), m.p. 129–130°. (Found: C, 66·31; H, 6·05. $C_{19}H_{20}O_6$ requires: C, 66·27; H, 5·85%).

3. *Synthesis of* 3,4,7,8-*tetracarbomethoxy*-1-*methoxydibenzo*-p-*dioxin* (IIa)

(a) 1-*Methoxy*-3,8-*dimethyldibenzo*-p-*dioxin* (IIc).[15] A soln of 5-bromocreosol (86·8 g) and *m*-bromo-*p*-cresol (88·2 g) in MeOH (50 ml) was added to methanolic KOH (49·3 g in 150 ml MeOH). The solvent was removed *in vacuo* and the residue dried thoroughly at 120°/1 mm for 6 hr. The dry mixture of K salts was suspended in *p*-cymene (1 l.) and heated with stirring with Cu bronze (28 g). At 150–160° there was an exothermic reaction and heating was discontinued for ½ hr. The mixture was refluxed for 8 hr, cooled, filtered and the inorganic residue washed with *p*-cymene (200 ml). The filtrate was passed through a column of Al_2O_3 (1·2 kg) and the column eluted with benzene–hexane (1:1) (2 l.). The eluates were evaporated to dryness *in vacuo* and the solid residue rechromatographed over Al_2O_3 (1·5 kg). The column was successively eluted with hexane, benzene–hexane (1:2), benzene–hexane (2:1) and finally benzene. The fractions were examined by TLC and like fractions combined to yield the following products in increasing order of polarity. The hexane eluates gave Va (5 g), m.p. 109–110° (from EtOH); NMR: δ 6·57 (6H, br s) (Ar–H), 2·18 ppm (6H, s) (Ar—CH_3) [Lit.[15] m.p. 109–111°]. The benzene–hexane (1:2) eluates yielded IIc (6.5 g), m.p. 119–121° (from EtOH); NMR δ 6·75 (1H, s), 6·67 (2H, s) and 6·30 (2H, s) (Ar—H), 3·82 (3H, s) (OMe), 2·18 (6H, s) (Ar—Me) [lit.[16] m.p. 119–120°]. The benzene–hexane (1:1) and benzene eluates yielded Vb (5·5 g), m.p. 195–197° (from EtOH); NMR: δ 6·43 (2H, d, J = 1) and 6·38 (2H, d, J = 1) (Ar—H), 3·85 (6H, s) (OMe), 2·22 (6H, s) (Ar—Me) [lit.[15] m.p. 194–196°].

(b) 4,7-*Diacetyl*-1-*methoxy*-3,8-*dimethyldibenzo*-p-*dioxin* (IId). A soln of IIc (4·8 g) and acetyl chloride (3·8 ml) in dry CS_2 (50 ml) was added dropwise to a stirred suspension of anhyd $AlCl_3$ (6·2 g) in CS_2 (50 ml). The mixture was stirred at 30° for 3 hr, solvent removed *in vacuo* and the residue decomposed with ice and HCl. Extraction with $CHCl_3$ gave the crude product (5·5 g) which was refluxed with methanolic KOH (4 g in 80 ml MeOH) for 3 hr. The solvent was removed *in vacuo*, the residue diluted with water, acidified and extracted with $CHCl_3$. The product (5 g) was suspended in MeOH and treated with excess ethereal CH_2N_2. The solvents were removed and the residue chromatographed in $CHCl_3$ over silica. The initial fractions gave the *monoacetyl derivative* VI (0·3 g), m.p. 136–138° (from EtOH). (Found: C, 71·75; H, 6·11. $C_{17}H_{16}O_4$ requires: C, 71·82; H, 5·67%), $\nu_{max}^{CH_2Cl_2}$ 1684 cm^{-1} (Ar—CO—Me); NMR: δ 6·73 (1H, s), 6·67 (2H, s) and 6·37 (1H, s) (Ar—H), 3·83 (3H, s) (OMe), 2·50 (3H, s) (Ar—CO—Me), 2·17 (6H, s) (Ar—Me). The later fractions in the chromatography yielded IId (3·8 g), m.p. 240–242° (from dioxan). (Found: C, 69·82; H, 5·45; OMe, 10·36. $C_{19}H_{18}O_5$ requires: C, 69·92; H, 5·56; 1 OMe, 9·78%), $\nu_{max}^{CH_2Cl_2}$ 1680 cm^{-1}; NMR: δ 7·23 (1H, s), 6·85 (1H, s) and 6·43 (1H, s) (Ar—H), 3·90 (3H, s) (OMe), 2·57 (3H, s) and 2·52 (3H, s) (Ar—CO—Me), 2·45 (3H, s) and 2·23 (3H, s) (Ar—Me).

The reaction when carried out at 0° gave V in higher proportions. Use of excess acetyl chloride in refluxing CS_2 gave 1-*acetoxy*-4,7-*diacetyl*-3,8-*dimethyldibenzo*-p-*dioxin* (VIIa) as the major product. This was purified by chromatography over silica in benzene–$CHCl_3$ (1:2). Crystallization from EtOH gave needles, m.p. 141–143°. (Found: C, 68·22; H, 5·17. $C_{20}H_{18}O_6$ requires: C, 67·79; H, 5·12%), $\nu_{max}^{CH_2Cl_2}$ 1775, 1683, 1192 cm^{-1}; NMR: δ 7·22 (1H, s), 6·72 (1H, s) and 6·57 (1H, s) (Ar—H), 2·52 (3H, s) and 2·45 (3H, s) (Ar—CO—Me), 2·38 (3H, s) and 2·13 (3H, s) (Ar—Me), 2·30 (3H, s) (OCOMe).

Hydrolysis of the pure acetoxy compound with methanolic KOH gave 4,7-*diacetyl*-1-*hydroxy*-3,8-*dimethyldibenzo*-p-*dioxin* (VIIb), m.p. 213–215° from EtOH. (Found: C, 68·91; H, 5·17. $C_{18}H_{16}O_5$ requires: C, 69·22; H, 5·16%); $\nu_{max}^{CH_2Cl_2}$ 3475, 1685 cm^{-1}, NMR: δ 8·42 (1H, br) (OH), 7·23 (1H, s) 6·77 (1H, s) and 6·43 (1H, s) (Ar—H), 2·53 (3H, s) and 2·48 (3H, s) (Ar—CO—Me), 2·40 (3H, s) and 2·13 (3H, s) (Ar—Me). The pure 1-hydroxy-diacetyl compound, on methylation with CH_2N_2, gave IId, m.p. and mixed m.p. 240–242°.

(c) NaOBr *Oxidation of* 4,7-*diacetyl*-1-*methoxy*-3,8-*dimethyldibenzo*-p-*dioxin*. NaOBr, prepared from Br_2 (1 ml) and NaOH aq (3 g in 30 ml water) at 0°, was added to IId (0·3 g) in dioxan (20 ml). The soln was heated at 55–60° for 2 hr, evaporated *in vacuo*, diluted with water and acidified. The solid was filtered, washed with water, dried and esterified with ethereal CH_2N_2 to yield 4,9-*dibromo*-7-*carbomethoxy*-1-*methoxy*-3,8-*dimethyl*-*dibenzo*-p-*dioxin* (IX; 0·2 g), m.p. 202–204° (from benzene). (Found: C, 44·68; H, 3·17. $C_{17}H_{14}O_5Br_2$ requires: C, 44·57; H, 3·08%); NMR: δ 7·58 (1H, s, H_6) and 6·82 (1H, s, H_2), 3·90 (3H, s) and 3·87 (3H, s) (OMe and COOMe), 2·50 (6H, s) (Ar—CH_3).

(d) 4,7-*Dicarboxy*-1-*methoxy*-3,8-*dimethyldibenzo*-p-*dioxin* (IIh). NaOCl was freshly prepared by passing Cl_2 (1·6 g) into a soln of NaOH (2·2 g) in water (3 ml) and ice (12·5 g). This was added to the soln of IId (0·6 g) in dioxan (100 ml). After heating with stirring at 60–70° for 1 hr, a pinch of $NaHSO_3$ was added

and the solvents removed *in vacuo*. The residue was dissolved in 1N NaOH (20 ml), filtered and acidified with HCl. The solid was extracted with CH_2Cl_2–MeOH (3:1) to yield the *diacid* (0·4 g), m.p. 325–327°(d) from MeOH. (Found: C, 61·58; H, 4·26. $C_{17}H_{14}O_7$ requires: C, 61·82; H, 4·27%).

(e) 3,4,7,8-*Tetracarbomethoxy*-1-*methoxydibenzo*-p-*dioxin* (IIa). A soln of the above diacid (1·5 g) in KOH aq (2 g in 50 ml water) was treated with $KMnO_4$ aq (10%; 60 ml). The mixture was heated at 70–75° for 1 hr, the MnO_2 filtered off and washed with water. The filtrate was concentrated *in vacuo* to 50 ml and acidified with conc HCl. The amorphous solid that separated was filtered and washed with water. The aqueous acidic filtrate was evaporated to dryness *in vacuo* and treated with excess ethereal CH_2N_2. The residue obtained on evaporation was extracted with hot benzene. The benzene soln was evaporated and the residue chromatographed in benzene over Al_2O_3 to yield the *tetracarboxylic ester* (0·3 g), m.p. 180–181° from benzene–hexane. (Found: C, 56·73; H, 4·38. $C_{21}H_{18}O_{11}$ requires: C, 56·50; H, 4·06%).

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