CONSTITUENTS OF WEST AFRICAN MEDICINAL PLANTS. XXVII.[1] ALKALOIDS OF *RHIGIOCARYA RACEMIFERA* AND *STEPHANIA DINKLAGEI*

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Abstract.—*Rhigiocarya racemifera* and *Stephania Dinklagei* are menispermaceous climbing shrubs of the forests of Ghana and other parts of West Africa which have been used natively as medicinal agents. Chromatography of an extract of the roots of *R. racemifera* afforded the alkaloids *O*-methylflavinantine (**1**), liriodenine (**2**), palmatine (**3**), menisperine (*N*-methylisocorydine) (**4**) and magnoflorine (**5**). A similar treatment of an extract of the stems of *S. Dinklagei* afforded the alkaloids *N*-methylglaucine (**7**) and *N*-methylcorydine (**9**).

Rhigiocarya racemifera Miers (Menispermaceae) is a climbing shrub indigenous to the forests of Ghana and other parts of West Africa (1). The roots have been added to palm wine while extracts of the plant have been used medicinally as nasal drops and as an aphrodisiac (1). The only reference to this genus in the literature cited the isolation of the morphinandienone alkaloid *O*-methylflavinantine (**1**) from an extract of the roots (2). The analgesic activity of *O*-methylflavinantine has been established (3), and further pharmacological investigation of this alkaloid continues (4).

It was decided to undertake a phytochemical investigation of this species in order to isolate additional compounds with potential biological activity and to further our knowledge of the constituents of this genus. This paper is to report the re-isolation of *O*-methylflavinantine (**1**) and the isolation of the oxoaporphine alkaloid liriodenine (**2**), the protoberberine alkaloid palmatine (**3**), and the aporphine alkaloids menisperine (*N*-methylisocorydine) (**4**) and magnoflorine (**5**) from extracts of the roots of *R. racemifera*. The dried, powdered roots were extracted with dilute acetic acid, and the aqueous acidic extract was alkalinized with ammonium hydroxide and extracted with chloroform. The chloroform extract was chromatographed over alumina in ether to afford *O*-methylflavinantine (**1**) and liriodenine (**2**). Both alkaloids were identified by direct comparison (uv, ir, nmr, ms, mp, mmp) with authentic reference samples. The alkaline solution remaining after extraction of the nonquaternary alkaloids was re-acidified with hydrochloric acid, and the quaternary bases were precipitated with Mayer's Reagent. The crude quaternary alkaloid complex was filtered, washed with water, dissolved in methanol, and treated with an anion exchange resin (iodide). After exchange, the quaternary alkaloid iodide mixture was chromatographed over silica gel in chloroform. Elution with 2% methanol in chloroform afforded plamatine iodide (3), and elution with 4% methanol in chloroform gave menisperine (*N*-methyliso-

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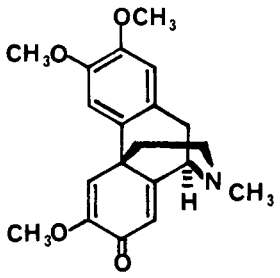

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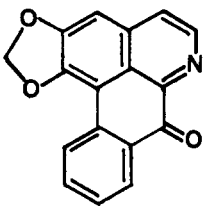

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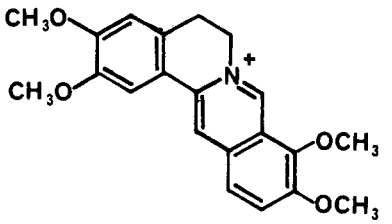

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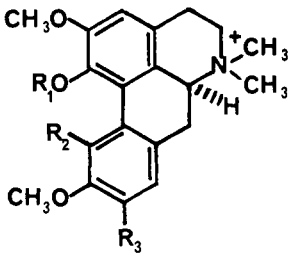
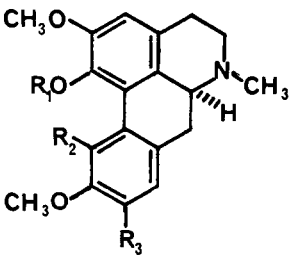


4 R_1=CH_3, R_2=OH, R_3=H
5 R_1=R_3=H, R_2=OH
7 R_1=CH_3, R_2=H, R_3=OCH_3
9 R_1=H, R_2=OCH_3, R_3=H



6 R_1=CH_3, R_2=OH, R_3=H
8 R_1=CH_3, R_2=H, R_3=OCH_3
10 R_1=H, R_2=OCH_3, R_3=H

corydine) iodide (**4**). These alkaloids were identified by direct comparison (uv, ir, nmr, ms, mp, mmp) with authentic reference samples. (Menisperine iodide was prepared by the addition of methyl iodide to an acetone solution of isocorydine (**6**)). Elution with 4% methanol in chloroform gave magnoflorine iodide (**5**), identified by direct comparison (uv, ir, ms, mp, mmp) with an authentic reference sample. Elution with 8% methanol in chloroform afforded trace amounts of

another base RRQB-3B; its identity is unknown pending the isolation of additional quantities.

Liriodenine (**2**), the first oxoaporphine alkaloid to be isolated from a natural source, was initially obtained from the heartwood of the yellow poplar tree, *Liriodendron tulipifera* L. (Magnoliaceae) in 1960 (5). Its structure was subsequently correctly assigned shortly thereafter (6). Liriodenine has demonstrated a cytotoxic activity against the 9-KB cell culture (7) and has been isolated from different genera in the families Annonaceae, Araceae, Eupomaticaceae, Lauraceae, Magnoliaceae, Menispermaceae, Monimiaceae, Nymphaceae, Papaveraceae, Rhanmaceae and Rutaceae (8, 9).

Palmatine (**3**) is a rather commonly occurring protoberberine alkaloid from selected genera in the families Annonaceae, Berberidaceae, Convolvulaceae, Fumariaceae, Lauraceae, Menispermaceae, Papaveraceae, Ranunculaceae and Rutaceae (10, 11). Palmatine was found to possess antiarrhythmic, positive inotropic, adrenocorticotropic, anticholinesterase, analgesic and bactericidal properties (12).

Menisperine (*N*-methylisocorydine) (**4**) is a quaternary aporphine alkaloid which has been isolated from certain genera of the families Annonaceae, Aristolochiaceae, Berberidaceae, Lauraceae, Menispermaceae, Papaveraceae and Rutaceae (9, 13). Administration of menisperine chloride (*N*-methylisocorydine chloride) to animals produced apnea and cardiac failure. An increase in excitability was observed in rabbits while a decrease was seen in rats (14). Menisperine iodide (*N*-methylisocorydine iodide) has been found to exert a hypotensive effect on anesthetized dogs, block neural transmission through feline superior cervical ganglia and, in large doses, block neuromuscular transmission in dogs and rabbits (15).

Magnoflorine (**5**) is perhaps the most widely distributed naturally occurring quaternary aporphine alkaloid. It has been found in numerous genera of the families Annonaceae, Aristolochiaceae, Berberidaceae, Euphorbiaceae, Magnoliaceae, Menispermaceae, Ranunculaceae and Rutaceae (16, 17). Magnoflorine has been shown to exert a hypotensive effect and a curare-like activity in animals (15). This is the first reported isolation of liriodenine, palmatine and menisperine from the genus *Rhigiocarya* and, accordingly, the first reported isolation of oxoaporphine, protoberberine and aporphine alkaloids within this genus.

Stephania Dinklagei (Engl.) Diels (Menispermaceae) is a climbing shrub of the deciduous forests of both East and West Africa (18). The roots and stems have been used medicinally in Ghana in the treatment of menorrhagia and as a vermifuge, an analgesic, an aphrodisiac and a sedative (18). The leaves of the plant are used in folkloric medicine in the treatment of infertility in the female and impotence in the male (19). The stems have also been used as a fish poison (18). Numerous phenylalanine-tyrosine derived alkaloids of the benzylisoquinoline, bisbenzylisoquinoline, proaporphine, aporphine, oxoaporphine, protoberberine, and hasubanan type have been isolated from varying *Stephania* species (20–25). An early examination of extracts of *S. Dinklagei* resulted in the isolation of an unknown alkaloid designated dinklageine (26). Later, a mixture of the aporphine alkaloids isocorydine and dicentrine were isolated from the same species (27). About ten years ago, corydine, isocorydine, and roemerine were isolated and five other alkaloids detected in extracts of *S. Dinklagei* (28). Finally, in 1974, Slatkin *et al.* reported the isolation of corydine, norcorydine, steporphine, stepharine, and the new alkaloid stephalagine from extracts of the stems (29). It was decided to

undertake an investigation of the quaternary alkaloids of this plant in order to complement our study of the nonquaternary bases (29) and to seek a source of compounds of potential biological or phytochemical importance.

The extraction, fractionation, and preparation of a crude Mayer's quaternary complex from the stems of the plant was the same as that described earlier in this paper for *R. racemifera*. The Mayer's quaternary complex was converted to a quaternary chloride mixture via an anion exchange resin. This mixture was chromatographed over alumina in chloroform. Elution with 25% methanol in chloroform afforded *N*-methylglaucine chloride (**7**), which was converted to the iodide via anion exchange resin, and identified by direct comparison (uv, ir, ms, mp, mmp) with an authentic reference sample (prepared by treating an acetone solution of glaucine (**8**) with methyl iodide). Continued elution with the same solvent gave *N*-methylcorydine chloride (**9**), which was identified in a like manner by conversion to the iodide via anion exchange resin and direct comparison (uv, ir, nmr, ms, mp, mmp) with an authentic reference sample (prepared by treating an acetone solution of corydine (**10**) with methyl iodide). Finally, continued elution with the same solvent afforded a small quantity of a yet unidentified alkaloid, designated SDQ–3.

To our knowledge, this is the first reported occurrence of the quaternary aporphine *N*-methylglaucine (**7**) as a naturally occurring alkaloid. Glaucine (**8**), the tertiary analogue of *N*-methylglaucine, has been isolated from selected genera of the families Annonaceae, Lauraceae, Magnoliaceae, Papaveraceae and Ranunculaceae (30). To our knowledge, no reports of the pharmacological properties of *N*-methylglaucine have appeared in the literature, but glaucine has been shown to induce hypotension and inhibit respiration in cats (15). In addition, glaucine has adrenolytic, antitussive, and hypotensive effects in cats and rats (15).

N-Methylcorydine (**9**) has been previously isolated from *Fagara nigrescens* (Rutaceae) (31, 32), *Polyathia oliveri* (Annonaceae) (33), and *Kolobopetalum auriculatum* (Menispermaceae) (34). *N*-Methylcorydine iodide has been shown to decrease the blood pressure of anesthetized dogs, block transmission of nerve impulses through the superior cervical ganglia of cats and, in large doses, block neuromuscular transmission in frogs and rabbits (15). To our knowledge, this is the first reported isolation of *N*-methylcorydine from the genus *Stephania*.

EXPERIMENTAL[3]

PLANT MATERIAL.—The plant material used in this study was collected in Ghana in 1977. Voucher specimens are on deposit at the Faculty of Pharmacy, University of Science and Technology, Kumasi, Ghana.[4] The leaves, stems, and roots were separated, dried, and ground to a coarse powder.

[3]Melting points were taken on a Thomas-Hoover apparatus or a Fisher-Johns Apparatus and are uncorrected. The uv spectra were obtained on a Perkin-Elmer model 202 recording spectrophotometer in methanol 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 (unless otherwise designated) on a Hitachi Perkin-Elmer model R–24 high resolution spectrometer with tetramethylsilane as internal standard and chemical shifts recorded in δ (ppm) units. The mass spectra were taken with a LKB–9000 mass spectrometer. The optical rotations were 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 or BDH) and alumina (neutral) (Spence) were used for column chromatography while silica gel G (Camag) was used for thin-layer chromatography. All solvents were evaporated under reduced pressure at 40°.

[4]The plant material was collected and identified by Mr. K. Obeng-Darko (F.L.S.) of the Faculty of Agriculture, University of Science and Technology, Kumasi, Ghana, West Africa.

PART 1—*Rhigiocarya racemifera*

EXTRACTION, FRACTIONATION AND CHROMATOGRAPHY.—Powdered dried roots (2 kg) of *Rhigiocarya racemifera* Miers (Menispermaceae) were percolated with aqueous acetic acid (8%) (4 liters) for 24 hours and filtered. The process was repeated three more times and the filtrates combined, alkalinized with conc NH_4OH to pH 9, and extracted with chloroform (10 liters) (3x). The chloroform extracts were combined, dried (anhydrous Na_2SO_4), filtered, and evaporated to afford a dark residue (11 g). This residue was dissolved in chloroform, adsorbed onto alumina (25 g), and chromatographed over a column of alumina (150 g) in diethyl ether.

ISOLATION OF *O*-METHYLFLAVINANTINE (**1**).—Elution of the column with diethyl ether (2 liters) afforded a residue (1.6 g) which upon treatment with diethyl ether or methanol, gave *O*-methylflavinantine (**1**) (1.05 g) as white feathery needles, mp 124–26°, $[\alpha]^{26}D-10°$ (c=0.29 in MeOH), identical by direct comparison (uv, ir, nmr, ms, mp, mmp) with an authentic sample (2).

ISOLATION OF LIRIODENINE (**2**).—Continued elution with diethyl ether (2 liters) gave a residue (110 mg) which, on treatment with methanol, afforded dark yellow needles of liriodenine (**2**) (85 mg), mp 263–65°, identical by direct comparison (uv, ir, ms, mp, mmp) with an authentic sample (35).

PREPARATION OF THE QUATERNARY COMPLEX AND CHROMATOGRAPHY.—The alkaline solution remaining after extraction of the non-quaternary alkaloids with chloroform was acidified to pH 2 with conc. HCl and treated with an excess of Mayer's Reagent (36) until precipitation ceased. The crude quaternary alkaloid complex was filtered by suction, washed with H_2O, dissolved in methanol-water (3:2) (1 liter) and passed over an anion exchange resin column (IRA-401S [Iodide])[5] (150 g). The column was rinsed with additional methanol-water (3:2) (600 ml), and the eluate and rinsings were combined and evaporated to leave a dark residue (40 g) of crude quaternary alkaloid iodide salts. The residue was dissolved in methanol (200 ml), adsorbed onto silica gel (80 g) in chloroform, and chromatographed over silica gel (250 g) in chloroform.

ISOLATION OF PALMATINE IODIDE (**3**).—Elution of the column with chloform-methanol (98:2) (200 ml) afforded a residue. Treatment of this residue with methanol gave yellow needles of palmatine iodide (**3**) (60 mg), mp 227–29°, identical to an authentic sample (37) by a direct comparison (uv, ir, mp, mmp).

ISOLATION OF MENISPERINE IODIDE (**4**).—Elution of the column with chloroform-methanol (96:4) (400 ml) afforded a pale brown residue, which on treatment with methanol gave white needles (82 mg) of menipserine iodide (**4**), mp 222–24° (after darkening at 215°) (lit. 219° (38)); $[\alpha]^{20}D+134°$ (c=0.67 in MeOH) (lit. +139° (MeOH) (38)); ir, νmax (KBr) 3210, 3010, 2970, 2950, 2830, 1595, 1470, 1425, 1230, 1117, 1045, 1003 and 810 cm^{-1}; uv λmax (MeOH) 223 nm (log ϵ 4.70), 272(4.26) and 304(3.91); nmr, dmso-d_6 . 2.90(s, 3H, $^+NCH_3$), 3.66(s, 3H, OCH_3), 3.78(s, 3H, OCH_3), 3.85(s, 3H, OCH_3), 6.95(s, 2H, ArH) and 7.03(s, 1H, ArH); ms, M^+ *m/e* 356 (1%), 355(2), 342(9), 341(33), 328(10), 284(10), 283(11), 270(67), 255(24), 212(18), 142(100), 127(38), 59(27) and 58(96) identical to an authentic sample prepared from isocorydine by direct comparison (uv, ir, ms, mp, mmp).

PREPARATION OF MENISPERINE IODIDE (*N*-METHYLSIOCORYDINE IODIDE) (**4**) FROM ISOCORYDINE (**6**).—To a solution of iosocorydine (**6**) (8 mg) (39) in acetone (3 ml) was added methyl iodide (0.2 ml). After standing overnight at room temperature, the resulting granular precipitate was filtered by suction and washed with acetone to yield *N*-methylisocorydine iodide (menisperine iodide) (**4**) (7 mg), mp 216°.

ISOLATION OF MAGNOFLORINE IODIDE (**5**).—Continued elution with chloroform-methanol (96:4) (400 ml) afforded a crystalline residue. Treatment of this residue with methanol gave magnoflorine iodide (**5**) as white rods (55 mg), mp 249–50° (after darkening at 230°), $[\alpha]^{22}D+198°$ (c=0.65 in MeOH) identical to an authentic sample (40) by direct comparison (uv, ir, nmr, ms, mp, mmp).

ISOLATION OF RRQB-3B.—Elution with chloroform-methanol (92:8) (200 ml) afforded a small amount (2 mg) of an uncharacterized alkaloid, designated RRQB-3B, mp. 185–95° (slow decomp.).

PART 2—*Stephania Dinklagei*

EXTRACTION, FRACTIONATION AND CHROMATOGRAPHY.—Powdered, dried stems (1.5 kg) of *Stephania Dinklagei* (Engl.) Diels (Menispermaceae) were percolated with aqueous acetic acid (6%) (3 liters) for 24 hours and filtered. The process was repeated three more times, and the

[5]Amberlite ion-exchange resin, Mallinckrodt, St. Louis, MO.

filtrates were combined, alkalinized with conc. NH_4OH to pH 9, and extracted with chloroform (9 liters) (3x). The chloroform extracts were combined, dried (anhydrous Na_2SO_4), filtered, and evaporated to leave a dark residue (83 g). This residue, containing the nonquaternary alkaloids, was placed aside due to our earlier investigation of this species (29).

PREPARATION OF A QUATERNARY COMPLEX AND CHROMATOGRAPHY.—The alkaline solution remaining after extraction of the nonquaternary alkaloids with chloroform was acidified to pH 2 with conc. HCl and treated with an excess of Mayer's Reagent (36) until precipitation ceased. The crude quaternary alkaloid complex was filtered by suction, washed with water, dissolved in acetone-water (1:9) (500 ml), and passed over an anion exchange resin column (IRA-401S [Cl])[5] (100 g). The column was rinsed with additional acetone-water (1:9) (400 ml); the eluate and rinsings were combined and evaporated to leave a dark residue (24 g) of crude quaternary chloride salts. The residue was dissolved in methanol (100 ml), adsorbed onto neutral alumina (40 g), and chromatographed over neutral alumina (240 g) in chloroform.

ISOLATION OF *N*-METHYLGLAUCINE IODIDE (7).—Elution of the column with chloroform-methanol (3:1) (300 ml) afforded a residue (423 mg). This residue was dissolved in methanol (50 ml) and passed over an anion exchange resin column (IRA-301S [Iodide])[5] (20 g). The column was rinsed with methanol (50 ml), and the eluate and rinsings were evaporated to leave a brownish-white residue. Treatment of this residue with methanol afforded (+)-*N*-methylglaucine iodide (7) as white needles (108 mg), mp 217–220° after softening at 213° (ref 216–19° 30)): $[\alpha]_D$ +81° (c=0.53 in MeOH) (ref $[\alpha]^{17}_D$ −72° (30)); ir νmax (KBr) 3000 cm^{-1}, 1518, 1480, 1460, 1432, 1421, 1398, 1390, 1358, 1342, 1325, 1272, 1250, 1235, 1225, 1122, 1105, 1033, 1007, 973, 955, 923, 877 and 770; uv, λmax (MeOH) 223 nm (log ε 4.61), 283(4.12) and 304(4.14); nmr (MeOH-d_4), δ 3.09(s, 3H, $^+NCH_3$), 3.47(s, 3H, $^+NCH_3$), 3.68(s, 3H, OCH_3), 3.83(s, 3H, OCH_3), 3.89(s, 6H, $2OCH_3$), 6.88(s, 1H, ArH), 7.04(s, 1H, ArH) and 7.95(s, 1H, ArH); ms, M^+ *m/e* 370(1), 369(3), 355(1), 142(4), 128(6), 127(4), 59(3) and 58(1000). The alkaloid was identical (uv, ir, ms, mp, mmp) to an authentic reference sample of *N*-methylglaucine iodide (7) prepared by the treatment of a solution of (+) glaucine (8) in acetone with methyl iodide.

PREPARATION OF *N*-METHYLGLAUCINE IODIDE (7).—To a solution of (+)-glaucine (8) (6 mg) in acetone (5 ml) was added methyl iodide (0.2 ml). After standing overnight, the resulting crystalline mass was filtered, rinsed with acetone, and dried to afford white rods of *N*-methylglaucine iodide (7) (5 mg), mp 216–18°.

ISOLATION OF *N*-METHYLCORYDINE IODIDE (9).—Elution of the column with additional chloroform-methanol (3:1) (200 ml) afforded a tan residue (810 mg). This residue was dissolved in methanol (100 ml) and passed over an anion exchange resin column (IRA-401S [Iodide])[5] (40 g). The column was rinsed with methanol, and the eluate and rinsings were evaporated to leave a pale brown residue. Treatment of this residue with methanol afforded *N*-methylcorydine iodide (9) as white needles (206 mg), mp. 202–04° after darkening at 195°; $[\alpha]^{20}_D$ +154° (c=1.09 in MeOH), identical to an authentic sample by direct comparison (34).

ISOLATION OF SDQ-3.—Continued elution with the same solvent (300 ml) afforded a small amount (5 mg) of an uncharacterized alkaloid, designated SDQ-3, mp. 240° dec.

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