CONSITITUENTS OF WEST AFRICAN MEDICINAL PLANTS. XXIII.[1] THE POSITION OF THE PHENOLIC FUNCTION IN DINKLACORINE—A CONFIRMATION OF STRUCTURE

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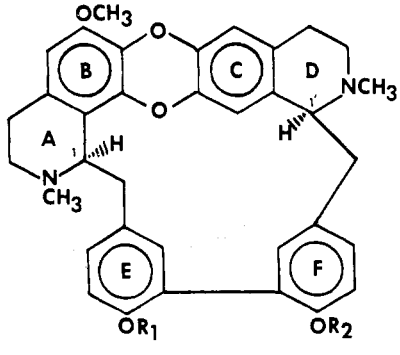
Abstract.—Dinklacorine was first isolated in 1974 from extracts of the roots of *Tiliacora dinklagei* Engl. (Menispermaceae) and was initially described as an incompletely characterized base. In 1976 chemical and spectrometric studies led to the structural assignment of dinklacorine as a phenolic dibenzodioxin biphenyl alkaloid which was a positional isomer of tiliacorine. In this paper, a controlled oxidation of dinklacorine with potassium permanganate in acetone was used to afford a product which was consistent with the recently described structure of dinklacorine and thus serves as a structural confirmation.

Dinklacorine was first isolated in 1974 from extracts of the roots of *Tiliacora dinklagei* Engl. (Menispermaceae) (1), a woody climber of the rain forests of Ghana (2). At that time, dinklacorine was described as an incompletely characterized base TD-2 (1). However, a subsequent study (3) showed that the ir, uv, and mass spectra of dinklacorine were very similar to those of the dibenzodioxin biphenyl alkaloid tiliacorine, but the two alkaloids differed in their mp, specific rotation, and nmr spectra. Methylation of dinklacorine with diazomethane afforded *O*-methyltiliacorine, while treatment of dinklacorine with sodium methoxide and



1 $R_1 = H$, $R_2 = CH_3$
2 $R_1 = CH_3$, $R_2 = H$
3 $R_1 = R_2 = CH_3$
4 $R_1 = CH_3$, $R_2 = COCH_3$
5 $R_1 = COCH_3$, $R_2 = CH_3$

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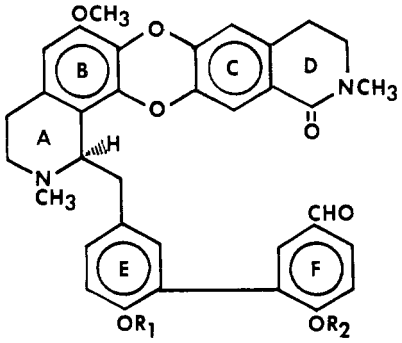
methyl iodide gave *O*-methyltiliacorine dimethiodide. However, prolonged treatment of tiliacorine and dinklacorine with diazoethane afforded different *O*-ethyl ethers. In addition, *O*-ethyldinklacorine dimethiodide and *O*-ethyltiliacorine dimethiodide were different. Furthermore, acetylation of the two alkaloids with acetic anhydride and pyridine gave *O*-acetyl esters which were not identical. A consideration of these data and, especially, the mass spectral fragmentation patterns indicated dinklacorine is a positional isomer of tiliacorine with the phenolic hydroxy group present in the biphenyl portion of the molecule on the opposite side to that of tiliacorine. At that time, the gross structure of tiliacorine had been determined to be **1** or **2** by degradative reactions (4) and an unequivocal synthesis of *O*-methyltiliacorine (**3**) (5). Therefore, if tiliacorine was **1**, then dinklacorine was **2**, or vice versa. However, after the acceptance of but prior to

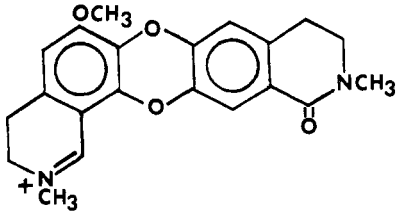


5 $R_1 = CH_3$, $R_2 = COCH_3$
6 $R_1 = CH_3$, $R_2 = H$
8 $R_1 = COCH_3$, $R_2 = CH_3$
9 $R_1 = H$, $R_2 = CH_3$

the publication of (3), the position of the phenolic group in tiliacorine was established in ring F, via a mild oxidative procedure, with tiliacorine being subsequently represented as **2** (6). Hence, since tiliacorine was represented as **2**, the phenolic group of dinklacorine must be in ring E, and dinklacorine was logically represented as **1**. The assignment of phenolic group of tiliacorine to ring F was established by a systematic study of the potassium permanganate in acetone oxidation of numerous bisbenzylisoquinoline alkaloids which demonstrated that, in every case, oxidative cleavage occurred at the benzylic bond of the isoquinoline moiety, which is unsubstituted at C-8′ (or C-8) (7), independent of relative stereochemistry. Thus, treatment of a solution of tiliacorine acetate (**4**) in acetone with potassium permanganate followed by preparative tlc of the products gave the aldehydo lactam **5** in about 8% yield (6). Hydrolysis of the acetate ester of **5** with methanolic potassium carbonate afforded the phenolic aldehydo lactam **6**, whose ultraviolet spectrum in ethanolic alkali (OH^-) showed a strong bathochromic shift indicative of a phenolic function para to an aromatic aldehyde (6, 8). Thus, tiliacorine was represented as **2** (6).

This paper is to confirm the structure of dinklacorine as **1** via the same type of mild, controlled oxidation as that used on tiliacorine. A solution of dinklacorine

acetate (**7**) (3) in acetone was oxidized in the same manner as tiliacorine acetate with potassium permanganate to afford, as the major high R_F tlc product, the aldehydo lactam acetate ester **8**, mp 139–49°; $[\alpha]^{17}D-9.76$ (c 0.59, $CHCl_3$). The ir spectrum (KBr) showed bands at 1760 cm^{-1} (phenolic acetate), 1690 (aromatic aldehyde) and 1650 (tertiary lactam) (9) while the uv spectrum showed λ max (MeOH) 228 nm (log ε 4.27), 279 (sh) (3.81) and 313 (sh) (3.38) and was similar to that of the aldehydo lactam of tiliacorine acetate (**5**) (6). The nmr spectrum indicated the presence of one aromatic acetate at δ2.05 (3H, s); one *N*-methyl group at 2.44 (3H, s); one lactam *N*-methyl group at 3.10 (3H, s); two *O*-methyl groups at 3.83 (6H, s); an aromatic proton peri to a lactam carbonyl at 7.22 (1H, s); and an aromatic aldehyde at 9.91 (1H, s). The mass spectrum showed the molecular ion at *m/e* 648 (2%) for $C_{38}H_{36}N_2O_8$ and the base peak at *m/e* 365 (100%) for the fragmentation ion **10** formed by facile benzylic cleavage.



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Hydrolysis of the aldehydo lactam acetate ester **8** with methanolic potassium carbonate afforded the aldehydo lactam **9**, mp 108–12° and $[\alpha]^{25}D+0.34$ (c 1.16, $CHCl_3$). The ir spectrum (KBr) showed bands at 1680 cm^{-1} (aromatic aldehyde) and 1650 (tertiary lactam). The mass spectrum showed the molecular ion at *m/e* 606 (<1%) for $C_{36}H_{34}N_2O_7$ and the base peak at *m/e* 365 (100%). The uv spectrum showed λ max (MeOH) 220 mn (log ε 4.08), 286 (sh) (3.44) and 312 (sh) (3.16) and was similar to the aldehydo lactam of tiliacorine (**6**) (6). However, the uv spectrum of **9** in methanolic NaOH did not show a bathochromic shift as did tiliacorine aldehydo lactam (**6**), thus indicating that **9** did not contain a phenolic function para to an aromatic aldehyde. This is consistent with the assignment of dinklacorine as **1** and serves as both an additional and final confirmation of the earlier structural proposal (1). The absolute configuration of tiliacorine (**2**) and, thus, dinklacorine (**1**) has recently been established to be (*R*) and (*S*) at the asymmetric centers C–1 and C–1', respectively (11).

EXPERIMENTAL[3]

OXIDATION OF DINKLACORINE ACETATE (**7**).—To dinklacorine acetate (**7**) (300 mg) in Me_2CO (200 ml) was added a solution of $KMnO_4$ (120 mg) in Me_2CO (100 ml) dropwise with stirring at

[3]Melting points were taken on a Thomas-Hoover or a Fisher-Johns apparatus and are uncorrected. The uv spectra were obtained on a Perkin-Elmer model 202 recording spectrophotometer and the ir spectra were determined on a Perkin-Elmer model 257 recording spectrophotometer in KBr pellets. The nmr spectra were recorded in deuterated chloroform on a Hitachi Perkin-Elmer model R–24 high resolution spectrometer with tetramethylsilane as internal standard and chemical shifts reported in δ (ppm) units. The mass spectra were taken with a LKB–9000 mass spectrometer. The optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Silicic acid (100 mesh) (Mallinckrodt), silica gel G (Camag) and alumina (neutral) Spence) were used for column chromatography while silica gel G (Camag) was used for thin-layer chromatography. The solvent system chloroform-methanol (9:1) was used for thin-layer chromatography unless otherwise designated. All reagents were analytical grade unless otherwise noted. All solvents were evaporated under reduced pressure at 40°C.

room temperature over 1½ hours. After an additional 6 hours of stirring, the solution was filtered to remove MnO_2. The filtrate was reduced in volume and applied to preparative tlc plates. After the plates were developed, the high running alkaloid-positive (Dragendorff Reagent) (10) band was eluted ($CHCl_3$-MeOH [9:1]) to afford the aldehydo lactam **8** (32 mg) mp 139–49° (petroleum ether-$CHCl_3$); $[\alpha]^{17}D-9.76$ (c 0.59, $CHCl_3$); uv, λ max (MeOH) 228 nm (log ε 4.27), 279 (sh) (3.81) and 313 (sh) (3.38); ir, ν max (KBr) 1760 cm^{-1} (ArOCOCH$_3$), 1690 (ArCHO) and 1650 (tertiary lactam); nmr, δ 2.05 (s, 3H, ArOCO*CH*$_3$), 2.44 (s, 3H, N*CH*$_3$), 3.10 (s, 3H, lactam N*CH*$_3$), 3.83 (s, 6H, O*CH*$_3$), 7.22 (s, 1H, Ar*H* peri to lactam carbonyl) and 9.91 (s, 1H, Ar*CH*O); ms, M^+ *m/e* 648 (2%) for $C_{38}H_{36}N_2O_8$ and *m/e* 365 (100).

HYDROLYSIS OF ALDEHYDO LACTAM ACETATE **8** TO ALDEHYDO LACTAM **9**.—To **8** (29.2 mg) was added a saturated solution of K_2CO_3 in MeOH (20 ml) and the mixture was stirred at room temperature for 2 hours. The solution was then evaporated and the residue dissolved in HCl (2%) (40 ml). The aqueous acidic solution was alkalinized with NH_4OH to pH 9, extracted with $CHCl_3$ (40 ml) (4x), and the combined $CHCl_3$ extracts were dried (anhydrous Na_2SO_4), filtered, and evaporated to afford **9** as a colorless residue (22.2 mg), mp 108–112°; $[\alpha]^{25}D+0.34$ (c 1.16, $CHCl_3$); uv, λ max (MeOH) 220 nm (log ε 4.08), 286 (sh) (3.44) and 312 (sh) (3.16) with no bathochromic shift in methanolic NaOH; ir, ν max (KBr) 1680 cm^{-1} (ArCHO), 1650 (tertiary lactam); ms, M^+ *m/e* 606 (<1%) for $C_{36}H_{34}N_2O_7$ and 365 (100).

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