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TRIGILLETINE AND TRICORDATINE: TWO NEW BISBENZYLISOQUINOLINE ALKALOIDS FROM *TRICLISIA* SPECIES*

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Abstract—Trigilletine and tricordatine, two new alkaloids from Ghanian menispermaceous species, have structures Ib and Ic, respectively and are examples of phenolic isotrilobine-type (Ia) alkaloids from higher plants.

THE MENISPERMACEOUS plants *Triclisia gilletii* (De Wild.) Staner and *T. subcordata* Oliv., indigenous to Ghana and other West African countries, afforded two new phenolic bisbenzylisoquinoline alkaloids, trigilletine (Ib) and tricordatine (Ic), respectively.

Trigilletine (Ib), $C_{35}H_{34}N_2O_5$, m.p. 272–274° (abs. EtOH), $[\alpha]_D^{22}+348{\cdot}2°$ (*c* 1·05 pyr)., λ_{max}^{MeOH} 234 nm (log ϵ 4·72), 275 (3·73) (sh), 289 (3·77) and 307 (3·58) (sh), was obtained from an ethanolic extract of the roots of *T. gilletii*. The alkaloid gave a blue color with a mixture of nitric and sulfuric acids indicative of the presence of a dibenzodioxin system.[1] The 100 MHz NMR spectrum (in $CDCl_3$) exhibited major signals at δ 2·39 (*s*, 3H, NMe), 2·57 (*s*, 3H, NMe) and 3·83 (*s*, 3H, OMe) while the MS showed important fragments at *m/e* 562 (39%) (M^+), 350 (32), 349 (100), 335 (35) and 175 (70). The formula and spectral data were suggestive of a phenolic bisbenzylisoquinoline alkaloid of the isotrilobine-type (Ia). Treatment of trigilletine with acetic anhydride and pyridine afforded a monoacetate, $C_{37}H_{36}N_2O_6$, m.p. 166–168° (hexane–EtOAc), *m/e* 604 (31%) (M^+), 350 (31), 349 (100), 335 (38), and 175 (75) while reaction with ethereal diazoethane yielded the *O*-ethyl ether, $C_{37}H_{38}N_2O_5$, m.p. 212·5–214·5° (EtOH), *m/e* 590 (58%) (M^+), 350 (31), 349 (100), 335 (33) and 175 (48). The intense ions at *m/e* 350, 349, 335, and 175 in the MS of the alkaloid and its *O*-acetyl and *O*-ethyl derivatives corresponded to fragments formed from the established double benzylic cleavage of alkaloids of the isotrilobine-type (Ia)[2–4] and indicated that the phenolic hydroxy group was present in a benzyl residue. This was confirmed by treatment of trigilletine with ethereal diazomethane to give isotrilobine (Ia) (IR, UV, MS, m.p.,

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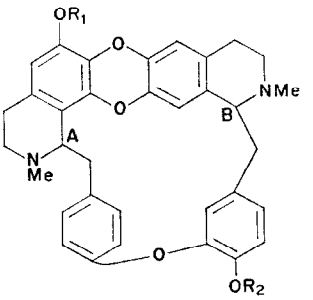
m.m.p.), $[\alpha]_D^{30}$ +303·4° (*c* 1·0, $CHCl_3$) (lit value[5] $[\alpha]_D$ +312·6° [$CHCl_3$]). Hence, the position of oxygenation was fixed and the structure of trigilletine established as Ib.



(I a) $R_1 = R_2 = CH_3$; A = B = S
(I b) $R_1 = CH_3$, $R_2 = H$
(I c) $R_1 = R_2 = H$

Tricordatine, $C_{34}H_{32}N_2O_5$, m.p. 280° *d* ($CHCl_3$–EtOH), $[\alpha]_D^{22}$ +247·9° (*c* 1·17 pyr.), λ_{max}^{MeOH} 227 nm (log ε 4·60), 275 (3·69) (sh), 284 (3·71) and 304 (3·44) (sh) was obtained from an ethanolic extract of the roots of *T. subcordata*. This alkaloid also exhibited a positive test for the dibenzodioxin moiety.[1] The MS of tricordatine exhibited important fragments at *m/e* 548 (27%) (M^+), 336 (31), 335 (100), 321 (32) and 168 (49). Although the relative insolubility of the alkaloid in all common organic solvents precluded the recording of a NMR spectrum, the formula and MS data were indicative of a phenolic bisbenzylisoquinoline alkaloid of the isotrilobine-type (Ia). Treatment of tricordatine with ethereal diazoethane afforded the oily *O,O*-diethyltricordatine $C_{38}H_{40}N_2O_5$, *m/e* 604 (41%) (M^+), 364 (29), 363 (100), 349 (18), 335 (26), 182 (23) and 168 (25) while reaction of the base with acetic anhydride in pyridine gave the *O,O*- diacetate, $C_{38}H_{36}N_2O_7$ (m.p. of dimethiodide, 230–232° *d* [Me_2CO–Et_2O]), *m/e* 632 (10%) (M^+), 590 (30), 548 (23), 377 (37), 336 (31), 335 (100), 321 (34) and 168 (60). Tricordatine did not react with formalin and sodium borohydride indicating the absence of a secondary amine function. The MS fragments of the base, the *O,O*-diethyl ether and the *O,O*-diacetate were likewise formed from double benzylic cleavages[2–4] of the respective compounds suggesting one phenolic hydroxy group in the isoquinoline portion and a second phenolic function in the benzyl portion of tricordatine. Finally, prolonged treatment of tricordatine with ethereal diazomethane afforded isotrilobine (Ia) (IR, UV, MS, [m.p. and m.m.p. of the dimethiodide]), $[\alpha]_D^{30}$ +301·9° (*c* 1·0, $CHCl_3$), hence establishing the position of oxygenation of the alkaloid and determining its structure as Ic. The optical activity of the methylation products of both trigilletine (Ib) and tricordatine (Ic) suggests identical stereochemistry with that of isotrilobine (Ia) (A = B = *S*). This is only the second reported isolation[6,7] of phenolic isotrilobine-like alkaloids from natural sources although tricordatine (also called anhydrodemethylrepandine) has been synthesized from repandine.[8]

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EXPERIMENTAL

M.ps were determined in capillaries and are uncorrected. IR were recorded in KBr pellets; UV in MeOH or EtOH; optical rotation in $CHCl_3$ on a Rudolph polarimeter; NMR in $CDCl_3$ with TMS as internal standard on a M.P.C. Corporation 100 MHz spectrometer; MS on a LKB-9000 mass spectrometer.

Isolation of the bases. The detailed isolation procedure of trigilletine and tricordatine, as well as other alkaloids of *T. gilletii* and *T. subcordata*, will be presented elsewhere in due course.

Acetylation of trigilletine. To trigilletine (50 mg) in pyridine (4·0 ml) was added Ac_2O (2·0 ml). The resulting solution was maintained at 40° for 24 hr, poured into H_2O (10 ml), basified with NH_4OH to pH 9 and extracted 3× with Et_2O (30 ml). The Et_2O extracts were washed, dried and evaporated to leave a residue. Treatment of this residue with petrol.–EtOAc afforded *O*-acetyltrigilletine (40 mg) as rosettes of prisms, m.p. 166–168° *d*; λ_{max}^{MeOH} 207 nm (log ε 4·76), 232 (4·63), 267 (sh) (3·55), 275 (sh) (3·60) and 283 (3·62); λ_{min}^{MeOH} 260 nm (log ε 3.45); ν_{max}^{KBr} 1765 cm^{-1} (ArOCOMe) and 1505 (ArC=C); MS M^+ *m/e* 604 (31%) for $C_{37}H_{36}N_2O_6$, 350 (31), 349 (100), 335 (38) and 175 (48).

Ethylation of trigilletine. To trigilletine (40 mg) in Et_2O-EtOH (1:1) (100 ml) was added ethereal diazoethane[9] (50 ml). The reaction mixture was lightly stoppered and placed in the dark. After 24 and 48 hr respectively, two additional charges (50 ml each) of ethereal diazoethane were added to the mixture. Approximately 24 hr later, the solvent was removed and the residue crystallized from abs. EtOH to afford rosettes of *O*-ethyltrigilletine (28 mg), m.p. 212·5–214·5° *d*; λ_{max}^{MeOH} 206 nm (log ε 4·78), 235 (4·63), 274 (sh) (3·63), 286 (3·66) and 304 (sh) (3·52); λ_{min}^{MeOH} 260 nm (log ε 3·45); ν_{max}^{KBr} 1505 cm^{-1} (ArC=C); MS M^+ *m/e* 590 (58%), 350 (31), 349 (100), 335 (33) and 175 (48).

Methylation of trigilletine. To trigilletine (50 mg) in Et_2O-MeOH (1:1) (50 ml) was added ethereal diazomethane[10] (40 ml). After standing in the dark for 24 hr, the solvent was removed and the resulting oil dissolved in $CHCl_3$ (5 ml) and passed through a silicic acid (10 g) column. Elution with $CHCl_3$–MeOH (9:1) afforded a residue which crystallized from MeOH to yield cubes of isotrilobine (Ia) (40 mg), m.p. 212 *d*; $[\alpha]_D^{30}$ +303·4° (*c* 1·0, $CHCl_3$); identical with a reference sample by direct comparison (IR, UV, MS, m.p., m.m.p.).

Ethylation of tricordatine. Tricordatine (20 mg) was ethylated in a manner similar to trigilletine. The reaction mixture was evaporated to afford an oil which was dissolved in $CHCl_3$ (5 ml) and chromatographed over silicic acid (10 g). Elution with $CHCl_3$–MeOH (9:1) afforded *O,O*-diethyltricordatine as a light yellow oil (10 mg), MS:M^+ *m/e* 604 (41%) for $C_{38}H_{40}N_2O_5$, 364 (29), 363 (100), 349 (18), 335 (26), 182 (23) and 168 (25).

Acetylation of tricordatine. Tricordatine (20 mg) was acetylated in a manner similar to trigilletine. The crude diacetate from the reaction was dissolved in $CHCl_3$ (5 ml) and chromatographed over silicic acid (10 g). Elution with $CHCl_3$–MeOH (9:1) afforded *O,O*-diacetyltricordatine as a light yellow oil, MS M^+ *m/e* 632 (10%) for $C_{38}H_{36}N_2O_7$, 590 (30), 548 (23), 377 (37), 336 (31), 335 (100), 321 (34) and 168 (60). Treatment of an Et_2O–Me_2CO solution of this oil with MeI (0·5 ml) yielded *O,O*-diacetyltricordatine dimethiodide (10 mg) as a yellow powder, m.p. 230–232° *d*, ν_{max}^{KBr} 1765 cm^{-1} (ArOCOMe) and 1500 (ArC=C).

Attempted N-methylation of tricordatine. To tricordatine (18 mg) in MeOH (25 ml) was added formalin (37% CH_2O) (0·5 ml) dropwise with stirring. After stirring for 8 hr, the resulting solution was cooled in an ice bath, $NaBH_4$ (100 mg) added slowly, and stirring continued another 16 hr. The solution was evaporated and the residue dissolved in HCl (1%) (20 ml) and extracted with $CHCl_3$ (20 ml). The acidic layer was separated, basified with NH_4OH to pH 9 and extracted 3× with $CHCl_3$ (50 ml). The $CHCl_3$ extracts were dried and the solvent removed to afford a crystalline residue (15 mg). Crystallization from petrol.–$CHCl_3$ afforded starting material (IR, UV, MS, m.p., m.m.p.).

Methylation of tricordatine. Tricordatine (20 mg) was methylated in a manner similar to trigilletine. The crude *O,O*-dimethyltricordatine was dissolved in $CHCl_3$ (5 ml) and chromatographed over silicic acid (10 g). Elution with $CHCl_3$–MeOH (9:1) afforded a light yellow oil $[\alpha]_D^{30}$ +301·9° (*c* 1·0, $CHCl_3$), identical with authentic isotrilobine (Ia) (IR, UV, MS). Treatment of the oil with MeOH (5 ml) and MeI (0·3 ml) for 24 hr, and evaporation of the solvent afforded an oily residue. Treatment of this residue with Me_2CO afforded a yellow crystalline product identical to authentic isotrilobine dimethiodide (IR, MS, m.p., m.m.p.).

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